FDA Adverse Event Reporting System (FAERS)
FOIA Batch Printing Report for Cases

Date - Time: 09-Jan-2024 15:43:02 EST

Run by: KIA.BAZEMORE@FDA.HHS.GOV

Disclaimer:

Submission of a safety report does not constitute an admission that medical personnel, user facility, importer, distributor, manufacturer or product caused or contributed to the event. The information in these reports has not been scientifically or otherwise verified as to a cause and effect relationship and cannot be used to estimate the incidence of these events.

Data provided in the Quarterly Data Extract (QDE) or a FAERS FOIA report are a snapshot of FAERS at a given time. There are several reasons that a case captured in this snapshot can be marked as inactive and not show up in subsequent reports. Manufacturers are allowed to electronically delete reports they submitted if they have a valid reason for deletion. FDA may merge cases that are found to describe a single event, marking one of the duplicate reports as inactive. The data marked as inactive are not lost but may not be available under the original case number.

The cover page will display all Case ID(s) included in the Batch Printing Report and FOIA case report information may include both Electronic Submissions (Esubs) and MedWatch Reports (Non-Esubs).

Cover page Case ID(s) with an asterisk ('*') indicate an invalid status and are not captured in the body of the report.

Cover page Case ID(s) with an asterisk ('**') indicate an failed status and are not captured in the body of the report.

Case ID(s) Printed:

22800701	22810953	22813239	22818499
22844011	22844498	22852516	22856052
22871187	22873106	22910526	22949407

Total Cases: 12

Total number of Inactive cases: *0

FDA - Adverse Event Reporting System (FAERS)
FOIA Case Report Information

Case ID: 22800701

Case Information:

Case Type : Expedited (15-Day) **eSub:** Y **HP:** **Country:** NL **Event Date:** **Outcomes:** DE , LT , HO **Application Type:**

FDA Rcvd Date: 21-Aug-2023 **Mfr Rcvd Date:** 11-Aug-2023 **Mfr Control #:** NL-BAUSCH-BL-2023-011732 **Application #:** 21748

Patient Information:

Age: 55 YR **Sex:** Female **Weight:** 125 KG

Suspect Products:

#	Product Name:	Compounded Drug ?	Dose/Frequency	Route	Dosage Text	Start Date	End Date	Indication(s)
1	METFORMIN		500 Mg Milligram(S) /	Oral	165 tablets of metformin 500 mg (82.5 g or 660 mg/kg)			10070592
2	ACETAMINOPHEN		500 Mg Milligram(S) /	Oral	20 tablets of acetaminophen 500 mg (10 g or 80 mg/kg)			10070592
3	SIMVASTATIN		40 Mg Milligram(S) /	Oral	38 tablets of simvastatin 40 mg (1520 mg or 12 mg/kg)			10070592
4	SEMAGLUTIDE		14 Mg Milligram(S) /	Oral	30 tablets of semaglutide 14 mg (420 mg or 3.4 mg/kg)			10070592

#	Product Name:	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler	OTC
1	METFORMIN		Unknown	NA				SANTARUS	
2	ACETAMINOPHEN		Unknown	NA					
3	SIMVASTATIN		Unknown	NA					

Case ID: 22800701

4	SEMAGLUTIDE	Unknown	NA

Device Products:

#	Brand Name / Common Device Name / Product Code	Similar Device?	Malfunction ?	Device Lot#	Device Usage/ Operator of Device	Remedial Action	Device Problem	Manufacturer Name
1	//	No			/			
2	//	No			/			
3	//	No			/			
4	//	No			/			

Event Information:

Preferred Term (MedDRA Version: v.26.1)	ReC
Vasoplegia syndrome	
Suicide attempt	
Toxicity to various agents	
Hyperlactacidaemia	
Lactic acidosis	
Intentional overdose	

Event/Problem Narrative:

This serious spontaneous literature case was received on 31/Jul/2023 from a other health professional via medical literature article and concerned a patient of 55 years age and female gender. Literature reference: Workum JD, Keyany A, Jaspers TCC. Methylene blue as treatment for vasoplegic shock in severe metformin overdose: A case report. Toxicology Reports 2023 Jul 17;11:141-4. The patient's medical history comprised of earlier suicide attempts with chronic depression and type II diabetes mellitus. On an unknown date, the patient started ingested suspect 165 tablets of metformin 500 mg (82.5 g or 660 mg/kg) and co-suspects 20 tablets of acetaminophen 500 mg (10 g, or 80 mg/kg), 38 tablets of simvastatin 40 mg (1520 mg or 12 mg/kg) and 30 tablets of semaglutide 14 mg (420 mg or 3.4 mg/kg) via oral route as a suicide attempt. The batch number and expiry date were not reported. Immediately after ingestion, she alerted the emergency services herself and presented within 1 h of ingestion. In the emergency department (ED) she was alert and cooperative. Her initial vital signs were normal. On day 0 hemoglobin was 8.5 mmol/L (Normal values: 8.5-11), she had a normal respiratory rate and an oxygen saturation of 95 % without supplemental oxygen, blood pressure was 122/51 mmHg with a normal sinus rhythm of 89/min, and she was alert with a glasgow coma scale of 15. Glucose was mildly elevated 18.4 mmol/L (Normal values: 3.9-6.1). Her body temperature was 35.7 degree celsius. Initial blood gas analysis showed a potential of hydrogen (pH) (arterial) was 7.19 (Normal values: 7.35-7.45), pO2 (arterial) was 14.3 kPa (Normal values:11-13), pCO2 (arterial) was 5.6 kPa (Normal values:4.7-6), bicarbonate (arterial) was 16 mmol/L (22-26), base excess (arterial) was -11.8 mmol/L (Normal values: -2 to 2), lactate (arterial) was 9.5 mmol/L (Normal values: 0.5-1.6). Liver panel, coagulation and creatine kinase (CK) levels were normal. Serum creatinine was 90 umol/L (Normal values: 45-90), hematocrit was 0.43 (Normal values: 0.4-0.54), white blood cells (WBC) was 5.3x10e9/L (Normal values: 4-11), platelets were 152x10e9/L (Normal values: 150-450), urea was 3.8 mmol/L (Normal values: 2.5-7.8),

glomerular filtration rate was 62 ml/min/1.73 m2 (Normal values: 90-120), sodium was 139 mmol/L (Normal values: 135-145), potassium was 5.2 mmol/L (Normal values: 3.5-5.1), magnesium was 0.8 mmol/L (Normal values: 0.7-1), phosphate was 1.02 mmol/L (Normal values: 0.8-1.5), ionized calcium was 1.01 mmol/L (Normal values: 1.05-1.3), albumin was 38 g/L (Normal values: 35-50), total bilirubin was 11 micromol/L (Normal values: 3-22), alkaline phosphatase was 107 U/L (Normal values: 40-150), gamma glutamyl transferae (GGT) was 40 U/L (Normal values: 10-60), aspartate aminotransferase (ASAT) was 52 U/L (Normal values: 10-40), alanine aminotransferase (ALAT) was 52 U/L (Normal values: 10-45), lactate dehydrogenase (LDH) was 176 U/L (Normal values: 125-220). Due to the expected severityof the intoxication and the early presentation, she was treated with activated charcoal and immediately admitted to the intensive care unit (ICU) for continuous hemodialysis as the severe lactic acidosis indicated a severe metformin overdose. After admission to the ICU, she deteriorated rapidly. She became tachypneic and was intubated for exhaustion. She developed rapid onset shock, which required continuous fluid resuscitation, noradrenalin (rapidly increasing up to 1.2 microgram/kg/min) and vasopressin (0.03 IE/min). Patient received noradrenalin and vasopressin within 12 hours of presentation. Time to metformin associated lactic acidosis (MALA) was approximately 4 hours after ingestion of metformin/semaglutide. Hydrocortisone was added because of the refractory nature of the shock. Continuous hemodialysis was initiated within 3 h after presentation. Arterial blood gas and lactate levels were monitored every two hours as a marker for resolution of the metformin overdose. On day 1, hemoglobin was 7.2 mmol/L, hematocrit was 0.37, WBC was 36.7x10e9/L, platelets were 244x10e9/L, glucose was 5.6 mmol/L, urea was 0.9 mmol/L, creatinine was 60 umol/L, glomerular filtration rate was greater than 90 ml/min/1.73 m2, sodium was 142 mmol/L, potassium was 3.2 mmol/L, magnesium was 0.67 mmol/L, phosphate was 1.17 mmol/L, ionized calcium was 0.88 mmol/L, total bilirubin was 12 umol/L, alkaline phosphatase was 90 U/L, GGT was 38 U/L, ASAT was 224 U/L, ALAT was 99 U/L, LDH was 428 U/L, pH (arterial) was 7.1, pO2 (arterial) was 12.7 kPa, pCO2 (arterial) was 6.2 kPa, bicarbonate (arterial) was 14.6 mmol/L, base excess (arterial) was -14.6 mmol/L, lactate (arterial) was 25 mmol/L. She became hypoglycemic, most likely due to co-ingestion of metformin and semaglutide, for which a continuous 50 % glucose infusion was started. Four hours post-ingestion, approximately three hours after presentation but prior to the initiation of hemodialysis, both acetaminophen and metformin levels were drawn. Acetaminophen levels 4 h after ingestion were 29 mg/L, so treatment with N-acetylcysteine was withheld. Metformin levels were drawn with the intent of retrospective analysis, as the results took one week to complete. Results revealed a level of 622.9 mg/L. However, as these findings were not available during the initial treatment, they had no bearing on medical decision making. Using bedside ultrasonography in conjunction with invasive hemodynamic monitoring using a pulse index continuous cardiac output device (PiCCO), cardiogenic, obstructive, and hypovolemic shock were excluded. Causes of distributive shock other than vasoplegia, such as septic shock and anaphylaxis, were considered unlikely due to the clinical presentation and otherwise normal appearance. As there was no cardiogenic component to the shock, venoarterial extracorporeal membrane oxygenation (va-ECMO) was not considered to be of added value. On day 2, hemoglobin was 6.8 mmol/L, hematocrit was 0.32, WBC was 24.2x10e9/L, platelets were 146x10 e9/L, glucose was 8 mmol/L, urea was 1.3 mmol/L, creatinine was 51 umol/L, glomerular filtration rate was greater than 90 ml/min/1.73 m2, sodium was 137 mmol/L, potassium was 4.3 mmol/L, magnesium was 0.71 mmol/L, phosphate was 0.5 mmol/L, ionized calcium was 0.89 mmol/L, total bilirubin was 26 umol/L, alkaline phosphatase was 80 U/L, GGT was 34 U/L, ASAT was 805 U/L, ALAT was 148 U/L, LDH was 782 U/L, pH (arterial) was 7.43, pO2 (arterial) was 9.5 kPa, pCO2 (arterial) was 4.9 kPa, bicarbonate (arterial) was 24.3 mmol/L, base excess (arterial) was 0.1 mmol/L, lactate (arterial) was 9.2 mmol/L. On day 3, hemoglobin was 6.6 mmol/L, hematocrit was 0.32, WBC was 18.7x10e9/L, glucose was 10.8 mmol/L, urea was 4.3 mmol/L, creatinine was 122 micromol/L, glomerular filtration rate was greater than 43 ml/min/1.73 m2, sodium was 139 mmol/L, potassium was 4.5 mmol/L, magnesium was 1.16 mmol/L, phosphate was 1.85 mmol/L, ionized calcium was 0.87 mmol/L, albumin was 25 g/L, total bilirubin was 78 umol/L, alkaline phosphatase was 139 U/L, GGT was 71 U/L, ASAT was 3100 U/L, ALAT was 757 U/L, LDH was 2799 U/L, pH (arterial) was 7.36, pO2 (arterial) was 11.3 kPa, pCO2 (arterial) was 4.9 kPa, bicarbonate (arterial) was 20.5 mmol/L, base excess (arterial) was -4.4 mmol/L, lactate (arterial) was 7.9 mmol/L. Therefore, the current condition was considered severe vasoplegic shock due to metformin. As the already high doses of noradrenalin and vasopressin were considered insufficient, it was decided to treat the patient with methylene blue. Subsequently, 250 mg of methylene blue (2 mg/kg) was administered intravenously over 5 min. The noradrenalin dose could be reduced from 1.2 microgram/kg/min to 0.5 microgram/kg/ min within 15 min, indicating rapid shock reversal, which was maintained at 0.5 microgram/kg/min for 6 h without additional intervention. A second bolus of methylene blue 2 mg/kg was then administered in an attempt to further reduce noradrenalin levels. This allowed the noradrenalin dose to be lowered to 0.25 microgram/kg/min. The patient remained stable for the next 24 h. Lactate levels decreased from a maximum of 29 mmol/L to 4.4 mmol/L, indicating metformin clearance and improvement of shock. On day 4 lactate levels began to increase again while still on hemodialysis. She developed severe liver test abnormalities, with alanine aminotransferase (ASAT) of 10518 U/L and aspartate aminotransferase (ALAT) of 4171 U/ L and developed progressive shock again. Time to second onset of shock was approximately 65 hours after commencement of noradrenalin and 58 hours after commencement of vasopressin. Hemoglobin was 6.3 mmol/L, hematocrit was 0.32, WBC was 20x10e9/L, platelets were 85x10e9/L, glucose was 8.1 mmol/L, urea was 4.7 mmol/ L, creatinine was 136 umol/L, glomerular filtration rate was greater than 38 ml/min/1.73 m2, sodium was 136 mmol/L, potassium was 4.5 mmol/L, magnesium

was 1.35 mmol/L, phosphate was 1.51 mmol/L, ionized calcium was 0.96 mmol/L, total bilirubin was 112 umol/L, alkaline phosphatase was 831 U/L, GGT was 111 U/L, LDH was 7896 U/L, pH (arterial) was 7.27, pO2 (arterial) was 9.6 kPa, pCO2 (arterial) was 6 kPa, bicarbonate (arterial) was 20.6 mmol/L, base excess (arterial) was -6 mmol/L, lactate (arterial) was 4.4 mmol/L. A computed tomography (CT) scan of both the thorax and abdomen showed extensive necrosis of the liver. As there were no curative options, treatment was switched to palliative care, and she passed away. The patient's cause of death was ruled to be due to progressive shock secondary to liver necrosis and metformin overdose. Permission for post-mortem examination was not obtained. Action taken with suspect metformin and co-suspects in response to the event multiple drug overdose intentional was not applicable and rest of the events were unknown. The outcome of the event vasoplegic syndrome, multiple drug overdose intentional was fatal, drug toxicity, metformin associated lactic acidosis and hyperlactatemia were not resolved and rest of the events were unknown. Therapy status with the suspect and co-suspects at the time of death were unknown. The reporter assessed the causality of the events drug toxicity and metformin associated lactic acidosis as related and rest of the events as possibly related to the suspect medication. This case is considered serious due to the event vasoplegic syndrome (fatal), multiple drug overdose intentional (fatal, hospitalization), hyperlactatemia (life threatening), suicide attempt, drug toxicity and metformin associated lactic acidosis (life threatening and hospitalization). Follow-up information was received on 02/Aug/2023 from the initial reporter via EMA MLM Service (NL-MLMSERVICE-20230727-4439527-1) via medical literature article. Reference number (NL-MLMSERVICE-20230727-4439527-1) was added. Corresponding fields were updated, and narrative was amended accordingly. Follow-up information received on 11/Aug/2023 via EMA MLM Service (NL-MLMSERVICE-20230727-4439527-1) via author response. Updated cause of death from unknown to progressive shock, liver necrosis and metformin overdose. Updated seriousness of events vasoplegic syndrome, multiple drug overdose intentional from (life threatening to fatal). Added author's comment (Time to MALA was approximately 4 hours after ingestion of metformin/semaglutide. Patient received noradrenalin and vasopressin within 12 hours of presentation. Time to second onset of shock was approximately 65 hours after commencement of noradrenalin and 58 hours after commencement of vasopressin. There was a large resolvement of both shock and lactate levels, before the 2nd onset of shock occurred). EMA MLM Comment: Follow-up information has been requested. This case is cross referred to NL-MLMSERVICE-20230728-4446731-1 due to unspecified reason.

Relevant Medical History:

Disease/Surgical Procedure	Start Date	End Date	Continuing?
Suicide attempt			No
Depression			Yes
Type 2 diabetes mellitus			Yes

Medical History Product(s)	Start Date	End Date	Indications	Events

Relevant Laboratory Data:

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail
10018876	8.5	mmol/L	8.5	11	
10018876	7.2	mmol/L	8.5	11	
10018876	6.8	mmol/L	8.5	11	

Case ID: 22800701

10018876	6.6	mmol/L	8.5	11
10018876	6.3	mmol/L	8.5	11
10018837				
10018837				
10018837				
10018837				
10018837				
10047939	5.3	10*9/L	4	11
10047939	36.7	10*9/L	4	11
10047939	24.2	10*9/L	4	11
10047939	18.7	10*9/L	4	11
10047939	20	10*9/L	4	11
10035525	152	10*9/L	150	450
10035525	244	10*9/L	150	450
10035525	146	10*9/L	150	450
10035525	85	10*9/L	150	450
10005553	18.4	mmol/L	3.9	6.1
10005553	5.6	mmol/L	3.9	6.1
10005553	8	mmol/L	3.9	6.1
10005553	10.8	mmol/L	3.9	6.1
10005553	8.1	mmol/L	3.9	6.1
10005845	3.8	mmol/L	2.5	7.8
10005845	0.9	mmol/L	2.5	7.8
10005845	1.3	mmol/L	2.5	7.8
10005845	4.3	mmol/L	2.5	7.8
10005845	4.7	mmol/L	2.5	7.8
10005480	90	umol/L	45	90
10005480	60	umol/L	45	90
10005480	51	umol/L	45	90

Case ID: 22800701

10005480	122	umol/L	45	90
10005480	136	umol/L	45	90
10018355	62	mL/min/{1.73_m2}	90	120
10018355				
10018355				
10018355	43	mL/min/{1.73_m2}	90	120
10018355	38	mL/min/{1.73_m2}	90	120
10005799	139	mmol/L	135	145
10005799	142	mmol/L	135	145
10005799	137	mmol/L	135	145
10005799	139	mmol/L	135	145
10005799	136	mmol/L	135	145
10005721	5.2	mmol/L	3.5	5.1
10005721	3.2	mmol/L	3.5	5.1
10005721	4.3	mmol/L	3.5	5.1
10005721	4.5	mmol/L	3.5	5.1
10005721	4.5	mmol/L	3.5	5.1
10005651	0.8	mmol/L	0.7	1
10005651	0.67	mmol/L	0.7	1
10005651	0.71	mmol/L	0.7	1
10005651	1.16	mmol/L	0.7	1
10005651	1.35	mmol/L	0.7	1
10005717	1.02	mmol/L	0.8	1.5
10005717	1.17	mmol/L	0.8	1.5
10005717	0.5	mmol/L	0.8	1.5
10005717	1.85	mmol/L	0.8	1.5
10005717	1.51	mmol/L	0.8	1.5
10060900	1.01	mmol/L	1.05	1.3
10060900	0.88	mmol/L	1.05	1.3

Case ID: 22800701

10060900	0.89	mmol/L	1.05	1.3
10060900	0.87	mmol/L	1.05	1.3
10060900	0.96	mmol/L	1.05	1.3
10005285	38	mmol/L	35	50
10005285	25	mmol/L	35	50
10005362	11	umol/L	3	22
10005362	12	umol/L	3	22
10005362	26	umol/L	3	22
10005362	78	umol/L	3	22
10005362	112	umol/L	3	22
10005298	107	U/L	40	150
10005298	90	U/L	40	150
10005298	80	U/L	40	150
10005298	139	U/L	40	150
10005298	831	U/L	40	150
10017687	40	U/L	10	60
10017687	38	U/L	10	60
10017687	34	U/L	10	60
10017687	71	U/L	10	60
10017687	111	U/L	10	60
10003476	52	U/L	10	40
10003476	224	U/L	10	40
10003476	805	U/L	10	40
10003476	3100	U/L	10	40
10003476	10518	U/L	10	40
10001546	52	U/L	10	45
10001546	99	U/L	10	45
10001546	148	U/L	10	45
10001546	757	U/L	10	45

10001546	4171	U/L	10	45
10005626	176	U/L	125	220
10005626	428	U/L	125	220
10005626	782	U/L	125	220
10005626	2799	U/L	125	220
10005626	7896	U/L	125	220
10061346				
10061346				
10061346				
10061346				
10061346				
10035766	14.3	kPa	11	13
10035766	12.7	kPa	11	13
10035766	9.5	kPa	11	13
10035766	11.3	kPa	11	13
10035766	9.6	kPa	11	13
10034180	5.6	kPa	4.7	6.0
10034180	6.2	kPa	4.7	6
10034180	4.9	kPa	4.7	6
10034180	4.9	kPa	4.7	6
10034180	6	kPa	4.7	6.0
10005357	16	mmol/L	22	26
10005357	14.6	mmol/L	22	26
10005357	24.3	mmol/L	22	26
10005357	20.5	mmol/L	22	26
10005357	20.6	mmol/L	22	26
10059961				
10059961				
10059961	0.1	mmol/L		

FDA - Adverse Event Reporting System (FAERS)
FOIA Case Report Information

Case ID: 22800701

10059961				
10059961				
10005632	9.5	mmol/L	0.5	1.6
10005632	25	mmol/L	0.5	1.6
10005632	9.2	mmol/L	0.5	1.6
10005632	7.9	mmol/L	0.5	1.6
10005632	4.4	mmol/L	0.5	1.6
10072952				
10038709				
10033316	95	%		
10076581				
10048815	89	/min		
10069708				
10005906	35.7	Cel		
10060105				
10063556				
10005467				
10061823	29	mg/L		
10061823	622.9	mg/L		
10045434				
10005632	29	mmol/L		
10005632				
10010234				
10053876				

Concomitant Products:

#	Product Name:	Dose/Frequency	Route	Dosage Text	Start Date	End Date	Indication(s)	Interval 1st Dose to Event

FDA - Adverse Event Reporting System (FAERS)
FOIA Case Report Information

Case ID: 22800701

Reporter Source:

Study report?:	No	**Sender organization:**	BAUSCH AND LOMB	**503B Compounding Outsourcing Facility?:**	

Literature Text: Workum J, Keyany A, Jaspers T. Methylene blue as treatment for vasoplegic shock in severe metformin overdose: A case report. Toxicology Reports. 2023 JUL 17;11:141-144. doi:10.1016/j.toxrep.2023.07.005

FDA - Adverse Event Reporting System (FAERS)
FOIA Case Report Information

Case ID: 22810953

Case Information:

Case Type : Expedited (15-Day) **eSub:** Y **HP:** N **Country:** NL **Event Date:** **Outcomes:** DE , HO , OT **Application Type:**

FDA Rcvd Date: 01-Sep-2023 **Mfr Rcvd Date:** 24-Aug-2023 **Mfr Control #:** NL-EMD Serono-2023465576 **Application #:** 020357

Patient Information:

Age: 55 YR **Sex:** Female **Weight:** 125 KG

Suspect Products:

#	Product Name:	Compounded Drug ?	Dose/Frequency	Route	Dosage Text	Start Date	End Date	Indication(s)
1	METFORMIN		/		165 tablets of 500 mg (82.5 g, or 660 mg/kg).			10070592
2	ACETAMINOPHEN		/		20 tablets of acetaminophen 500 mg (10 g, or 80 mg/kg)			10070592
3	RYBELSUS		/		30 tablets of semaglutide 14 mg (420 mg or 3.4 mg/ kg)			10070592
4	SIMVASTATIN		/		38 tablets 40 mg (1520 mg, or 12 mg/kg)			10070592

#	Product Name:	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler	OTC
1	METFORMIN		Not Applicable	NA	Unknown				
2	ACETAMINOPHEN		Not Applicable	NA	Unknown				
3	RYBELSUS		Not Applicable	NA	Unknown				
4	SIMVASTATIN		Not Applicable	NA	Unknown				

FDA - Adverse Event Reporting System (FAERS)
FOIA Case Report Information

Case ID: 22810953

Device Products:

#	Brand Name / Common Device Name / Product Code	Similar Device?	Malfunction ?	Device Lot#	Device Usage/ Operator of Device	Remedial Action	Device Problem	Manufacturer Name
1	//	No			/			
2	//	No			/			
3	//	No			/			
4	//	No			/			

Event Information:

Preferred Term (MedDRA Version: v.26.1)	ReC
Distributive shock	
Hypoglycaemia	
Hepatic necrosis	
Completed suicide	
Lactic acidosis	
Toxicity to various agents	
Intentional overdose	

Event/Problem Narrative:

This case was initially retrieved via global literature search process in Netherlands process at Merck Healthcare KGaA (PI161226) on 01-Aug-2023. * A 55 year-old female patient was Hypoglycemic, had Necrosis of the liver, Suicide/suicide attempt, Severe vasoplegic shock, Lactic acidosis, Multiple drug toxicity/ingestion of 165 tablets of metformin 500 mg (82.5 g, or 660 mg/kg), 20 tablets of acetaminophen 500 mg (10 g, or 80 mg/kg), 38 tablets of simvastatin 40 mg (1520 mg, or 12 mg/kg) and 30 tablets of semaglutide, Overdose/ingestion of 165 tablets of metformin 500 mg (82.5 g, or 660 mg/kg), 20 tablets of acetaminophen 500 mg (10 g, or 80 mg/kg), 38 tablets of simvastatin 40 mg (1520 mg and or 12 mg/kg) and 30 tablets of semaglutide 14 mg (420 mg or 3.4 mg/ kg) while being treated with Metformin. Seriousness criteria of Multiple drug toxicity/ingestion of 165 tablets of metformin 500 mg (82.5 g, or 660 mg/kg), 20 tablets of acetaminophen 500 mg (10 g, or 80 mg/kg), 38 tablets of simvastatin 40 mg (1520 mg, or 12 mg/kg) and 30 tablets of semaglutide, Overdose/ingestion of 165 tablets of metformin 500 mg (82.5 g, or 660 mg/kg), 20 tablets of acetaminophen 500 mg (10 g, or 80 mg/kg), 38 tablets of simvastatin 40 mg (1520 mg and or 12 mg/kg) and 30 tablets of semaglutide 14 mg (420 mg or 3.4 mg/ kg): Death and Hospitalization. Seriousness criteria of Lactic acidosis, Necrosis of the liver, Suicide/suicide attempt and Severe vasoplegic shock: Death, Hospitalization and Other medically important condition. Seriousness criteria of Hypoglycemic: Other medically important condition. Medical history: Suicide attempt, Chronic depression and Type 2 diabetes mellitus. Concomitant medication was not reported. The patient received Metformin (metformin hydrochloride) (dose and start date was not reported) 500 milligrams tablet for an unknown indication. Additionally, the patient received the following non-Merck suspected drugs: Acetaminophen (paracetamol) (dose and start date was not reported) 500 milligrams tablet, Rybelsus (semaglutide) 14 milligrams tablet (dose and start date was not reported) and Simvastatin (dose and start date was not reported) 40 milligrams tablet all for an

unknown indication. The patient had the following serious events: Hypoglycemic, Necrosis of the liver, Suicide/suicide attempt, Severe vasoplegic shock, Lactic acidosis, Multiple drug toxicity/ingestion of 165 tablets of Metformin 500 mg (82.5 g, or 660 mg/kg), 20 tablets of acetaminophen 500 mg (10 g, or 80 mg/kg), 38 tablets of simvastatin 40 mg (1520 mg, or 12 mg/kg) and 30 tablets of semaglutide, Overdose/ingestion of 165 tablets of metformin 500 mg (82.5 g, or 660 mg/kg), 20 tablets of acetaminophen 500 mg (10 g, or 80 mg/kg), 38 tablets of simvastatin 40 mg (1520 mg and or 12 mg/kg) and 30 tablets of semaglutide 14 mg (420 mg or 3.4 mg/ kg) (onset date not reported). The patient presented to the emergency department (ED) after ingestion of 165 tablets of Metformin at a dose of 500 mg (82.5 g, or 660 mg/kg), 20 tablets of Acetaminophen at a dose of 500 mg (10 g, or 80 mg/kg), 38 tablets of Simvastatin at a dose of 40 mg (1520 mg, or 12 mg/kg) and 30 tablets of Semaglutide 14 mg (420 mg or 3.4 mg/ kg) as a suicide attempt. Immediately after ingestion, she alerted the emergency services herself and presented within 1 hour of ingestion. In the ED she was alert and cooperative. Her medical history comprised of earlier suicide attempts with chronic depression and type 2 diabetes. Her initial vital signs were normal, she had a normal respiratory rate and an oxygen saturation of 95 percent without supplemental oxygen, blood pressure was 122/51 mmHg with a normal sinus rhythm of 89/min, and she was alert with a Glasgow Coma Scale of 15. Glucose was mildly elevated (18.4 mmol/L). Her body temperature was 35.7 degrees centigrade. Initial blood gas analysis showed a pH of 7.19, pCO2 of 5.6 kPa (Pascal or kilopascal), bicarbonate of 16 mmol/L, base excess of -11.8 (mmol/L) and lactate levels of 9.5 mmol/L. Liver panel, coagulation, and creatine kinase (CK) levels were normal. Serum creatinine was 90 micromole per litre. Due to the expected severity of the intoxication and the early presentation, she was treated with activated charcoal and immediately admitted to the intensive care unit (ICU) for continuous hemodialysis as the severe lactic acidosis indicated a severe metformin overdose. After admission to the ICU, she deteriorated rapidly. She became tachypneic and was intubated for exhaustion. She developed rapid onset shock, which required continuous fluid resuscitation, Noradrenalin (rapidly increasing up to 1.2 microgram/kg/min) and Vasopressin (0.03 IE/min). Hydrocortisone was added because of the refractory nature of the shock. Continuous hemodialysis was initiated within 3 hours after presentation. Arterial blood gas and lactate levels were monitored every two hours as a marker for resolution of the Metformin overdose. She became hypoglycaemic, most likely due to co-ingestion of Metformin and Semaglutide, for which a continuous 50 percent glucose infusion was started. Four hours post-ingestion, approximately three hours after presentation but prior to the initiation of hemodialysis, both Acetaminophen and Metformin levels were drawn. Acetaminophen levels 4 hour after ingestion were 29 mg/L, so treatment with N-acetylcysteine was withheld. Metformin levels were drawn with the intent of retrospective analysis, as the results took one week to complete. Results revealed a level of 622.9 mg/L. However, as these findings were not available during the initial treatment, they had no bearing on medical decision making. Used ultrasonography in conjunction with invasive hemodynamic monitoring using a pulse index continuous cardiac output device (PiCCO), cardiogenic, obstructive, and hypovolemic shock were excluded. Causes of distributive shock other than vasoplegia, such as septic shock and anaphylaxis, were considered unlikely due to the clinical presentation and otherwise normal appearance. As there was no cardiogenic component to the shock, venoarterial extracorporeal membrane oxygenation (va-ECMO) was not considered to be of added value. Therefore, the current condition was considered severe vasoplegic shock due to Metformin. As the already high doses of Noradrenalin and Vasopressin were considered insufficient, it was decided to treat the patient with Methylene blue. Subsequently, 250 mg of Methylene blue (2 mg/kg) was administered intravenously over 5 minutes. The Noradrenalin dose could be reduced from 1.2 micrograms/kg/minute to 0.5 micrograms/kg/min within 15 minutes, indicating rapid shock reversal, which was maintained at 0.5 micrograms/kg/min for 6 hours without additional intervention. A second bolus of methylene blue 2 mg/kg was then administered to further reduce Noradrenalin levels. This allowed the Noradrenalin dose to be lowered to 0.25 micrograms/kg/min. The patient remained stable for the next 24 hours. Lactate levels decreased from a maximum of 29 mmol/L to 4.4 mmol/L, indicating Metformin clearance and improvement of shock. However, the next day (date not reported), lactate levels began to increase again while still on hemodialysis. She developed severe liver test abnormalities, with alanine aminotransferase (ASAT) of 10518 U/L and aspartate aminotransferase (ALAT) of 4171 U/ L and developed progressive shock again. A computed tomography (CT) scan of both the thorax and abdomen showed extensive necrosis of the liver. As there were no curative options, treatment was switched to palliative care, and she passed away. Permission for post-mortem examination was not obtained. However, her next of kin signed informed consent for publication. Autopsy was not performed. Kindly refer the lab section for relevant laboratory data. Action taken with Metformin, Acetaminophen, Rybelsus and Simvastatin: Not applicable. Outcome of the events: Hypoglycemic: Unknown. Necrosis of the liver, Suicide/suicide attempt, Severe vasoplegic shock, Lactic acidosis, Multiple drug toxicity/ingestion of 165 tablets of metformin 500 mg (82.5 g, or 660 mg/kg), 20 tablets of acetaminophen 500 mg (10 g, or 80 mg/kg), 38 tablets of simvastatin 40 mg (1520 mg, or 12 mg/kg) and 30 tablets of semaglutide, Overdose/ingestion of 165 tablets of metformin 500 mg (82.5 g, or 660 mg/kg), 20 tablets of acetaminophen 500 mg (10 g, or 80 mg/kg), 38 tablets of simvastatin 40 mg (1520 mg and or 12 mg/kg) and 30 tablets of semaglutide 14 mg (420 mg or 3.4 mg/ kg): Fatal (date not reported). Reporter's Causality assessment: Relationship with Metformin for the events Hypoglycemic, Severe vasoplegic shock, Multiple drug toxicity/ingestion of 165 tablets of metformin 500 mg (82.5 g, or 660 mg/kg), 20 tablets of acetaminophen 500 mg (10 g, or 80 mg/kg), 38 tablets of simvastatin 40 mg (1520 mg, or 12 mg/kg) and 30 tablets of semaglutide and Overdose/ingestion of 165 tablets of

metformin 500 mg (82.5 g, or 660 mg/kg), 20 tablets of acetaminophen 500 mg (10 g, or 80 mg/kg), 38 tablets of simvastatin 40 mg (1520 mg, or 12 mg/kg) and 30 tablets of semaglutide 14 mg (420 mg or 3.4 mg/ kg): Related. Relationship with Metformin for the events Necrosis of the liver, Suicide/suicide attempt and Lactic acidosis: Not Reported. Relationship with Acetaminophen and Simvastatin for the events Hypoglycemic, Necrosis of the liver, Suicide/suicide attempt, Severe vasoplegic shock and Lactic acidosis: Not Reported. Relationship with Acetaminophen and Simvastatin for the events Multiple drug toxicity/ingestion of 165 tablets of metformin 500 mg (82.5 g, or 660 mg/kg), 20 tablets of acetaminophen 500 mg (10 g, or 80 mg/kg), 38 tablets of simvastatin 40 mg (1520 mg, or 12 mg/kg) and 30 tablets of semaglutide and Overdose/ingestion of 165 tablets of metformin 500 mg (82.5 g, or 660 mg/kg), 20 tablets of acetaminophen 500 mg (10 g, or 80 mg/kg), 38 tablets of simvastatin 40 mg (1520 mg, or 12 mg/kg) and 30 tablets of semaglutide 14 mg (420 mg or 3.4 mg/ kg): Related. Relationship with Rybelsus for the events Hypoglycemic, Multiple drug toxicity/ingestion of 165 tablets of metformin 500 mg (82.5 g, or 660 mg/kg), 20 tablets of acetaminophen 500 mg (10 g, or 80 mg/kg), 38 tablets of simvastatin 40 mg (1520 mg, or 12 mg/kg) and 30 tablets of semaglutide and Overdose/ingestion of 165 tablets of metformin 500 mg (82.5 g, or 660 mg/kg), 20 tablets of acetaminophen 500 mg (10 g, or 80 mg/kg), 38 tablets of simvastatin 40 mg (1520 mg, or 12 mg/kg) and 30 tablets of semaglutide 14 mg (420 mg or 3.4 mg/ kg): Related. Relationship with Rybelsus for the events Necrosis of the liver, Suicide/suicide attempt, Severe vasoplegic shock and Lactic acidosis: Not Reported. Author’s comment: The case of severe vasoplegic shock due to Metformin toxicity, which was treated with methylene blue in addition to conventional treatment, resulting in rapid shock resolution. Our patient presented with a metabolic acidosis with hyperlactatemia and a severe vasoplegic shock after a massive metformin overdose. Although scarcely described, methylene blue proved to be a highly effective therapy of vasoplegic shock, with an immediate and persistent effect, allowing a rapid reduction of noradrenalin. As methylene blue has only a few side effects, it is important for clinicians to consider methylene blue when treating patients with refractory shock due to severe metformin overdose. Follow-up version was created upon receipt of full text article from the physician via Regulatory authority EU-A-EMEA European Medical Agency (PM)-EPM (NLEMADD20230818664499307 5413) and at Merck Healthcare KGaA on 24-Aug-2023. It included the following new information: Event verbatim updated to Severe vasoplegic shock (previously Refractory Vasoplegic shock) and LLT updated updated to Vasodilatory shock (previously Refractory shock) for the same. Outcome updated to fatal (previously recovering). Severity added to the event. Seriousness death added to Severe vasoplegic shock. Event verbatim updated to Overdose/Ingestion of 165 tablets of metformin 500 mg (82.5 g, or 660 mg/kg), 20 tablets of acetaminophen 500 mg (10 g, or 80 mg/kg), 38 tablets of simvastatin 40 mg (1520 mg, or 12 mg/kg) and 30 tablets of semaglutide 14 mg (420 mg or 3.4 mg/ kg) (previously Intentionally ingested 82.5 grams of metformin), seriousness criteria death added for the same. Outcome updated to fatal (previously unknown). New serious events: Hypoglycemic, Lactic acidosis, necrosis of liver, suicide/Suicide attempt and Multiple drug toxicity/ Ingestion of 165 tablets of metformin 500 mg (82.5 g, or 660 mg/kg), 20 tablets of acetaminophen 500 mg (10 g, or 80 mg/kg), 38 tablets of simvastatin 40 mg (1520 mg, or 12 mg/kg) and 30 tablets of semaglutide added. Events Metabolic acidosis and hyperlactatemia deleted. Suspect drug Metformin details: Form strength added. Co-suspect drugs: Acetaminophen, Rybelsus and Rybelsus added. Lab data (1-139) added. Medical history added. Patient details: Date of death, autopsy, reported cause of death, weight and BMI added. Report duplicates added. **Company remarks continued** Comments: The level of detail in the report does not permit a conclusive assessment of the events Hepatic necrosis and Completed suicide. The company will continue to monitor all similar reports received and will re-evaluate the available evidence as further relevant information is received. Metformin is not an insulin secretagogue, and is unlikely to have any contributory role in causing hypoglycaemia. Use of semaglutide is a risk factor for hypoglycaemia. Lactic acidosis might have developed due to accumulation of metformin after intentional overdose of metformin. Intentional overdose of metformin can also explain Toxicity to various agents. Hence, considering the known product safety profile, a causal role of metformin cannot be denied in the occurrence of Lactic acidosis. Lactic acidosis leading to Distributive shock is assessed as related to metformin. Causality of Intentional overdose is not applicable considering the nature of the event. TEST RESULT ILTRATION RATE (GFR) (CKD-EPI),On y 2, Less than 90 mL/min/1.73 m2 <Record Number51>SODIUM, <Record Number52>SODIUM, <Record Number53>SODIUM, <Record Number54>SODIUM, <Record Number55>SODIUM, <Record Number56>POTASSIUM, <Record Number57>POTASSIUM, <Record Number58>POTASSIUM, <Record Number59>POTASSIUM, <Record Number60>POTASSIUM, <Record Number61>MAGNESIUM, <Record Number62>MAGNESIUM, <Record Number63>MAGNESIUM, <Record Number64>MAGNESIUM, <Record Number65>MAGNESIUM, <Record Number66>PHOSPHATE, <Record Number67>PHOSPHATE, <Record Number68>PHOSPHATE, <Record Number69>PHOSPHATE, <Record Number70>PHOSPHATE, <Record Number71>IONIZED CALCIUM, <Record Number72>IONIZED CALCIUM, <Record Number73>IONIZED CALCIUM, <Record Number74>IONIZED CALCIUM, <Record Number75>IONIZED CALCIUM, <Record Number76>ALBUMIN, <Record Number77>ALBUMIN, <Record Number78>TOTAL BILIRUBIN, <Record Number79>TOTAL BILIRUBIN, <Record Number80>TOTAL BILIRUBIN, <Record Number81>TOTAL BILIRUBIN, <Record Number82>TOTAL BILIRUBIN, <Record Number83>ALKALINE PHOSPHATASE, <Record Number84>ALKALINE PHOSPHATASE, <Record Number85>ALKALINE PHOSPHATASE, <Record Number86>ALKALINE PHOSPHATASE, <Record Number87>ALKALINE PHOSPHATASE, <Record Number88>GAMMA-GLUTAMYL

TRANSFERASE (GGT), <Record Number89>GAMMA-GLUTAMYL TRANSFERASE (GGT), <Record Number90>GAMMA-GLUTAMYL TRANSFERASE (GGT), <Record Number91>GAMMA-GLUTAMYL TRANSFERASE (GGT), <Record Number92>GAMMA-GLUTAMYL TRANSFERASE (GGT), <Record Number93>ASPARTATE AMINOTRANSFERASE (ASAT), <Record Number94>ASPARTATE AMINOTRANSFERASE (ASAT), <Record Number95>ASPARTATE AMINOTRANSFERASE (ASAT), <Record Number96>ASPARTATE AMINOTRANSFERASE (ASAT), <Record Number97>ASPARTATE AMINOTRANSFERASE (ASAT), <Record Number98>ALANINE AMINOTRANSFERASE (ALAT), <Record Number99>ALANINE AMINOTRANSFERASE (ALAT), <Record Number100>ALANINE AMINOTRANSFERASE (ALAT), <Record Number101>ALANINE AMINOTRANSFERASE (ALAT), <Record Number102>ALANINE AMINOTRANSFERASE (ALAT), <Record Number103>LACTATE DEHYDROGENASE (LDH), <Record Number104>LACTATE DEHYDROGENASE (LDH), <Record Number105>LACTATE DEHYDROGENASE (LDH), <Record Number106>LACTATE DEHYDROGENASE (LDH), <Record Number107>LACTATE DEHYDROGENASE (LDH), <Record Number108>PH (ARTERIAL), <Record Number109>PH (ARTERIAL), <Record Number110>PH (ARTERIAL), <Record Number111>PH (ARTERIAL), <Record Number112>PH (ARTERIAL), <Record Number113>PO2 (ARTERIAL), <Record Number114>PO2 (ARTERIAL), <Record Number115>PO2 (ARTERIAL), <Record Number116>PO2 (ARTERIAL), <Record Number117>PO2 (ARTERIAL), <Record Number118>PCO2 (ARTERIAL), <Record Number119>PCO2 (ARTERIAL), <Record Number120>PCO2 (ARTERIAL), <Record Number121>PCO2 (ARTERIAL), <Record Number122>PCO2 (ARTERIAL), <Record Number123>BICARBONATE (ARTERIAL), <Record Number124>BICARBONATE (ARTERIAL), <Record Number125>BICARBONATE (ARTERIAL), <Record Number126>BICARBONATE (ARTERIAL), <Record Number127>BICARBONATE (ARTERIAL), <Record Number128>BASE EXCESS (ARTERIAL),On day 0, it was -11.8 millimole per litre <Record Number129>BASE EXCESS (ARTERIAL),On day 1, it was -14.6 millimole per litre <Record Number130>BASE EXCESS (ARTERIAL), <Record Number131>BASE EXCESS (ARTERIAL),On day 3, it was -4.4 millimole per litre <Record Number132>BASE EXCESS (ARTERIAL),On day 4, it was -6 millimole per litre <Record Number133>LACTATE (ARTERIAL), <Record Number134>LACTATE (ARTERIAL), <Record Number135>LACTATE (ARTERIAL), <Record Number136>LACTATE (ARTERIAL), <Record Number137>LACTATE (ARTERIAL), <Record Number138>HEMOGLOBIN, <Record Number139>CREATINE KINASE,Normal

Relevant Medical History:

Disease/Surgical Procedure	Start Date	End Date	Continuing?
Suicide attempt			
Chronic depression			
Type 2 diabetes mellitus			

Medical History Product(s)	Start Date	End Date	Indications	Events

Relevant Laboratory Data:

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail
10062026					
10033316	95	02			
10005727					

Case ID: 22810953

10048815	89	{beats}/min		
10058476				
10018414	18.4	mmol/L		
10005906	35.7	Cel		
10061823	29	mg/L		
10061823	622.9	mg/L		
10077423				
10057825				
10019481	8.5	mmol/L	8.5	11
10019481	7.2	mmol/L	8.5	11
10019481	6.8	mmol/L	8.5	11
10019481	6.6	mmol/L	8.5	11
10019481	6.3	mmol/L	8.5	11
10019422			0.40	0.54
10019422			0.40	0.54
10019422			0.40	0.54
10019422			0.40	0.54
10019422			0.40	0.54
10047955	5.3	10e9/L	4	11
10047955	36.7	10e9/L	4	11
10047955	24.2	10e9/L	4	11
10047955	18.7	10e9/L	4	11
10047955	20.0	10e9/L	4	11
10035525	152	10*9/L	150	450
10035525	244	10*9/L	150	450
10035525	146	10*9/L	150	450
10035525	85	10*9/L	150	450
10018414	18.4	mmol/L	3.9	6.1
10018414	5.6	mmol/L	3.9	6.1

Case ID: 22810953

10018414	8.0	mmol/L	3.9	6.1
10018414	10.8	mmol/L	3.9	6.1
10018414	8.1	mmol/L	3.9	6.1
10046346	3.8	mmol/L	2.5	7.8
10046346	0.9	mmol/L	2.5	7.8
10046346	1.3	mmol/L	2.5	7.8
10046346	4.3	mmol/L	2.5	7.8
10046346	4.7	mmol/L	2.5	7.8
10011358	90	umol/L	45	90
10011358	60	umol/L	45	90
10011358	51	umol/L	45	90
10011358	122	umol/L	45	90
10011358	136	umol/L	45	90
10018355	62	mL/min/{1.73_m2}	90	120
10018355	43	mL/min/{1.73_m2}	90	120
10018355	38	mL/min/{1.73_m2}	90	120
10018355			90	120
10018355			90	120
10041263	139	mmol/L	135	145
10041263	142	mmol/L	135	145
10041263	137	mmol/L	135	145
10041263	139	mmol/L	135	145
10041263	136	mmol/L	135	136
10036439	5.2	mmol/L	3.5	5.1
10036439	3.2	mmol/L	3.5	5.1
10036439	4.3	mmol/L	3.5	5.1
10036439	4.5	mmol/L	3.5	5.1
10036439	4.5	mmol/L	3.5	5.1
10025430	0.8	mmol/L	0.7	1.0

Case ID: 22810953

10025430	0.67	mmol/L	0.7	1.0
10025430	0.71	mmol/L	0.7	1.0
10025430	1.16	mmol/L	0.7	1.0
10025430	1.35	mmol/L	0.7	1.0
10034928	1.02	mmol/L	0.8	1.5
10034928	1.17	mmol/L	0.8	1.5
10034928	0.50	mmol/L	0.8	1.5
10034928	1.85	mmol/L	0.8	1.5
10034928	1.51	mmol/L	0.8	1.5
10022929	1.01	nmol/L	1.05	1.3
10022929	0.88	nmol/L	1.05	1.3
10022929	0.89	nmol/L	1.05	1.3
10022929	0.87	nmol/L	1.05	1.3
10022929	0.96	nmol/L	1.05	1.3
10001558	38	g/L	35	50
10001558	25	g/L	35	50
10004696	11	umol/L	3	22
10004696	12	umol/L	3	22
10004696	26	umol/L	3	22
10004696	78	umol/L	3	22
10004696	112	umol/L	3	22
10001674	107	U/L	40	150
10001674	90	U/L	40	150
10001674	80	U/L	40	150
10001674	139	U/L	40	150
10001674	831	U/L	40	150
10017687	40	U/L	10	60
10017687	38	U/L	10	60
10017687	34	U/L	10	60

Case ID: 22810953

10017687	71	U/L	10	60
10017687	111	U/L	10	60
10003476	52	U/L	10	40
10003476	224	U/L	10	40
10003476	805	U/L	10	40
10003476	3100	U/L	10	40
10003476	10518	U/L	10	40
10001546	52	U/L	10	45
10001546	99	U/L	10	45
10001546	148	U/L	10	45
10001546	757	U/L	10	45
10001546	4171	U/L	10	45
10023653	176	U/L	125	220
10023653	428	U/L	125	220
10023653	782	U/L	125	220
10023653	2799	U/L	125	220
10023653	7896	U/L	125	220
10034772	7.19	pH	7.35	7.45
10034772	7.10	pH	7.35	7.45
10034772	7.43	pH	7.35	7.45
10034772	7.36	pH	7.35	7.45
10034772	7.27	pH	7.35	7.45
10035766	14.3	Pascal or kilopascal	11	13
10035766	12.7	Pascal or kilopascal	11	13
10035766	9.5	Pascal or kilopascal	11	13
10035766	11.3	Pascal or kilopascal	11	13
10035766	9.6	Pascal or kilopascal	11	13
10034180	5.6	Pascal or kilopascal	4.7	6.0
10034180	6.2	Pascal or kilopascal	4.7	6.0

FDA - Adverse Event Reporting System (FAERS)
FOIA Case Report Information

Case ID: 22810953

10034180	4.9	Pascal or kilopascal	4.7	6.0
10034180	4.9	Pascal or kilopascal	4.7	6.0
10034180	6.0	Pascal or kilopascal	4.7	6.0
10004544	16	mmol/L	22	26
10004544	14.6	mmol/L	22	26
10004544	24.3	mmol/L	22	26
10004544	20.5	mmol/L	22	26
10004544	20.6	mmol/L	22	26
10059961			-2	+2
10059961			-2	+2
10059961	0.1	mmol/L	-2	+2
10059961			-2	+2
10059961			-2	+2
10023649	9.5	mmol/L	0.5	1.6
10023649	25	mmol/L	0.5	1.6
10023649	9.2	mmol/L	0.5	1.6
10023649	7.9	mmol/L	0.5	1.6
10023649	4.4	mmol/L	0.5	1.6
10019481	8.5	mmol/L	8.5	11
10011334				

Concomitant Products:

#	Product Name:	Dose/Frequency	Route	Dosage Text	Start Date	End Date	Indication(s)	Interval 1st Dose to Event

Reporter Source:

Study report?: No **Sender organization:** EMD SERONO INC **503B Compounding Outsourcing Facility?:**

FDA - Adverse Event Reporting System (FAERS)
FOIA Case Report Information

Case ID: 22810953

Literature Text: Workum JD, Keyany A, Jaspers TC. Methylene blue as treatment for vasoplegic shock in severe metformin overdose: A case report.. Toxicology reports. 2023 Jul 17;11: 141-144. doi:10.1016/j.toxrep.2023.07.005.

Toxicology Reports 11 (2023) 141–144

Contents lists available at ScienceDirect

Toxicology Reports

journal homepage: www.elsevier.com/locate/toxrep

Methylene blue as treatment for vasoplegic shock in severe metformin overdose: A case report

Jessica D. Workum [a,b,*], Ala Keyany [c], Tessa C.C. Jaspers [c,d]

[a] Department of Intensive Care, Elisabeth-TweeSteden Hospital, Tilburg, the Netherlands
[b] Department of Electrical Engineering, Eindhoven University of Technology, the Netherlands
[c] Department of Pharmacy, Elisabeth-TweeSteden Hospital, Tilburg, the Netherlands
[d] Department of Clinical Pharmacy and Pharmacology, University Medical Center Groningen, the Netherlands

ARTICLE INFO

Handling Editor: Dr. L.H. Lash

Keywords:
Metformin toxicity
Methylene blue
Vasoplegic shock
Critically ill

ABSTRACT

Introduction: Severe metformin overdose can result in life-threatening conditions such as metabolic acidosis with hyperlactatemia and vasoplegic shock. Current treatment guidelines recommend hemodialysis and supportive care. However, this case report presents the use of methylene blue as an additional treatment for severe metformin overdose-induced vasoplegic shock, which is not commonly described in the literature or guidelines.
Case report: A 55-year-old woman presented to the emergency department after ingesting 82.5 g of metformin, resulting in severe metabolic acidosis with hyperlactatemia and refractory vasoplegic shock. Despite continuous hemodialysis and high levels of noradrenalin and vasopressin, the shock persisted. Methylene blue was administered, leading to an immediate and persistent reduction in the noradrenalin dose and rapid shock resolution.
Discussion: This case illustrates the potential use of methylene blue in the treatment of severe metformin overdose. The mechanism for metformin-induced vasoplegia is likely mediated by nitric oxide (NO). Methylene blue has been used to treat NO-mediated vasoplegia in other conditions, such as sepsis and poisoning with beta-blockers and calcium channel blockers, but it is rarely described in metformin toxicity. Methylene blue has a rapid onset of action, with only a few mild side effects. This case report emphasizes the need for clinicians to consider methylene blue as a potential treatment option in cases of refractory vasoplegic shock due to severe metformin overdose.

1. Introduction

Severe metformin overdose is a life-threatening condition that can lead to metabolic acidosis with hyperlactatemia and cardiovascular collapse, including vasoplegic shock. Treatment consists of hemodialysis and supportive care. We present a case of severe vasoplegic shock due to severe metformin toxicity, treated with methylene blue in addition to conventional treatment, which resulted in rapid shock resolution. The use of methylene blue in the treatment of severe metformin overdose has only been described in a few cases and is not described in current guidelines as a treatment option. This case illustrates the potential use of methylene blue in severe metformin overdose.

2. Case description

A 55-year-old female (125 kg, body mass index 46 kg/m^2) presented to the emergency department (ED) after ingestion of 165 tablets of metformin 500 mg (82.5 g, or 660 mg/kg), 20 tablets of acetaminophen 500 mg (10 g, or 80 mg/kg), 38 tablets of simvastatin 40 mg (1520 mg, or 12 mg/kg) and 30 tablets of semaglutide 14 mg (420 mg or 3.4 mg/kg) as a suicide attempt. Immediately after ingestion, she alerted the emergency services herself and presented within 1 h of ingestion. In the ED she was alert and cooperative. Her medical history comprised of earlier suicide attempts with chronic depression and type II diabetes. Her initial vital signs were normal: she had a normal respiratory rate and an oxygen saturation of 95 % without supplemental oxygen, blood pressure was 122/51 mmHg with a normal sinus rhythm of 89/min, and she was alert with a Glasgow Coma Scale of 15. Glucose was mildly

* Correspondence to: Department of Intensive Care, Elisabeth-TweeSteden Hospital, 5022 GC Tilburg, the Netherlands.
E-mail address: j.workum@etz.nl (J.D. Workum).

https://doi.org/10.1016/j.toxrep.2023.07.005
Received 6 June 2023; Received in revised form 1 July 2023; Accepted 15 July 2023
Available online 17 July 2023

elevated (18.4 mmol/L). Her body temperature was 35.7 °C. Initial blood gas analysis showed a pH of 7.19, a pCO2 of 5.6 kPa, bicarbonate of 16 mmol/L, base excess of 11.8 and lactate levels of 9.5 mmol/L. Liver panel, coagulation and creatine kinase (CK) levels were normal. Serum creatinine was 90 μmol/L. Results are shown in Table 1. Due to the expected severity of the intoxication and the early presentation, she was treated with activated charcoal and immediately admitted to the intensive care unit (ICU) for continuous hemodialysis as the severe lactic acidosis indicated a severe metformin overdose [1].

After admission to the ICU, she deteriorated rapidly. She became tachypneic and was intubated for exhaustion. She developed rapid onset shock, which required continuous fluid resuscitation, noradrenalin (rapidly increasing up to 1.2 μg/kg/min) and vasopressin (0.03 IE/min). Hydrocortisone was added because of the refractory nature of the shock. Continuous hemodialysis was initiated within 3 h after presentation. Arterial blood gas and lactate levels were monitored every two hours as a marker for resolution of the metformin overdose. She became hypoglycemic, most likely due to co-ingestion of metformin and semaglutide, for which a continuous 50 % glucose infusion was started. Four hours post-ingestion, approximately three hours after presentation but prior to the initiation of hemodialysis, both acetaminophen and metformin levels were drawn. Acetaminophen levels 4 h after ingestion were 29 mg/L, so treatment with N-acetylcysteine was withheld. Metformin levels were drawn with the intent of retrospective analysis, as the results took one week to complete. Results revealed a level of 622.9 mg/L. However, as these findings were not available during the initial treatment, they had no bearing on medical decision making.

Table 1
Laboratory results during admission.

Measurement	Normal values	Day 0	Day 1	Day 2	Day 3	Day 4
Hemoglobin (mmol/L)	8.5–11	8.5	7.2	6.8	6.6	6.3
Hematocrit	0.40–0.54	0.43	0.37	0.32	0.32	0.32
White Blood Cells ($10^{9/L}$)	4–11	5.3	36.7	24.2	18.7	20.0
Platelets ($10^{9/L}$)	150–450	152	244	146	-	85
Glucose (mmol/L)	3.9–6.1	18.4	5.6	8.0	10.8	8.1
Urea (mmol/L)	2.5–7.8	3.8	0.9	1.3	4.3	4.7
Creatinine (μmol/L)	45–90	90	60	51	122	136
Glomerular Filtration Rate (GFR) (CKD-EPI) (mL/min/1.73 $m^{2)}$	90–120	62	> 90	> 90	43	38
Sodium (mmol/L)	135–145	139	142	137	139	136
Potassium (mmol/L)	3.5–5.1	5.2	3.2	4.3	4.5	4.5
Magnesium (mmol/L)	0.7–1.0	0.8	0.67	0.71	1.16	1.35
Phosphate (mmol/L)	0.8–1.5	1.02	1.17	0.50	1.85	1.51
Ionized Calcium (mmol/L)	1.05–1.3	1.01	0.88	0.89	0.87	0.96
Albumin (g/L)	35–50	38	-	-	25	-
Total Bilirubin (μmol/L)	3–22	11	12	26	78	112
Alkaline Phosphatase (U/L)	40–150	107	90	80	139	831
Gamma-Glutamyl Transferase (GGT) (U/L)	10–60	40	38	34	71	111
Aspartate Aminotransferase (ASAT) (U/L)	10–40	52	224	805	3100	10,518
Alanine Aminotransferase (ALAT) (U/L)	10–45	52	99	148	757	4171
Lactate Dehydrogenase (LDH) (U/L)	125–220	176	428	782	2799	7896
pH (arterial)	7.35–7.45	7.19	7.10	7.43	7.36	7.27
pO2 (arterial) (kPa)	11–13	14.3	12.7	9.5	11.3	9.6
pCO2 (arterial) (kPa)	4.7–6.0	5.6	6.2	4.9	4.9	6.0
Bicarbonate (arterial) (mmol/L)	22–26	16	14.6	24.3	20.5	20.6
Base Excess (arterial) (mmol/L)	-2 to + 2	-11.8	-14.6	0.1	-4.4	-6
Lactate (arterial) (mmol/L)	0.5–1.6	9.5	25.0	9.2	7.9	4.4

Using bedside ultrasonography in conjunction with invasive hemodynamic monitoring using a pulse index continuous cardiac output device (PiCCO), cardiogenic, obstructive, and hypovolemic shock were excluded. Causes of distributive shock other than vasoplegia, such as septic shock and anaphylaxis, were considered unlikely due to the clinical presentation and otherwise normal appearance. As there was no cardiogenic component to the shock, venoarterial extracorporeal membrane oxygenation (va-ECMO) was not considered to be of added value. Therefore, the current condition was considered severe vasoplegic shock due to metformin. As the already high doses of noradrenalin and vasopressin were considered insufficient, we decided to treat the patient with methylene blue. Subsequently, 250 mg of methylene blue (2 mg/kg) was administered intravenously over 5 min. The noradrenalin dose could be reduced from 1.2 μg/kg/min to 0.5 μg/kg/min within 15 min, indicating rapid shock reversal, which was maintained at 0.5 μg/kg/min for 6 h without additional intervention. A second bolus of methylene blue 2 mg/kg was then administered in an attempt to further reduce noradrenalin levels. This allowed the noradrenalin dose to be lowered to 0.25 μg/kg/min (Fig. 1).

The patient remained stable for the next 24 h. Lactate levels decreased from a maximum of 29 mmol/L to 4.4 mmol/L, indicating metformin clearance and improvement of shock. However, the next day, lactate levels began to increase again while still on hemodialysis. She developed severe liver test abnormalities, with alanine aminotransferase (ASAT) of 10518 U/L and aspartate aminotransferase (ALAT) of 4171 U/L, and developed progressive shock again. A computed tomography (CT) scan of both the thorax and abdomen showed extensive necrosis of the liver. As there were no curative options, treatment was switched to palliative care and she passed away. Permission for post-mortem examination was not obtained. However, her next of kin signed informed consent for publication.

3. Discussion

We presented a case of severe vasoplegic shock due to metformin toxicity, which was treated with methylene blue in addition to conventional treatment, resulting in rapid shock resolution.

Severe metformin poisoning can lead to metabolic acidosis with hyperlactatemia (metformin associated lactic acidosis, or MALA), glucose derangement (both hyperglycemia and hypoglycemia) and shock. Treatment consists of enhancement of drug elimination via hemodialysis and supportive care. In a scoping review, Juneja et al. summarize the symptomology, clinical interventions and outcomes of 242 patients with metformin poisoning [2]. MALA, defined as lactate levels above 5 mmol/L with concurrent acidosis, was found in 92.6 % of patients and 68.6 % required renal replacement therapy. In patients with acute ingestion, they report a median ingested dose of 42.5 g, mean serum levels of 108.7 mg/L and a mortality of 19.3 %. They did not report any use of methylene blue.

The mechanism of hyperlactatemia in metformin toxicity mainly follows two pathways: the inhibition of mitochondrial glycerol 3-phosphate dehydrogenase (mGPD) and the inhibition of mitochondrial respiratory chain complex 1 (mRCC1) of the electron transport chain [3]. Inhibition of mGPD causes a decrease in gluconeogenesis, which reduces the production of glucose from pyruvate and results in the conversion of pyruvate to lactate. Inhibition of mRCC1 impairs oxidative phosphorylation, leading to mitochondrial dysfunction. This increases the amount of reduced nicotinamide adenine dinucleotide (NADH), which enhances the conversion of pyruvate into lactate. The mechanism for metformin induced vasoplegia is most likely mediated by nitric oxide (NO). Metformin has been shown to increase adenosine monophosphate-activated

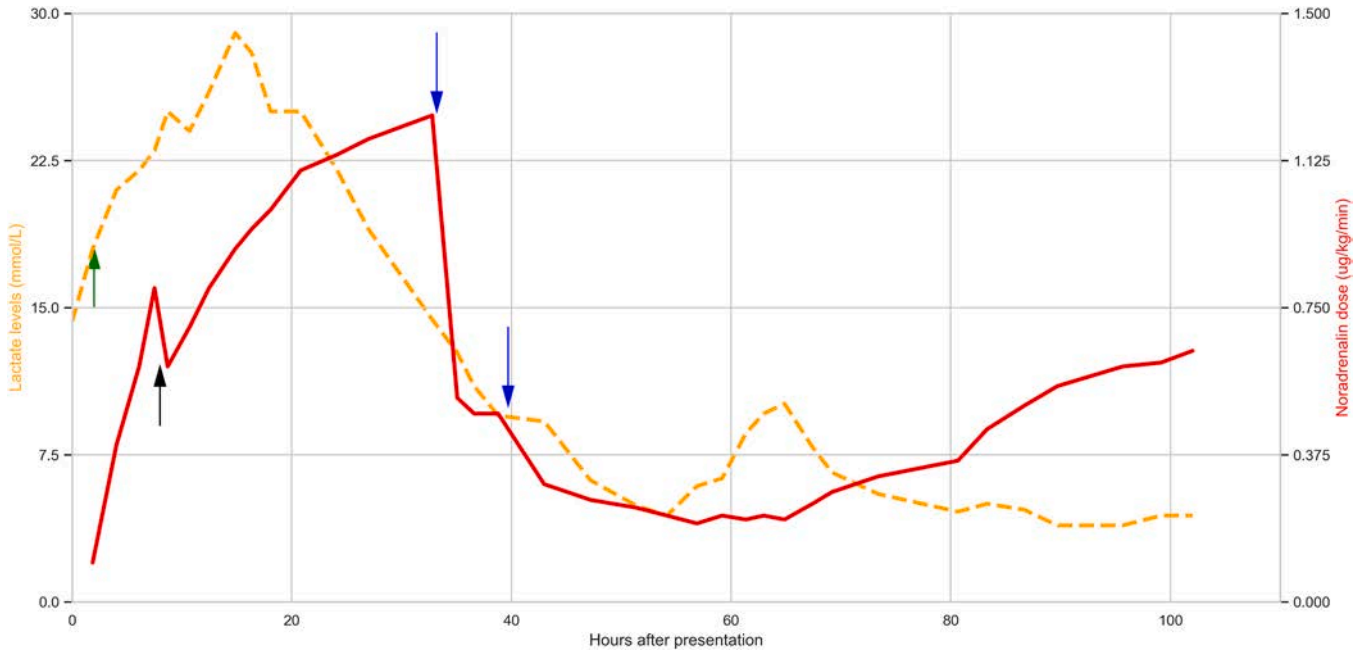

Fig. 1. The course of serum lactate (orange dashed line, left y-axis) and noradrenalin dose (red solid line, right y-axis). The green arrow (arrow 1) indicates the initiation of continuous hemodialysis. The black arrow (arrow 2) indicated the addition of vasopressin and hydrocortisone to noradrenalin. The blue arrows (arrows 3 and 4) indicate a bolus of methylene blue 2 mg/kg intravenously. As noradrenalin levels could be rapidly decreased after the first methylene blue injection, the first blue arrow therefore also indicates the start of shock reversal.

protein kinase phosphorylation, which activates endothelial nitric oxide synthase (eNOS) and increases NO bioactivity, leading to increased NO levels and subsequent vasodilation [4]. NO-mediated vasoplegia contributes to hyperlactatemia in several ways: first, it leads to shock which causes systemic tissue hypoxia; second, NO itself can cause mitochondrial dysfunction which may increase the production of lactic acid via a mechanism similar to sepsis induced lactic acidosis.

Methylene blue is a commonly used synthetic dye, but is also used in medicine to reverse methemoglobinemia. In toxicology, it is therefore known to reverse the effects of sodium nitrite poisoning [5]. However, methylene blue also reduces NO production, by directly inhibiting NO synthase, but also by binding to the iron heme-moiety of soluble guanylate cyclase, thus competitively blocking the target enzyme of NO [6,7]. This reduces NO-mediated vasodilation. Therefore, methylene blue has been used in cases where NO-mediated vasoplegia is suspected, such as in sepsis and poisoning with beta-blockers and calcium channel blockers [8,9].

Methylene blue as rescue therapy for metformin toxicity has only been described in literature in a few case reports. Graham et al. [10] described a case of 44 year old man who ingested 35 g of metformin and developed severe lactic acidosis and shock. He received daily hemodialysis and methylene blue (2 mg/kg bolus with a continuous infusion of 0.25 mg/kg/h for 20 h). He was weaned off vasopressors after 2 days of ICU admission and made a full recovery. Plumb et al. [11] described a case of a 66 year old woman presenting with severe lactic acidosis due to an accidental metformin overdose of unknown quantity, also successfully treated with renal replacement therapy and methylene blue (2 mg/kg loading dose and continuous infusion of 2 mg/kg/h for 12 h). Tallman et al. [12] used va-ECMO as the mainstay of their treatment in addition to conventional treatment, but also describe a beneficial effect of methylene blue on the patient's blood pressure.

Other than by reducing NO levels, methylene blue may also have a direct positive effect on hyperlactatemia in metformin poisoning. It can act as an alternative electron carrier by accepting electrons from NADH and subsequently delivering them to ubiquinone or cytochrome c, therefore bypassing the electron transport chain impediment at mRCC1, which is impaired in severe metformin poisoning [2]. Therefore, it may also improve MALA. In our patient, this effect could not have been distinguished from the effect of hemodialysis on lactate clearance.

Methylene blue works within minutes and has a maximum effect in 30–60 min after administration. The recommended dose is 1–2 mg/kg intravenously, with a maximum of 7 mg/kg. Approximately 75 % of methylene blue is excreted by the kidneys, either unchanged or as leucomethylene blue. It has a terminal half-life of approximately 25 h [13]. Due to the long half-life of methylene blue, we decided that continuous infusion would not have any benefits over repeated boluses, but would increase the chance of exceeding the recommended dose.

The side effects of methylene blue are mild. They include short-term blue discoloration of the skin, urine and feces, which also occurred in our patient. Other side effects include gastro-intestinal side effects such as nausea and diarrhea. Methylene blue should be administered with caution in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency, as it can induce hemolytic anemia. In patients with serotonergic co-medication, methylene blue could increase the risk of developing serotonergic syndrome. In both cases, the risk should be weighed against the potential benefits. In doses that exceed the recommended maximum dose of 7 mg/kg, methylene blue can itself induce the formation of methemoglobinemia.

Our patient presented with a severe metformin overdose. She ingested 82.5 g (660 mg/kg), which is double the median dose described in the literature. The metformin level sampled approximately 4 h after ingestion was 622.9 mg/L, which is 6 times the average metformin levels in toxicologic literature [2]. Despite continuous hemodialysis being initiated early, lactate levels continued to rise until 16 h after presentation. Lactate levels served as a treatment efficacy marker: when lactate levels started to decrease, this indicated that metformin levels themselves were also decreasing [14,15]. We therefore hypothesized that metformin-induced NO production would also decrease. This is why, in contrast to the use of methylene blue in sepsis in which NO production is ongoing, we expected a positive treatment effect of methylene blue in our patient. The effect of methylene blue was immediate and persistent.

Despite being stable for 24 h after the first injection of methylene blue, the patient developed progressive shock again. It is unlikely that

this was caused by metformin toxicity, since our patient had been treated with continuous hemodialysis for more than 48 h, given that the half-life for metformin during continuous hemodialysis is approximately 4 h [14]. Therefore, we did not repeat methylene blue as we suspected other causes for the shock. A CT scan showed extensive liver necrosis, which has not been described in metformin toxicity. Considering the known side effects of methylene blue, none of which include liver necrosis or exacerbation of shock, it is unlikely that methylene blue itself contributed to the patient's worsening condition. Acetaminophen levels 4 h after ingestion were 29 mg/L, which is below the toxic threshold, and liver panel at presentation was normal, ruling out acetaminophen toxicity as a cause. A potential interaction between acetaminophen and simvastatin as a CYP3A4 inducer was considered highly unlikely. As CK levels remained low and no hepatotoxic medication was administered in our ICU, we therefore hypothesize that the severity of the initial shock with high vasopressor doses may have compromised hepatic blood flow, resulting in liver ischemia and subsequent necrosis. This observation further highlights the potential value of methylene blue to reduce vasopressor need in vasoplegic shock. As methylene blue allowed for a rapid reduction in noradrenalin dose in our case, early application could have potentially mitigated the harmful effects of prolonged high-dose vasopressor therapy, such as impaired hepatic blood flow leading to liver necrosis.

4. Conclusion

Our patient presented with a metabolic acidosis with hyperlactatemia and a severe vasoplegic shock after a massive metformin overdose. Although scarcely described, methylene blue proved to be a highly effective therapy of vasoplegic shock, with an immediate and persistent effect, allowing a rapid reduction of noradrenalin. As methylene blue has only a few side effects, it is important for clinicians to consider methylene blue when treating patients with refractory shock due to severe metformin overdose.

Previous presentation

None.

Funding

None.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data Availability

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

References

[1] D.P. Calello, K.D. Liu, T.J. Wiegand, et al., Extracorporeal treatment for metformin poisoning: systematic review and recommendations from the extracorporeal treatments in poisoning workgroup, Crit. Care Med. 43 (2015) 1716–1730.
[2] D. Juneja, P. Nasa, R. Jain, Metformin toxicity: a meta-summary of case reports, World J. Diabetes 13 (2022) 654–664.
[3] G.S. Wang, C. Hoyte, Review of biguanide (metformin) toxicity, J. Intensive Care Med. 34 (2019) 863–876.
[4] B.J. Davis, Z. Xie, B. Viollet, M. Zou, Activation of the AMP-activated kinase by antidiabetes drug metformin stimulates nitric oxide synthesis in vivo and endothelial nitric oxide synthase, Diabetes (2006) 55.
[5] J.D. Workum, L.L.A. Bisschops, M.J.W. Van Den Berg, Auto-intoxication with 'suicide powder', Ned. Tijdschr. Geneeskd. (2019) 163.
[6] B. Mayer, F. Brunner, K. Schmidt, Novel actions of methylene blue, Eur. Heart J. 14 Suppl. I (1993) 22–26.
[7] B. Mayer, F. Brunner, K. Schmidt, Inhibition of nitric oxide synthesis by methylene blue, Biochem. Pharm. 45 (1993) 367–374.
[8] E.S.H. Kwok, D.W. Howes, Use of methylene blue in sepsis: a systematic review, J. Intensive Care Med. 21 (2006) 359–363.
[9] N. Aggarwal, Y. Kupfer, C. Seneviratne, S. Tessler, Methylene blue reverses recalcitrant shock in β-blocker and calcium channel blocker overdose, BMJ Case Rep. (2013) 2013.
[10] R.E. Graham, M. Cartner, J. Winearls, Case report: a severe case of vasoplegic shock following metformin overdose successfully treated with methylene blue as a last line therapy, BMJ Case Rep. (2015) 2015.
[11] B. Plumb, A. Parker, P. Wong, Feeling blue with metformin-associated lactic acidosis, BMJ Case Rep. 2013 (2013), bcr2013008855.
[12] C. Ives Tallman, Y. Zhang, N. Black, K. Lynch, M. Fayed, P. Armenian, Refractory vasodilatory shock secondary to metformin overdose supported with VA ECMO, Toxicol. Rep. 9 (2022) 64–67.
[13] Methylthioninium chloride: summary of product characteristics, 2022.
[14] P. Ayoub, P.O. Hétu, M. Cormier, et al., Toxicokinetics of metformin during hemodialysis, Anu. Psicol. 47 (2017) 759–762.
[15] M. Prikis, E.L. Mesler, V.L. Hood, W.J. Weise, When a friend can become an enemy! Recognition and management of metformin-associated lactic acidosis, Kidney Int. 72 (2007) 1157–1160.

FDA - Adverse Event Reporting System (FAERS)
FOIA Case Report Information

Case ID: 22813239

Case Information:

Case Type : Expedited (15-Day) **eSub:** Y **HP:** Y **Country:** NL **Event Date:** **Outcomes:** DE , LT , HO , OT **Application Type:** ANDA

FDA Rcvd Date: 22-Aug-2023 **Mfr Rcvd Date:** 11-Aug-2023 **Mfr Control #:** NL-MACLEODS PHARMACEUTICALS US LTD-MAC2023042868 **Application #:** 206955

Patient Information:

Age: **Sex:** **Weight:**

Suspect Products:

#	Product Name:	Compounded Drug ?	Dose/Frequency	Route	Dosage Text	Start Date	End Date	Indication(s)
1	Metformin		165 Dosage Form /	Oral	165 dosage form, single (Time to onset: 4 hours)			Product used for unknown indication
2	Paracetamol 500mg tablet		20 Dosage Form /	Oral	20 dosage form, single			Product used for unknown indication
3	Semaglutide		30 Dosage Form /	Oral	30 dosage form, single			Product used for unknown indication
4	Simvastatin		38 Dosage Form /	Oral	38 dosage form, single			Product used for unknown indication

#	Product Name:	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler	OTC
1	Metformin		Unknown	NA				MACLEODS	
2	Paracetamol 500mg tablet		Unknown	NA					
3	Semaglutide		Unknown	NA					
4	Simvastatin		Unknown	NA					

FDA - Adverse Event Reporting System (FAERS)
FOIA Case Report Information

Case ID: 22813239

Device Products:

#	Brand Name / Common Device Name / Product Code	Similar Device?	Malfunction ?	Device Lot#	Device Usage/ Operator of Device	Remedial Action	Device Problem	Manufacturer Name
1	//	No			/			
2	//	No			/			
3	//	No			/			
4	//	No			/			

Event Information:

Preferred Term (MedDRA Version: v.26.1)	ReC
Distributive shock	
Hepatic necrosis	
Shock	
Lactic acidosis	
Suicide attempt	
Hypoglycaemia	
Intentional overdose	

Event/Problem Narrative:

Case number: MAC2023042868 This case was derived from the scientific literature published in Toxicology Reports (PMID: 37520772) via EMA MLMSERVICE (NL-MLMSERVICE-20230727-4439527-1) and describes a 55 years old female patient who was hypoglycemic (hypoglycaemia) after suicide attempt and died due to severe vasoplegic shock due to metformin (distributive shock), metformin associated lactic acidosis (MALA) (lactic acidosis), severe metformin overdose as a suicide attempt (intentional overdose), liver necrosis (hepatic necrosis) and shock while receiving metformin and acetaminophen (paracetamol) for the treatment of an unknown indication. Other suspect drug semaglutide and simvastatin received for the treatment of an unknown indication. Workum JD, Keyany A, Jaspers TCC. Methylene blue as treatment for vasoplegic shock in severe metformin overdose: A case report. Toxicology Reports. 2023; 11:141-4. Medical history included unsuccessful suicide. Current conditions included type II diabetes mellitus and chronic depression. Concomitant medications were not reported. On an unknown date, the patient presented to the emergency department (ED) after ingestion of 165 tablets of metformin 500 mg (82.5 g, or 660 mg/kg), 20 tablets of acetaminophen 500 mg (10 g, or 80 mg/kg), 38 tablets of simvastatin 40 mg (1520 mg, or 12 mg/kg) and 30 tablets of semaglutide 14 mg (420 mg or 3.4 mg/ kg) as a suicide attempt. Immediately after ingestion, she alerted the emergency services herself and presented within 1 h of ingestion. In the ED she was alert and cooperative. Her medical history comprised of earlier suicide attempts with chronic depression and type II diabetes. Her initial vital signs were normal: she had a normal respiratory rate and an oxygen saturation of 95 % without supplemental oxygen, blood pressure was 122/51 mmHg with a normal sinus rhythm of 89/ min, and she was alert with a Glasgow Coma Scale of 15. Glucose was mildly elevated (18.4 mmol/L). Her body temperature was 35.7 degrees C. Initial blood gas analysis showed a pH of 7.19, a pCO2 of 5.6 kPa, bicarbonate of 16 mmol/L, base excess of -11.8 and lactate levels of 9.5 mmol/L. Liver panel, coagulation

and creatine kinase (CK) levels were normal. Serum creatinine was 90 umol/L. Laboratory results during admission were found on initial day the hemoglobin was 8.5 mmol/ L (normal range: 8.5-11 mmol/ L), hematocrit was 0.43 (normal range: 0.40-0.54), white blood cells was 5.3 10^9/L (normal range: 4-11 10^9/L), platelets 152 10^9/L (normal range: 150-450 10^9/L), glucose was 18.4 mmol/L (normal range: 3.9-6.1 mmol/L), urea was 3.8 mmol/L (normal range: 2.5-7.8 mmol/L), creatinine was 90 umol/L (normal range: 45-90 umol/L), glomerular filtration rate (GFR) (CKD-EPI) was 62 mL/min/1.73 m2 (normal range: 90-120), sodium was 139 mmol/L (normal range: 135-145 mmol/L), potassium was 5.2 mmol/L (normal range: 3.5-5.1 mmol/L), magnesium was 0.8 mmol/ L (normal range: 0.7-1.0 mmol/ L), phosphate was 1.02 mmol/L (normal range: 0.8-1.5 mmol/L), ionized calcium was 1.01mmol/L (normal range: 1.05-1.3 mmol/L), Albumin was 38 g/L (normal range: 35-50 g/L), total bilirubin was 11 umol/L (normal range: 3-22 umol/L), alkaline phosphatase was 107 U/L (normal range: 40-150 U/L), gamma-glutamyl transferase (GGT) was 40 U/L (normal range: 10-60 U/L), aspartate aminotransferase (ASAT) was 52 U/L (normal range: 10-40 U/L), alanine aminotransferase (ALAT) was 52 U/L (normal range: 10-45 U/L), lactate dehydrogenase (LDH) was 176 U/L (normal range: 125-220 U/L), pH (arterial) was 7.19 (normal range: 7.35-7.45), pO2 (arterial) was 14.3 kPa (normal range: 11-13 kPa), pCO2 (arterial) was 5.6 kPa (normal range: 4.7-6.0 kPa), bicarbonate (arterial) was 16 mmol/L (normal range: 22-26 mmol/L), base excess (arterial) was -11.8 mmol/L (normal range: -2 to + 2 mmol/L) and lactate (arterial) was 9.5 mmol/L (normal range: 0.5-1.6 mmol/L). On first day of hospitalization, the laboratory result shows that, the patients hemoglobin was 7.2 mmol/ L (normal range: 8.5-11 mmol/ L), hematocrit was 0.37 (normal range: 0.40-0.54), white blood cells was 36.7 10^9/L (normal range: 4-11 10^9/L), platelets 244 10^9/L (normal range: 150-450 10^9/L), glucose was 5.6 mmol/L (normal range: 3.9-6.1 mmol/L), urea was 0.9 mmol/L (normal range: 2.5-7.8 mmol/L), creatinine was 60 umol/ L (normal range: 45-90 umol/L), glomerular filtration rate (GFR) (CKD-EPI) was >90 mL/min/1.73 m2 (normal range: 90-120), sodium was 142 mmol/L (normal range: 135-145 mmol/L), potassium was 3.2 mmol/L (normal range: 3.5-5.1 mmol/L), magnesium was 0.67 mmol/ L (normal range: 0.7-1.0 mmol/ L), phosphate was 1.17 mmol/L (normal range: 0.8-1.5 mmol/L), ionized calcium was 0.88 mmol/L (normal range: 1.05-1.3 mmol/L), total bilirubin was 12 umol/L (normal range: 3-22 umol/L), alkaline phosphatase was 90 U/L (normal range: 40-150 U/L), gamma-glutamyl transferase (GGT) was 38U/L (normal range: 10-60 U/L), aspartate aminotransferase (ASAT) was 224 U/L (normal range: 10-40 U/L), alanine aminotransferase (ALAT) was 99 U/L (normal range: 10-45 U/L), lactate dehydrogenase (LDH) was 428 U/L (normal range: 125-220 U/L), pH (arterial) was 7.10 (normal range: 7.35-7.45), pO2 (arterial) was 12.7 kPa (normal range: 11-13 kPa), pCO2 (arterial) was 6.2 kPa (normal range: 4.7-6.0 kPa), bicarbonate (arterial) was 14.6 mmol/L (normal range: 22-26 mmol/L), base excess (arterial) was -14.6 mmol/ L (normal range: -2 to + 2 mmol/L) and lactate (arterial) was 25.0 mmol/L (normal range: 0.5-1.6 mmol/L). On second day of hospitalization, the laboratory result shows that, the patients hemoglobin was 86.8 mmol/ L (normal range: 8.5-11 mmol/ L), hematocrit was 0.32 (normal range: 0.40-0.54), white blood cells was 24.2 10^9/L (normal range: 4-11 10^9/L), platelets 146 10^9/L (normal range: 150-450 10^9/L), glucose was 8.0 mmol/L (normal range: 3.9-6.1 mmol/L), urea was 1.3 mmol/L (normal range: 2.5-7.8 mmol/L), creatinine was 51 umol/L (normal range: 45-90 umol/L), glomerular filtration rate (GFR) (CKD-EPI) was >90 mL/min/1.73 m2 (normal range: 90-120), sodium was 137 mmol/L (normal range: 135-145 mmol/L), potassium was 4.3 mmol/L (normal range: 3.5-5.1 mmol/L), magnesium was 0.71 mmol/ L (normal range: 0.7-1.0 mmol/ L), phosphate was 0.50 mmol/L (normal range: 0.8-1.5 mmol/L), ionized calcium was 0.89 mmol/L (normal range: 1.05-1.3 mmol/L), total bilirubin was 26 umol/L (normal range: 3-22 umol/L), alkaline phosphatase was 80 U/L (normal range: 40-150 U/L), gamma-glutamyl transferase (GGT) was 34 U/L (normal range: 10-60 U/L), aspartate aminotransferase (ASAT) was 805 U/L (normal range: 10-40 U/L), alanine aminotransferase (ALAT) was 148 U/L (normal range: 10-45 U/L), lactate dehydrogenase (LDH) was 782 U/L (normal range: 125-220 U/L), pH (arterial) was 7.43 (normal range: 7.35-7.45), pO2 (arterial) was 9.5 kPa (normal range: 11-13 kPa), pCO2 (arterial) was 4.9 kPa (normal range: 4.7-6.0 kPa), bicarbonate (arterial) was 24.3 mmol/L (normal range: 22-26 mmol/L), base excess (arterial) was 0.1 mmol/L (normal range: -2 to + 2 mmol/L) and lactate (arterial) was 9.2 mmol/L (normal range: 0.5-1.6 mmol/L). On third day of hospitalization, the laboratory result shows that, the patients hemoglobin was 6.6 mmol/ L (normal range: 8.5-11 mmol/ L), hematocrit was 0.32 (normal range: 0.40-0.54), white blood cells was 18.7 10^9/L (normal range: 4-11 10^9/L), glucose was 10.8 mmol/L (normal range: 3.9-6.1 mmol/L), urea was 4.3 mmol/L (normal range: 2.5-7.8 mmol/L), creatinine was 122 umol/L (normal range: 45-90 umol/L), glomerular filtration rate (GFR) (CKD-EPI) was 43 mL/min/1.73 m2 (normal range: 90-120), sodium was 139 mmol/L (normal range: 135-145 mmol/L), potassium was 4.5 mmol/L (normal range: 3.5-5.1 mmol/ L), magnesium was 1.16 mmol/ L (normal range: 0.7-1.0 mmol/ L), phosphate was 1.85 mmol/L (normal range: 0.8-1.5 mmol/L), ionized calcium was 0.87 mmol/ L (normal range: 1.05-1.3 mmol/L), albumin was 25 g/L (normal range: 35-50 g/L), total bilirubin was 78 umol/L (normal range: 3-22 umol/L), alkaline phosphatase was 139 U/L (normal range: 40-150 U/L), gamma-glutamyl transferase (GGT) was 71 U/L (normal range: 10-60 U/L), aspartate aminotransferase (ASAT) was 3100 U/L (normal range: 10-40 U/L), alanine aminotransferase (ALAT) was 757 U/L (normal range: 10-45 U/L), lactate dehydrogenase (LDH) was 2799 U/L (normal range: 125-220 U/L), pH (arterial) was 7.36 (normal range: 7.35-7.45), pO2 (arterial) was 11.3 kPa (normal range: 11-13 kPa), pCO2 (arterial) was 4.9 kPa (normal range: 4.7-6.0 kPa), bicarbonate (arterial) was 20.5 mmol/L (normal range: 22-26 mmol/L), base excess (arterial) was -4.4 mmol/L (normal range: -2 to + 2 mmol/L) and lactate (arterial) was 7.9 mmol/L (normal range: 0.5-1.6 mmol/L). On fourth day of hospitalization, the laboratory result shows that, the patients

hemoglobin was 6.3 mmol/ L (normal range: 8.5-11 mmol/ L), hematocrit was 0.32 (normal range: 0.40-0.54), white blood cells was 20.0 10^9/L (normal range: 4-11 10^9/L), platelets 85 10^9/L (normal range: 150-450 10^9/L), glucose was 8.1 mmol/L (normal range: 3.9-6.1 mmol/L), urea was 4.7 mmol/L (normal range: 2.5-7.8 mmol/L), creatinine was 136 umol/L (normal range: 45-90 umol/L), glomerular filtration rate (GFR) (CKD-EPI) was 38 mL/min/1.73 m2 (normal range: 90-120), sodium was 136 mmol/L (normal range: 135-145 mmol/L), potassium was 4.5 mmol/L (normal range: 3.5-5.1 mmol/L), magnesium was 1.35 mmol/ L (normal range: 0.7-1.0 mmol/ L), phosphate was 1.51 mmol/L (normal range: 0.8-1.5 mmol/L), ionized calcium was 0.96 mmol/L (normal range: 1.05-1.3 mmol/ L), total bilirubin was 112 umol/L (normal range: 3-22 umol/L), alkaline phosphatase was 831 U/L (normal range: 40-150 U/L), gamma-glutamyl transferase (GGT) was 111 U/L (normal range: 10-60 U/L), aspartate aminotransferase (ASAT) was 10518 U/L (normal range: 10-40 U/L), alanine aminotransferase (ALAT) was 4171 U/L (normal range: 10-45 U/L), lactate dehydrogenase (LDH) was 7896 U/L (normal range: 125-220 U/L), pH (arterial) was 7.27 (normal range: 7.35-7.45), pO2 (arterial) was 9.6 kPa (normal range: 11-13 kPa), pCO2 (arterial) was 6.0 kPa (normal range: 4.7-6.0 kPa), bicarbonate (arterial) was 20.6 mmol/L (normal range: 22-26 mmol/L), base excess (arterial) was -6 mmol/L (normal range: -2 to + 2 mmol/L) and lactate (arterial) was 4.4 mmol/L (normal range: 0.5-1.6 mmol/ L). Due to the expected severity of the intoxication and the early presentation; she was treated with activated charcoal and immediately admitted to the intensive care unit (ICU) for continuous hemodialysis as the severe lactic acidosis indicated a severe metformin overdose. After admission to the ICU, she deteriorated rapidly. She became tachypneic and was intubated for exhaustion. She developed rapid onset shock, which required continuous fluid resuscitation, noradrenalin (rapidly increasing up to 1.2 ug/kg/min) and vasopressin (0.03 IE/min). Hydrocortisone was added because of the refractory nature of the shock. Continuous hemodialysis was initiated within 3 h after presentation. Arterial blood gas and lactate levels were monitored every two hours as a marker for resolution of the metformin overdose. She became hypoglycemic, most likely due to co-ingestion of metformin and semaglutide, for which a continuous 50 % glucose infusion was started. Four hours post-ingestion, approximately three hours after presentation but prior to the initiation of hemodialysis, both acetaminophen and metformin levels were drawn. Acetaminophen levels 4 h after ingestion were 29 mg/L, so treatment with N-acetylcysteine was withheld. Metformin levels were drawn with the intent of retrospective analysis, as the results took one week to complete. Results revealed a level of 622.9 mg/L. However, as these findings were not available during the initial treatment, they had no bearing on medical decision making. Using bedside ultrasonography in conjunction with invasive hemodynamic monitoring using a pulse index continuous cardiac output device (PiCCO), cardiogenic, obstructive, and hypovolemic shock were excluded. Causes of distributive shock other than vasoplegia, such as septic shock and anaphylaxis, were considered unlikely due to the clinical presentation and otherwise normal appearance. As there was no cardiogenic component to the shock, venoarterial extracorporeal membrane oxygenation (va-ECMO) was not considered to be of added value. Therefore, the current condition was considered severe vasoplegic shock due to metformin. As the already high doses of noradrenalin and vasopressin were considered insufficient, the authors decided to treat the patient with methylene blue. Subsequently, 250 mg of methylene blue (2 mg/kg) was administered intravenously over 5 min. The noradrenalin dose could be reduced from 1.2 ug/kg/min to 0.5 ug/kg/ min within 15 min, indicating rapid shock reversal, which was maintained at 0.5 ug/ kg/min for 6 h without additional intervention. A second bolus of methylene blue 2 mg/kg was then administered in an attempt to further reduce noradrenalin levels. This allowed the noradrenalin dose to be lowered to 0.25 ug/kg/min. The patient remained stable for the next 24 h. Lactate levels decreased from a maximum of 29 mmol/L to 4.4 mmol/L, indicating metformin clearance and improvement of shock. However, the next day, lactate levels began to increase again while still on hemodialysis. She developed severe liver test abnormalities, with alanine aminotransferase (ASAT) of 10518 U/L and aspartate aminotransferase (ALAT) of 4171 U/ L and developed progressive shock again. A computed tomography (CT) scan of both the thorax and abdomen showed extensive necrosis of the liver. As there were no curative options, treatment was switched to palliative care and she passed away. Permission for post-mortem examination was not obtained. However, her next of kin signed informed consent for publication. On an unknown date, the patient was died. The autopsy was not preformed and patient died due to severe vasoplegic shock due to metformin, MALA , severe metformin overdose as a suicide attempt (intentional overdose), shock and liver necrosis.. Action taken with suspect drugs was not applicable. Outcome of event for severe vasoplegic shock due to metformin, MALA (Metformin associated lactic acidosis), severe metformin overdose as a suicide attempt (Intentional overdose), liver necrosis and shock was fatal and for event hypoglycemia, outcome was recovering. The case considered as serious (Death, life threatening, hospitalization and medically significant). Case outcome is fatal. Dechallenge and rechallenge are not applicable. Authors comment: The authors presented a case of severe vasoplegic shock due to metformin toxicity, which was treated with methylene blue in addition to conventional treatment, resulting in rapid shock resolution. Severe metformin poisoning can lead to metabolic acidosis with hyperlactatemia (metformin associated lactic acidosis, or MALA), glucose derangement (both hyperglycemia and hypoglycemia) and shock. This patient presented with a severe metformin overdose. She ingested 82.5 g (660 mg/kg), which is double the median dose described in the literature. The metformin level sampled approximately 4 h after ingestion was 622.9 mg/L, which is 6 times the average metformin levels in toxicologic literature. Despite continuous hemodialysis being initiated early, lactate levels continued to rise until 16 h after presentation. Lactate levels served as a treatment efficacy marker: when lactate levels started to decrease, this indicated that metformin

Case ID: 22813239

levels themselves were also decreasing. Therefore hypothesized that metformin-induced NO production would also decrease. This is why, in contrast to the use of methylene blue in sepsis in which NO production is ongoing, they expected a positive treatment effect of methylene blue in this patient. The effect of methylene blue was immediate and persistent. Despite being stable for 24 h after the first injection of methylene blue, the patient developed progressive shock again. It is unlikely that this was caused by metformin toxicity, since this patient had been treated with continuous hemodialysis for more than 48 h, given that the half-life for metformin during continuous hemodialysis is approximately 4 h. Therefore, the authors did not repeat methylene blue as they suspected other causes for the shock. A CT scan showed extensive liver necrosis, which has not been described in metformin toxicity. Considering the known side effects of methylene blue, none of which include liver necrosis or exacerbation of shock, it is unlikely that methylene blue itself contributed to the patient's worsening condition. Acetaminophen levels 4 h after ingestion were 29 mg/L, which is below the toxic threshold, and liver panel at presentation was normal, ruling out acetaminophen toxicity as a cause. A potential interaction between acetaminophen and simvastatin as a CYP3A4 inducer was considered highly unlikely. As CK levels remained low and no hepatotoxic medication was administered in ICU, therefore the author's hypothesize that the severity of the initial shock with high vasopressor doses may have compromised hepatic blood flow, resulting in liver ischemia and subsequent necrosis. This observation further highlights the potential value of methylene blue to reduce vasopressor need in vasoplegic shock. As methylene blue allowed for a rapid reduction in noradrenalin dose in this case, early application could have potentially mitigated the harmful effects of prolonged high-dose vasopressor therapy, such as impaired hepatic blood flow leading to liver necrosis. In conclusion, this patient presented with a metabolic acidosis with hyperlactatemia and a severe vasoplegic shock after a massive metformin overdose. Although scarcely described, methylene blue proved to be a highly effective therapy of vasoplegic shock, with an immediate and persistent effect, allowing a rapid reduction of noradrenalin. As methylene blue has only a few side effects, it is important for clinicians to consider methylene blue when treating patients with refractory shock due to severe metformin overdose. Author stated that Time to MALA was approximately 4 hours after ingestion of metformin/semaglutide. Patient received noradrenalin and vasopressin within 12 hours of presentation. Time to 2nd onset of shock was approximately 65 hours after commencement of noradrenalin and 58 hours after commencement of vasopressin. There was a large resolvement of both shock and lactate levels, before the 2nd onset of shock occurred; however, cause of death was ruled to be due to progressive shock secondary to liver necrosis and metformin overdose. Follow up 01: Follow up information was received from EMA MLMSERVICE (NL-MLMSERVICE-20230727-4439527-1) on 11 Aug 2023. Addition of new information included new reporter (other), new events (liver necrosis and shock) and cause of death (Severe vasoplegic shock due to metformin, MALA, Severe metformin overdose), updated outcome of events intentional overdose, distributive shock, metformin associated lactic acidosis from recovering to fatal, deleted event (Unknown cause of death) and narrative was amended accordingly. It is a significant follow up.

Relevant Medical History:

Disease/Surgical Procedure	Start Date	End Date	Continuing?
Type 2 diabetes mellitus			Yes
Depression			Yes
Suicide attempt			

Medical History Product(s)	Start Date	End Date	Indications	Events

Relevant Laboratory Data:

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail

ALANINE AMINOTRANSFERASE	52	U/L	10	45	Y
ALANINE AMINOTRANSFERASE	99	U/L	10	45	Y
ALANINE AMINOTRANSFERASE	148	U/L	10	45	Y
ALANINE AMINOTRANSFERASE	757	U/L	10	45	Y
ALANINE AMINOTRANSFERASE	4171	U/L	10	45	Y
ASPARTATE AMINOTRANSFERASE	52	U/L	10	40	Y
ASPARTATE AMINOTRANSFERASE	52	U/L	10	40	Y
ASPARTATE AMINOTRANSFERASE	224	U/L	10	40	Y
ASPARTATE AMINOTRANSFERASE	805	U/L	10	40	Y
ASPARTATE AMINOTRANSFERASE	3100	U/L	10	40	Y
ASPARTATE AMINOTRANSFERASE	10518	U/L	10	40	Y
BASE EXCESS	-11.8	mmol/l	-2	+2	Y
BASE EXCESS	-14.6	mmol/l	-2	+2	Y
BASE EXCESS	24.3	mmol/l	-2	+2	N
BASE EXCESS	20.5	mmol/l	-2	+2	N
BASE EXCESS	20.6	mmol/l	-2	+2	N
BASE EXCESS	0.1	mmol/l	-2	+2	Y
BLOOD ALBUMIN	38	g/L	35	50	Y
BLOOD ALBUMIN	38	g/L	35	50	Y
BLOOD ALKALINE PHOSPHATASE	107	U/L	40	150	Y
BLOOD ALKALINE PHOSPHATASE	90	U/L	40	150	Y
BLOOD ALKALINE PHOSPHATASE	80	U/L	40	150	Y
BLOOD ALKALINE PHOSPHATASE	139	U/L	40	150	Y
BLOOD ALKALINE PHOSPHATASE	831	U/L	40	150	Y
BLOOD BICARBONATE	16	mmol/l	22	26	Y
BLOOD BICARBONATE	14.6	mmol/l	22	26	Y
BLOOD BICARBONATE	24.3	mmol/l	22	26	Y
BLOOD BICARBONATE	20.5	mmol/l	22	26	Y
BLOOD BICARBONATE	20.6	mmol/l	22	26	Y

Case ID: 22813239

BLOOD BILIRUBIN	11	umol/L	3	22	Y
BLOOD BILIRUBIN	12	umol/L	3	22	Y
BLOOD BILIRUBIN	26	umol/L	3	22	Y
BLOOD BILIRUBIN	78	umol/L	3	22	Y
BLOOD BILIRUBIN	112	umol/L	3	22	Y
BLOOD CREATININE	90	umol/L	45	90	Y
BLOOD CREATININE	60	umol/L	45	90	Y
BLOOD CREATININE	51	umol/L	45	90	Y
BLOOD CREATININE	122	umol/L	45	90	Y
BLOOD CREATININE	136	umol/L	45	90	Y
BLOOD GLUCOSE	18.4	mmol/l	3.9	6.1	Y
BLOOD GLUCOSE	8	mmol/l	3.9	6.1	Y
BLOOD GLUCOSE	5.6	mmol/l	3.9	6.1	Y
BLOOD GLUCOSE	8.0	mmol/l	3.9	6.1	Y
BLOOD GLUCOSE	10.8	mmol/l	3.9	6.1	Y
BLOOD GLUCOSE	8.1	mmol/l	3.9	6.1	Y
BLOOD LACTATE DEHYDROGENASE	176	U/L	125	220	Y
BLOOD LACTATE DEHYDROGENASE	428	U/L	125	220	Y
BLOOD LACTATE DEHYDROGENASE	782	U/L	125	220	Y
BLOOD LACTATE DEHYDROGENASE	2799	U/L	125	220	Y
BLOOD LACTATE DEHYDROGENASE	7896	U/L	125	220	Y
BLOOD LACTIC ACID	9.5	mmol/l	0.5	1.6	Y
BLOOD LACTIC ACID	25.0	mmol/l	0.5	1.6	Y
BLOOD LACTIC ACID	9.2	mmol/l	0.5	1.6	Y
BLOOD LACTIC ACID	7.9	mmol/l	0.5	1.6	Y
BLOOD LACTIC ACID	4.4	mmol/l	0.5	1.6	Y
BLOOD MAGNESIUM	0.8	mmol/l	0.7	1.0	Y
BLOOD MAGNESIUM	0.67	mmol/l	0.7	1.0	Y
BLOOD MAGNESIUM	0.71	mmol/l	0.7	1.0	Y

Case ID: 22813239

BLOOD MAGNESIUM	1.16	mmol/l	0.7	1.0	Y
BLOOD MAGNESIUM	1.35	mmol/l	0.7	1.0	Y
BLOOD PHOSPHORUS	1.02	mmol/l	0.8	1.5	Y
BLOOD PHOSPHORUS	0.5	mmol/l	0.8	1.5	Y
BLOOD PHOSPHORUS	1.17	mmol/l	0.8	1.5	Y
BLOOD PHOSPHORUS	1.85	mmol/l	0.8	1.5	Y
BLOOD PHOSPHORUS	1.51	mmol/l	0.8	1.5	Y
BLOOD POTASSIUM	4.5	mmol/l	3.5	5.1	Y
BLOOD POTASSIUM	5.2	mmol/l	3.5	5.1	Y
BLOOD POTASSIUM	3.2	mmol/l	3.5	5.1	Y
BLOOD POTASSIUM	4.3	mmol/l	3.5	5.1	Y
BLOOD POTASSIUM	4.5	mmol/l	3.5	5.1	Y
BLOOD PRESSURE MEASUREMENT	122/51	mm[Hg]			Y
BLOOD SODIUM	139	mmol/l	135	145	Y
BLOOD SODIUM	142	mmol/l	135	145	Y
BLOOD SODIUM	137	mmol/l	135	145	Y
BLOOD SODIUM	139	mmol/l	135	145	Y
BLOOD SODIUM	136	mmol/l	135	145	Y
BLOOD UREA	3.8	mmol/l	2.5	7.8	Y
BLOOD UREA	0.9	mmol/l	2.5	7.8	Y
BLOOD UREA	1.3	mmol/l	2.5	7.8	Y
BLOOD UREA	4.3	mmol/l	2.5	7.8	Y
BLOOD UREA	4.7	mmol/l	2.5	7.8	Y
CALCIUM IONISED	1.01	mmol/l	1.05	1.3	Y
CALCIUM IONISED	0.88	mmol/l	1.05	1.3	Y
CALCIUM IONISED	0.89	mmol/l	1.05	1.3	Y
CALCIUM IONISED	0.87	mmol/l	1.05	1.3	Y
CALCIUM IONISED	0.96	mmol/l	1.05	1.3	Y
GAMMA-GLUTAMYLTRANSFERASE	40	U/L	10	60	Y

Case ID: 22813239

GAMMA-GLUTAMYLTRANSFERASE	38	U/L	10	60	Y
GAMMA-GLUTAMYLTRANSFERASE	34	U/L	10	60	Y
GAMMA-GLUTAMYLTRANSFERASE	71	U/L	10	60	Y
GAMMA-GLUTAMYLTRANSFERASE	111	U/L	10	60	Y
GLOMERULAR FILTRATION RATE	62	mL/min/{1.73_m2}	90	120	Y
GLOMERULAR FILTRATION RATE	>90	mL/min/{1.73_m2}	90	120	Y
GLOMERULAR FILTRATION RATE	>90	mL/min/{1.73_m2}	90	120	Y
GLOMERULAR FILTRATION RATE	43	mL/min/{1.73_m2}	90	120	Y
GLOMERULAR FILTRATION RATE	38	mL/min/{1.73_m2}	90	120	Y
HAEMOGLOBIN	6.6	mmol/l	8.5	11	Y
HAEMOGLOBIN	6.8	mmol/l	8.5	11	Y
HAEMOGLOBIN	7.2	mmol/l	8.5	11	Y
HAEMOGLOBIN	6.3	mmol/l	8.5	11	Y
HAEMOGLOBIN	8.5	mmol/l	8.5	11	Y
PLATELET COUNT	152x10^9	/L	150x10^9	450x10^9	Y
PLATELET COUNT	244x10^9	/L	150x10^9	450x10^9	Y
PLATELET COUNT	146x10^9	/L	150x10^9	450x10^9	Y
PLATELET COUNT	85x10^9	/L	150x10^9	450x10^9	N
WHITE BLOOD CELL COUNT	18.7x10^9	/L	4x10^9	11x10^9	Y
WHITE BLOOD CELL COUNT	5.3x10^9	/L	4x10^9	11x10^9	Y
WHITE BLOOD CELL COUNT	36.7x10^9	/L	4x10^9	11x10^9	Y
WHITE BLOOD CELL COUNT	24.2x10^9	/L	4x10^9	11x10^9	Y
WHITE BLOOD CELL COUNT	20.0x10^9	/L	4x10^9	11x10^9	Y

Concomitant Products:

#	Product Name:	Dose/Frequency	Route	Dosage Text	Start Date	End Date	Indication(s)	Interval 1st Dose to Event

FDA - Adverse Event Reporting System (FAERS)
FOIA Case Report Information

Case ID: 22813239

Reporter Source:

Study report?: No **Sender organization:** MACLEODS **503B Compounding Outsourcing Facility?:**

Literature Text: Workum JD, Keyany A, Jaspers TCC. Methylene blue as treatment for vasoplegic shock in severe metformin overdose: A case report. Toxicology Reports. 2023;11:141-144

Case Reports > Toxicol Rep. 2023 Jul 17;11:141-144. doi: 10.1016/j.toxrep.2023.07.005.
eCollection 2023 Dec.

Methylene blue as treatment for vasoplegic shock in severe metformin overdose: A case report

Jessica D Workum [1 2], Ala Keyany [3], Tessa C C Jaspers [3 4]

Affiliations

Affiliations

1 Department of Intensive Care, Elisabeth-TweeSteden Hospital, Tilburg, the Netherlands.
2 Department of Electrical Engineering, Eindhoven University of Technology, the Netherlands.
3 Department of Pharmacy, Elisabeth-TweeSteden Hospital, Tilburg, the Netherlands.
4 Department of Clinical Pharmacy and Pharmacology, University Medical Center Groningen, the Netherlands.

PMID: 37520772 PMCID: PMC10372494 DOI: 10.1016/j.toxrep.2023.07.005
Free PMC article

Abstract

Introduction: Severe metformin overdose can result in life-threatening conditions such as metabolic acidosis with hyperlactatemia and vasoplegic shock. Current treatment guidelines recommend hemodialysis and supportive care. However, this case report presents the use of methylene blue as an additional treatment for severe metformin overdose-induced vasoplegic shock, which is not commonly described in the literature or guidelines.

Case report: A 55-year-old woman presented to the emergency department after ingesting 82.5 g of metformin, resulting in severe metabolic acidosis with hyperlactatemia and refractory vasoplegic shock. Despite continuous hemodialysis and high levels of noradrenalin and vasopressin, the shock persisted. Methylene blue was administered, leading to an immediate and persistent reduction in the noradrenalin dose and rapid shock resolution.

Discussion: This case illustrates the potential use of methylene blue in the treatment of severe metformin overdose. The mechanism for metformin-induced vasoplegia is likely mediated by nitric oxide (NO). Methylene blue has been used to treat NO-mediated vasoplegia in other conditions, such as sepsis and poisoning with beta-blockers and calcium channel blockers, but it is rarely described in metformin toxicity. Methylene blue has a rapid onset of action, with only a few mild side effects. This case report emphasizes the need for clinicians to consider methylene blue as a potential treatment option in cases of refractory vasoplegic shock due to severe metformin overdose.

Keywords: Critically ill; Metformin toxicity; Methylene blue; Vasoplegic shock.

Figures

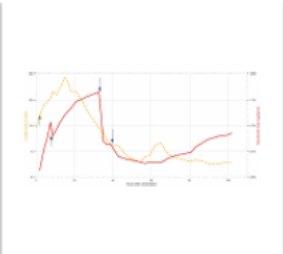

Fig. 1 The course of serum lactate...

LinkOut – more resources

Full Text Sources

Elsevier Science

PubMed Central

FDA - Adverse Event Reporting System (FAERS)
FOIA Case Report Information

Case ID: 22818499

Case Information:

Case Type : Expedited (15-Day) **eSub:** Y **HP:** N **Country:** NL **Event Date:** **Outcomes:** DE , HO , OT **Application Type:**

FDA Rcvd Date: 20-Sep-2023 **Mfr Rcvd Date:** 06-Sep-2023 **Mfr Control #:** NL-NOVOPROD-1101616 **Application #:** 213051

Patient Information:

Age: 55 YR **Sex:** Female **Weight:** 125 KG

Suspect Products:

#	Product Name:	Compounded Drug ?	Dose/Frequency	Route	Dosage Text	Start Date	End Date	Indication(s)
1	Rybelsus 14 mg		/		30 tablets of 14 mg			Product used for unknown indication
2	METFORMIN		/		165 tablets of 500 mg			Product used for unknown indication
3	ACETAMINOPHEN		/		20 tablets of 500 mg			Product used for unknown indication
4	SIMVASTATIN		/		38 tablets of 40 mg			Product used for unknown indication

#	Product Name:	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler	OTC
1	Rybelsus 14 mg		Not Applicable	NA				NOVO NORDISK	
2	METFORMIN		Not Applicable	NA					
3	ACETAMINOPHEN		Not Applicable	NA					
4	SIMVASTATIN		Not Applicable	NA					

Device Products:

#	Brand Name / Common Device Name / Product Code	Similar Device?	Malfunction ?	Device Lot#	Device Usage/ Operator of Device	Remedial Action	Device Problem	Manufacturer Name

FDA - Adverse Event Reporting System (FAERS)
FOIA Case Report Information

Case ID: 22818499

1	//	No	/
2	//	No	/
3	//	No	/
4	//	No	/

Event Information:

Preferred Term (MedDRA Version: v.26.1)	**ReC**
Completed suicide	
Hepatic necrosis	
Lactic acidosis	
Distributive shock	
Toxicity to various agents	
Hypoglycaemia	
Intentional overdose	

Event/Problem Narrative:

This serious Literature case received via Regulatory Authority from serious Literature case entitled "Methylene blue as treatment for vasoplegic shock in severe metformin overdose: A case report" from the NETHERLANDS was published in the journal "Toxicology Reports" NETHERLANDS was reported by a Other Health Care Professional as "Suicide/suicide attempt(Completed suicide)" with an unspecified onset date, "necrosis of the liver(Hepatic necrosis)" with an unspecified onset date, "Lactic acidosis(Lactic acidosis)" with an unspecified onset date, "severe vasoplegic shock(Vasodilatory shock)" with an unspecified onset date, "multiple drug toxicity/Ingestion of 165 tablets of metformin 500 mg (82.5 g, or 660 mg/kg), 20 tablets of acetaminophen 500 mg (10 g, or 80 mg/kg), 38 tablets of simvastatin 40 mg (1520 mg, or 12 mg/kg) and 30 tablets of semaglutide(Drug toxicity)" with an unspecified onset date, "hypoglycemic(Hypoglycemia)" with an unspecified onset date, "Overdose/Ingestion of 165 tablets of metformin 500 mg,(82.5 g, or 660 mg/kg), 20 tablets of acetaminophen,500 mg (10 g, or 80 mg/kg), 38 tablets of simvastatin,40 mg (1520 mg, or 12 mg/kg) and 30 tablets ofsemaglutide 14 mg (420 mg or 3.4 mg/ kg)(Intentional overdose)" with an unspecified onset date, and concerned a 55 Years old Female patient who was treated with Rybelsus 14 mg (SEMAGLUTIDE) from unknown start date for "product used for unknown indication", , a non-Novo Nordisk suspect product METFORMIN (METFORMIN) from unknown start date for "product used for unknown indication", , a non-Novo Nordisk suspect product ACETAMINOPHEN (ACETAMINOPHEN) from unknown start date for "product used for unknown indication", , a non-Novo Nordisk suspect product SIMVASTATIN (SIMVASTATIN) from unknown start date for "product used for unknown indication", Patient's weight: 125 kg Patient's Body mass index: 46 kg/m2 Patient's height was not reported. Current Condition: type II diabetes mellitus(Duration not reported), chronic depression Historical Condition: earlier suicide attempts. Treatment included - ACTIVATED CHARCOAL(CHARCOAL, ACTIVATED), GLUCOSE On an unknown date, the patient presented to the emergency department (ED) after ingestion of 165 tablets of metformin 500 mg (82.5 g, or 660 mg/kg), 20 tablets of acetaminophen 500 mg (10 g, or 80 mg/kg), 38 tablets of simvastatin 40 mg (1520 mg, or 12 mg/kg) and 30 tablets of semaglutide 14 mg (420 mg or 3.4 mg/ kg) as a suicide attempt. Immediately after ingestion, she alerted the emergency services herself and presented within 1 hr of ingestion. In the ED she was alert and cooperative. She was alert with a Glasgow Coma Scale of 15. Glucose(blood glucose) was mildly elevated tob18.4 mmol/L. Due to the expected severity of the intoxication and the early presentation, she was treated with activated charcoal and immediately admitted to the intensive care unit (ICU) for continuous hemodialysis as the severe lactic acidosis indicated a severe metformin overdose. After admission to the ICU, she deteriorated rapidly. Patient became tachypneic

and was intubated for exhaustion. Developed rapid onset shock which required continuous fluid resuscitation. Patient became hypoglycemic, most likely due to co-ingestion of metformin and semaglutide, for which a continuous 50 % glucose infusion was started. Four hours post-ingestion, approximately three hours after presentation but prior to the initiation of hemodialysis, both acetaminophen and metformin levels were drawn. On unknown dates, the patient's blood glucose(Blood glucose) was reported as 5.6 mmol/L on day 1, 8.0 mmol/L on day 2, 10.8mmol/L on day 3, 8.1 mmol/L on day 4. The patient remained stable for the next 24 h. Next day developed progressive shock again.As there were no curative options, treatment was switched to palliative care and she passed away. Treatment included - ACTIVATED CHARCOAL(CHARCOAL, ACTIVATED), GLUCOSE On an unknown date, the patient presented to the emergency department (ED) after ingestion of 165 tablets of metformin 500 mg (82.5 g, or 660 mg/kg), 20 tablets of acetaminophen 500 mg (10 g, or 80 mg/kg), 38 tablets of simvastatin 40 mg (1520 mg, or 12 mg/kg) and 30 tablets of semaglutide 14 mg (420 mg or 3.4 mg/kg) as a suicide attempt. Immediately after ingestion, she alerted the emergency services herself and presented within 1 hr of ingestion. In the ED she was alert and cooperative. She was alert with a Glasgow Coma Scale(Coma scale) of 15. Glucose(blood glucose) was mildly elevated tob18.4 mmol/L. Due to the expected severity of the intoxication and the early presentation, she was treated with activated charcoal and immediately admitted to the intensive care unit (ICU) for continuous hemodialysis as the severe lactic acidosis indicated a severe metformin overdose. After admission to the ICU, she deteriorated rapidly. Patient became tachypneic and was intubated for exhaustion. Developed rapid onset shock which required continuous fluid resuscitation. Patient became hypoglycemic, most likely due to co-ingestion of metformin and semaglutide, for which a continuous 50 % glucose infusion was started. Four hours post-ingestion, approximately three hours after presentation but prior to the initiation of hemodialysis, both acetaminophen and metformin levels were drawn. On unknown dates, the patient's blood glucose(Blood glucose) was reported as 5.6 mmol/L on day 1, 8.0 mmol/L on day 2, 10.8mmol/L on day 3, 8.1 mmol/L on day 4. The patient remained stable for the next 24 h. Next day developed progressive shock again.As there were no curative options, treatment was switched to palliative care and she passed away. On unknown date, the below tests were performed: Alanine Aminotransferase(Alanine Aminotransferase) : 99 U/L , 757 U/L, 148 U/L, 4171U/L Aspartate Aminotransferase(Aspartate Aminotransferase) :10518U/L, 52 U/L, 3100U/L, 805U/L, 224U/L Base Excess(Base excess) :-14.6 mmol/l, -11.8 mmol/l, -6 mmol/l, -4.4 mmol/l,0.1 mmo/l (Normal range -2 to 2 mmol/L) Albumin(Blood albumin) :25g/L, 38 g/L Alkaline Phosphatase(Blood alkaline phosphatase) : On unknown dates alkaline phosphatase was 80, 107, 831(units not specified) Bicarbonate (Blood bicarbonate) :16 mmol/L , 20.5 mmol/L , 20.6 mmol/L ,24.3 mmol/L ,16 mmol/L , 14.6 mmol/L Total Bilirubin(Blood bilirubin) :On unknown dates 12, 112, 78, 11 umol/L (micromole per litre) Units non codable Creatine kinase(Blood creatine phosphokinase) was normal Creatinine(Blood creatinine) :60 mmol/L, 90 mmol/L, 51 mmol/L, 136 mmol/L, 122 mmol/L serum creatinine(Blood creatinine) :~90 umol/L(micromole per litre), units non codable Lactate Dehydrogenase(Blood lactate dehydrogenase) :428 U/L, 7896U/L, 176U/L, 2799U/L, 782U/L Lactate(Blood lactic acid) : 7.9mmol/L, 25 mmol/L, 9.2mmol/L, 9.5mmol/L Magnesium (Blood magnesium) :0.67mmol/L , 1.35 mmol/L, 0.71 mmol/L, 1.16 mmol/L Phosphate(Blood phosphorus) : 0.5 mmol/L,1.02 mmol/L,1.51 mmol/L,1.17 mmol/L,1.85 mmol/L Potassium(Blood potassium) :3.2 mmol/L,5.2 mmol/L,4.5 mmol/L,4.3 mmol/L Blood pressure(Blood pressure measurement) :122/51mmHg Sodium(Blood sodium) :136 mmol/L,137 mmol/L,142 mmol/L,139 mmol/L Urea (blood Urea) :1.3 mmol/L, 4.7 mmol/L, 4.3 mmol/L,0.9 mmol/L,3.8 mmol/L Body temperature(Body temperature) :35.7degree Celsius Calcium ionized (Calcium ionized) :0.88mmol/L, 0.96mmol/L,0.89 mmol/L,0.87 mmol/L,1.01 mmol/L,0.88 mmol/L Coagulation(coagulation TEST) was normal CT scan (Computerised tomogram) : the thorax and abdomen showed extensive necrosis of the liver Gamma-Glutamyl Transferase(Gamma-Glutamyl Transferase) :111U/L,71U/L,34U/L,38U/L Glomerular Filtration Rate (GFR)(Glomerular Filtration Rate) :43 mL/min/1.73m2,90 mL/min/1.73m2,62 mL/min/1.73m2,38 mL/min/1.73m2 Hematocrit (Hematocrit): On an unknown date, Hematocrit values were reported 0.32,0.37,0.43(Units not reported) Hemoglobin(Haemoglobin) :7.2mmol/L,6.6 mmol/L,8.5 mmol/L,6.3 mmol/L,6.8 mmol/L Liver panel(Liver function test) : On unknown day, liver function test was normal PCO2(PCO2): 4.9kPa,6,5kPa.6,6kPa.2kPa pH(pH body fluid) : On unknown day, pH was 7.19,7.36,7.27,7.43,7.10 Platelets(Platelet count) : 152 10*9/L,244 10*9/L,85 10*9/L,146 10*9/L pO2(pO2) :14.3 kPa,11.3 kPa,9.6 kPa,9.5 kPa,12.7kPa pO2 arterial(pO2) :9.5 kPa, 11.3kPa Respiratory rate(Respiratory rate) :Normal Sinus rhythm(Sinus rhythm) :89/min White Blood Cells(White Blood Cell count) :5.3 10*9/L,24.2 10*9/L,36.7 10*9/L,18.7 10*9/L,4.4 10*9/L Batch numbers not provided. Action taken to Rybelsus 14 mg was Not reported. Action taken to METFORMIN was Not reported. Action taken to ACETAMINOPHEN was Not reported. Action taken to SIMVASTATIN was Not reported. The outcome for the event "Suicide/suicide attempt(Completed suicide)" was Fatal. The outcome for the event "necrosis of the liver(Hepatic necrosis)" was Fatal. The outcome for the event "Lactic acidosis(Lactic acidosis)" was Fatal. The outcome for the event "severe vasoplegic shock(Vasodilatory shock)" was Fatal. The outcome for the event "multiple drug toxicity/Ingestion of 165 tablets of metformin 500 mg (82.5 g, or 660 mg/kg), 20 tablets of acetaminophen 500 mg (10 g, or 80 mg/kg), 38 tablets of simvastatin 40 mg (1520 mg, or 12 mg/kg) and 30 tablets of semaglutide(Drug toxicity)" was Fatal. The outcome for the event "hypoglycemic(Hypoglycemia)" was Not Reported. The outcome for the event "Overdose/Ingestion of 165 tablets of metformin 500 mg,(82.5 g, or 660 mg/kg), 20 tablets of acetaminophen,500 mg (10 g, or 80 mg/kg), 38 tablets of simvastatin,40 mg (1520 mg, or 12 mg/kg) and 30 tablets ofsemaglutide 14 mg (420 mg or

Case ID: 22818499

3.4 mg/ kg)(Intentional overdose)" was Fatal. Since last submission: RA classification added Reports sent to RA updated to yes Lab data updated New events Hepatic necrosis,Vasodilatory shock,Lactic acidosis added Event verbatim updated for suicide, Overdose and hospitalization criteria added Cause of death updated Company Comment: Completed suicide, Hepatic necrosis, Lactic acidosis, Distributive shock and Toxicity to various agents are assessed as unlisted, Hypoglycaemia is assessed as listed according to the Novo Nordisk current CCDS on Rybelsus. Medical history of chronic depression and prior suicide attempts could be considered as a possible alternative explanation for the reported completed suicide. Intention overdose with various products is assessed as confounder. This single case report is not considered to change the current knowledge of the safety profile of Rybelsus. References included: Reference Type: E2B Company Number Reference ID#: NL-NOVOPROD-1101616 Reference Notes: EVDUP#NOVOPROD Reference Type: E2B Report Duplicate Reference ID#: NL-SANDOZ-SDZ2023NL009965 Reference Notes: NL-EMA-DD-20230818-6644993-075413 Reference Type: E2B Report Duplicate Reference ID#: NL-002147023-NVSC2023NL173469 Reference Notes: EVDUP#002147023 Reference Type: E2B Report Duplicate Reference ID#: NL-SANDOZ-SDZ2023NL009965 Reference Notes: EVDUP#ORG100006023 Reference Type: E2B Report Duplicate Reference ID#: NL-EMA-DD-20230818-6644993-075413 Reference Notes: NL-SANDOZ-SDZ2023NL009965 Reference Type: E2B Report Duplicate Reference ID#: NL-ORGANON-O2308NLD000287 Reference Notes: EVDUP#ORGANON Reference Type: E2B Report Duplicate Reference ID#: 10015693370 Reference Notes: EVDUP# Reference Type: E2B Report Duplicate Reference ID#: 10015703377 Reference Notes: EVDUP# Reference Type: E2B Report Duplicate Reference ID#: 10015719594 Reference Notes: EVDUP# Reference Type: E2B Report Duplicate Reference ID#: 10015725885 Reference Notes: EVDUP#

Relevant Medical History:

Disease/Surgical Procedure	Start Date	End Date	Continuing?
Type 2 diabetes mellitus			Yes
Depression			Yes
Suicide attempt			No

Medical History Product(s)	Start Date	End Date	Indications	Events

Relevant Laboratory Data:

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail
ALANINE AMINOTRANSFERASE	99	U/L	10	45	N
ALANINE AMINOTRANSFERASE	757	U/L	10	45	N
ALANINE AMINOTRANSFERASE	148	U/L	10	45	N
ALANINE AMINOTRANSFERASE	4171	U/L	10	45	N
ASPARTATE AMINOTRANSFERASE	10518	U/L	10	40	N
ASPARTATE AMINOTRANSFERASE	52	U/L	10	40	N
ASPARTATE AMINOTRANSFERASE	3100	U/L	10	40	N

Case ID: 22818499

ASPARTATE AMINOTRANSFERASE	805	U/L	10	40	N
ASPARTATE AMINOTRANSFERASE	224	U/L	10	40	N
BASE EXCESS					Y
BASE EXCESS					Y
BASE EXCESS					Y
BASE EXCESS					Y
BASE EXCESS					Y
BLOOD ALBUMIN	25	g/L	35	50	N
BLOOD ALBUMIN	38	g/L	35	50	N
BLOOD ALKALINE PHOSPHATASE					Y
BLOOD ALKALINE PHOSPHATASE					Y
BLOOD ALKALINE PHOSPHATASE					Y
BLOOD BICARBONATE	16	mmol/L	22	26	N
BLOOD BICARBONATE	20.5	mmol/L	22	26	N
BLOOD BICARBONATE	20.6	mmol/L	22	26	N
BLOOD BICARBONATE	24.3	mmol/L	22	26	N
BLOOD BICARBONATE	16	mmol/L	22	26	N
BLOOD BICARBONATE	14.6	mmol/L	22	26	N
BLOOD BILIRUBIN					Y
BLOOD BILIRUBIN					Y
BLOOD BILIRUBIN					Y
BLOOD BILIRUBIN					Y
BLOOD CREATINE PHOSPHOKINASE					Y
BLOOD CREATININE	60	mmol/L	45	90	N
BLOOD CREATININE	90	mmol/L	45	90	N
BLOOD CREATININE	51	mmol/L	45	90	N
BLOOD CREATININE	136	mmol/L	45	90	N
BLOOD CREATININE	122	mmol/L	45	90	N
BLOOD CREATININE					Y

FDA - Adverse Event Reporting System (FAERS)
FOIA Case Report Information

Case ID: 22818499

BLOOD GLUCOSE	18.4	mmol/L	3.9	6.1	N
BLOOD GLUCOSE	5.6	mmol/L	3.9	6.1	N
BLOOD GLUCOSE	8.0	mmol/L	3.9	6.1	N
BLOOD GLUCOSE	10.8	mmol/L	3.9	6.1	N
BLOOD GLUCOSE	8.1	mmol/L	3.9	6.1	N
BLOOD LACTATE DEHYDROGENASE	428	U/L	125	220	N
BLOOD LACTATE DEHYDROGENASE	7896	U/L	125	220	N
BLOOD LACTATE DEHYDROGENASE	176	U/L	125	220	N
BLOOD LACTATE DEHYDROGENASE	2799	U/L	125	220	N
BLOOD LACTATE DEHYDROGENASE	782	U/L	125	220	N
BLOOD LACTIC ACID	7.9	mmol/L	0.5	1.6	N
BLOOD LACTIC ACID	25	mmol/L	0.5	1.6	N
BLOOD LACTIC ACID	9.2	mmol/L	0.5	1.6	N
BLOOD LACTIC ACID	9.5	mmol/L	0.5	1.6	N
BLOOD MAGNESIUM	0.67	mmol/L	0.7	1	N
BLOOD MAGNESIUM	1.35	mmol/L	0.7	1	N
BLOOD MAGNESIUM	0.71	mmol/L	0.7	1	N
BLOOD MAGNESIUM	1.16	mmol/L	0.7	1	N
BLOOD PHOSPHORUS	0.5	mmol/L	0.8	1.5	N
BLOOD PHOSPHORUS	1.02	mmol/L	0.8	1.5	N
BLOOD PHOSPHORUS	1.51	mmol/L	0.8	1.5	N
BLOOD PHOSPHORUS	1.17	mmol/L	0.8	1.5	N
BLOOD PHOSPHORUS	1.85	mmol/L	0.8	1.5	N
BLOOD POTASSIUM	3.2	mmol/L			N
BLOOD POTASSIUM	5.2	mmol/L			N
BLOOD POTASSIUM	4.5	mmol/L			N
BLOOD POTASSIUM	4.3	mmol/L			N
BLOOD PRESSURE MEASUREMENT	122/51	mmHg			N
BLOOD SODIUM	136	mmol/L	135	145	N

Case ID: 22818499

BLOOD SODIUM	137	mmol/L	135	145	N
BLOOD SODIUM	142	mmol/L	135	145	N
BLOOD SODIUM	139	mmol/L	135	145	N
BLOOD UREA	1.3	mmol/L	2.5	7.8	N
BLOOD UREA	4.7	mmol/L	2.5	7.8	N
BLOOD UREA	4.3	mmol/L	2.5	7.8	N
BLOOD UREA	0.9	mmol/L	2.5	7.8	N
BLOOD UREA	3.8	mmol/L	2.5	7.8	N
BODY MASS INDEX	46	kg/m2			N
BODY TEMPERATURE	35.7	degree Celsius			N
BODY TEMPERATURE	35.7	degree Celsius			N
CALCIUM IONISED	0.96	mmol/L	1.05	1.3	N
CALCIUM IONISED	0.89	mmol/L	1.05	1.3	N
CALCIUM IONISED	0.87	mmol/L	1.05	1.3	N
CALCIUM IONISED	1.01	mmol/L	1.05	1.3	N
CALCIUM IONISED	0.88	mmol/L	1.05	1.3	N
COAGULATION TEST					Y
COMA SCALE					Y
COMPUTERISED TOMOGRAM					Y
GAMMA-GLUTAMYLTRANSFERASE	111	U/L	10	60	N
GAMMA-GLUTAMYLTRANSFERASE	71	U/L	10	60	N
GAMMA-GLUTAMYLTRANSFERASE	34	U/L	10	60	N
GAMMA-GLUTAMYLTRANSFERASE	38	U/L	10	60	N
GLOMERULAR FILTRATION RATE	43	mL/min/1.73m2	90	120	N
GLOMERULAR FILTRATION RATE	90	mL/min/1.73m2	90	120	N
GLOMERULAR FILTRATION RATE	62	mL/min/1.73m2	90	120	N
GLOMERULAR FILTRATION RATE	38	mL/min/1.73m2	90	120	N
GLOMERULAR FILTRATION RATE	90	mL/min/1.73m2	90	120	N
HAEMATOCRIT					Y

FDA - Adverse Event Reporting System (FAERS)
FOIA Case Report Information

Case ID: 22818499

HAEMATOCRIT					Y
HAEMATOCRIT					Y
HAEMATOCRIT					Y
HAEMOGLOBIN	7.2	mmol/L	8.5	11	N
HAEMOGLOBIN	6.6	mmol/L	8.5	11	N
HAEMOGLOBIN	8.5	mmol/L	8.5	11	N
HAEMOGLOBIN	6.3	mmol/L	8.5	11	N
HAEMOGLOBIN	6.8	mmol/L	8.5	11	N
LIVER FUNCTION TEST					Y
PCO2	4.9	kPa	4.7	6	N
PCO2	6	kPa	4.7	6	N
PCO2	5.6	kPa	4.7	6	N
PCO2	6.2	kPa	4.7	6	N
PH BODY FLUID					Y
PH BODY FLUID					Y
PH BODY FLUID					Y
PH BODY FLUID					Y
PH BODY FLUID					Y
PLATELET COUNT	152	10*9/L			N
PLATELET COUNT	244	10*9/L			N
PLATELET COUNT	85	10*9/L			N
PLATELET COUNT	146	10*9/L			N
PO2	14.3	kPa	11	13	N
PO2	11.3	kPa	11	13	N
PO2	9.6	kPa	11	13	N
PO2	9.5	kPa	11	13	N
PO2	12.7	kPa	11	13	N
PO2	9.5	kPa	11	13	N
PO2	11.3	kPa	11	13	N

FDA - Adverse Event Reporting System (FAERS)
FOIA Case Report Information

Case ID: 22818499

RESPIRATORY RATE					Y
SINUS RHYTHM	89	/min			N
WHITE BLOOD CELL COUNT	5.3	10*9/L	4	11	N
WHITE BLOOD CELL COUNT	24.2	10*9/L	4	11	N
WHITE BLOOD CELL COUNT	36.7	10*9/L	4	11	N
WHITE BLOOD CELL COUNT	18.7	10*9/L	4	11	N
WHITE BLOOD CELL COUNT	4.4	10*9/L	4	11	N
BASE EXCESS	0.1	mmol/L			N

Concomitant Products:

#	Product Name:	Dose/Frequency	Route	Dosage Text	Start Date	End Date	Indication(s)	Interval 1st Dose to Event

Reporter Source:

Study report?: No **Sender organization:** NOVO NORDISK **503B Compounding Outsourcing Facility?:**

Literature Text: Workum, Jessica D et. al;. Methylene blue as treatment for vasoplegic shock in severe metformin overdose: A case report. Toxicology Reports. 2023;11:141-144

Toxicology Reports 11 (2023) 141–144

Contents lists available at ScienceDirect

Toxicology Reports

journal homepage: www.elsevier.com/locate/toxrep

Methylene blue as treatment for vasoplegic shock in severe metformin overdose: A case report

Jessica D. Workum [a,b,*], Ala Keyany [c], Tessa C.C. Jaspers [c,d]

[a] Department of Intensive Care, Elisabeth-TweeSteden Hospital, Tilburg, the Netherlands
[b] Department of Electrical Engineering, Eindhoven University of Technology, the Netherlands
[c] Department of Pharmacy, Elisabeth-TweeSteden Hospital, Tilburg, the Netherlands
[d] Department of Clinical Pharmacy and Pharmacology, University Medical Center Groningen, the Netherlands

ARTICLE INFO

Handling Editor: Dr. L.H. Lash

Keywords:
Metformin toxicity
Methylene blue
Vasoplegic shock
Critically ill

ABSTRACT

Introduction: Severe metformin overdose can result in life-threatening conditions such as metabolic acidosis with hyperlactatemia and vasoplegic shock. Current treatment guidelines recommend hemodialysis and supportive care. However, this case report presents the use of methylene blue as an additional treatment for severe metformin overdose-induced vasoplegic shock, which is not commonly described in the literature or guidelines.
Case report: A 55-year-old woman presented to the emergency department after ingesting 82.5 g of metformin, resulting in severe metabolic acidosis with hyperlactatemia and refractory vasoplegic shock. Despite continuous hemodialysis and high levels of noradrenalin and vasopressin, the shock persisted. Methylene blue was administered, leading to an immediate and persistent reduction in the noradrenalin dose and rapid shock resolution.
Discussion: This case illustrates the potential use of methylene blue in the treatment of severe metformin overdose. The mechanism for metformin-induced vasoplegia is likely mediated by nitric oxide (NO). Methylene blue has been used to treat NO-mediated vasoplegia in other conditions, such as sepsis and poisoning with beta-blockers and calcium channel blockers, but it is rarely described in metformin toxicity. Methylene blue has a rapid onset of action, with only a few mild side effects. This case report emphasizes the need for clinicians to consider methylene blue as a potential treatment option in cases of refractory vasoplegic shock due to severe metformin overdose.

1. Introduction

Severe metformin overdose is a life-threatening condition that can lead to metabolic acidosis with hyperlactatemia and cardiovascular collapse, including vasoplegic shock. Treatment consists of hemodialysis and supportive care. We present a case of severe vasoplegic shock due to severe metformin toxicity, treated with methylene blue in addition to conventional treatment, which resulted in rapid shock resolution. The use of methylene blue in the treatment of severe metformin overdose has only been described in a few cases and is not described in current guidelines as a treatment option. This case illustrates the potential use of methylene blue in severe metformin overdose.

2. Case description

A 55-year-old female (125 kg, body mass index 46 kg/m^2) presented to the emergency department (ED) after ingestion of 165 tablets of metformin 500 mg (82.5 g, or 660 mg/kg), 20 tablets of acetaminophen 500 mg (10 g, or 80 mg/kg), 38 tablets of simvastatin 40 mg (1520 mg, or 12 mg/kg) and 30 tablets of semaglutide 14 mg (420 mg or 3.4 mg/kg) as a suicide attempt. Immediately after ingestion, she alerted the emergency services herself and presented within 1 h of ingestion. In the ED she was alert and cooperative. Her medical history comprised of earlier suicide attempts with chronic depression and type II diabetes. Her initial vital signs were normal: she had a normal respiratory rate and an oxygen saturation of 95 % without supplemental oxygen, blood pressure was 122/51 mmHg with a normal sinus rhythm of 89/min, and she was alert with a Glasgow Coma Scale of 15. Glucose was mildly

* Correspondence to: Department of Intensive Care, Elisabeth-TweeSteden Hospital, 5022 GC Tilburg, the Netherlands.
E-mail address: j.workum@etz.nl (J.D. Workum).

https://doi.org/10.1016/j.toxrep.2023.07.005
Received 6 June 2023; Received in revised form 1 July 2023; Accepted 15 July 2023
Available online 17 July 2023

elevated (18.4 mmol/L). Her body temperature was 35.7 °C. Initial blood gas analysis showed a pH of 7.19, a pCO2 of 5.6 kPa, bicarbonate of 16 mmol/L, base excess of − 11.8 and lactate levels of 9.5 mmol/L. Liver panel, coagulation and creatine kinase (CK) levels were normal. Serum creatinine was 90 μmol/L. Results are shown in Table 1. Due to the expected severity of the intoxication and the early presentation, she was treated with activated charcoal and immediately admitted to the intensive care unit (ICU) for continuous hemodialysis as the severe lactic acidosis indicated a severe metformin overdose [1].

After admission to the ICU, she deteriorated rapidly. She became tachypneic and was intubated for exhaustion. She developed rapid onset shock, which required continuous fluid resuscitation, noradrenalin (rapidly increasing up to 1.2 μg/kg/min) and vasopressin (0.03 IE/min). Hydrocortisone was added because of the refractory nature of the shock. Continuous hemodialysis was initiated within 3 h after presentation. Arterial blood gas and lactate levels were monitored every two hours as a marker for resolution of the metformin overdose. She became hypoglycemic, most likely due to co-ingestion of metformin and semaglutide, for which a continuous 50 % glucose infusion was started. Four hours post-ingestion, approximately three hours after presentation but prior to the initiation of hemodialysis, both acetaminophen and metformin levels were drawn. Acetaminophen levels 4 h after ingestion were 29 mg/L, so treatment with N-acetylcysteine was withheld. Metformin levels were drawn with the intent of retrospective analysis, as the results took one week to complete. Results revealed a level of 622.9 mg/L. However, as these findings were not available during the initial treatment, they had no bearing on medical decision making.

Table 1
Laboratory results during admission.

Measurement	Normal values	Day 0	Day 1	Day 2	Day 3	Day 4
Hemoglobin (mmol/L)	8.5–11	8.5	7.2	6.8	6.6	6.3
Hematocrit	0.40–0.54	0.43	0.37	0.32	0.32	0.32
White Blood Cells ($10^{9/L}$)	4–11	5.3	36.7	24.2	18.7	20.0
Platelets ($10^{9/L}$)	150–450	152	244	146	-	85
Glucose (mmol/L)	3.9–6.1	18.4	5.6	8.0	10.8	8.1
Urea (mmol/L)	2.5–7.8	3.8	0.9	1.3	4.3	4.7
Creatinine (μmol/L)	45–90	90	60	51	122	136
Glomerular Filtration Rate (GFR) (CKD-EPI) (mL/min/1.73 $m^{2)}$	90–120	62	> 90	> 90	43	38
Sodium (mmol/L)	135–145	139	142	137	139	136
Potassium (mmol/L)	3.5–5.1	5.2	3.2	4.3	4.5	4.5
Magnesium (mmol/L)	0.7–1.0	0.8	0.67	0.71	1.16	1.35
Phosphate (mmol/L)	0.8–1.5	1.02	1.17	0.50	1.85	1.51
Ionized Calcium (mmol/L)	1.05–1.3	1.01	0.88	0.89	0.87	0.96
Albumin (g/L)	35–50	38	-	-	25	-
Total Bilirubin (μmol/L)	3–22	11	12	26	78	112
Alkaline Phosphatase (U/L)	40–150	107	90	80	139	831
Gamma-Glutamyl Transferase (GGT) (U/L)	10–60	40	38	34	71	111
Aspartate Aminotransferase (ASAT) (U/L)	10–40	52	224	805	3100	10,518
Alanine Aminotransferase (ALAT) (U/L)	10–45	52	99	148	757	4171
Lactate Dehydrogenase (LDH) (U/L)	125–220	176	428	782	2799	7896
pH (arterial)	7.35–7.45	7.19	7.10	7.43	7.36	7.27
pO2 (arterial) (kPa)	11–13	14.3	12.7	9.5	11.3	9.6
pCO2 (arterial) (kPa)	4.7–6.0	5.6	6.2	4.9	4.9	6.0
Bicarbonate (arterial) (mmol/L)	22–26	16	14.6	24.3	20.5	20.6
Base Excess (arterial) (mmol/L)	-2 to + 2	-11.8	-14.6	0.1	-4.4	-6
Lactate (arterial) (mmol/L)	0.5–1.6	9.5	25.0	9.2	7.9	4.4

Using bedside ultrasonography in conjunction with invasive hemodynamic monitoring using a pulse index continuous cardiac output device (PiCCO), cardiogenic, obstructive, and hypovolemic shock were excluded. Causes of distributive shock other than vasoplegia, such as septic shock and anaphylaxis, were considered unlikely due to the clinical presentation and otherwise normal appearance. As there was no cardiogenic component to the shock, venoarterial extracorporeal membrane oxygenation (va-ECMO) was not considered to be of added value. Therefore, the current condition was considered severe vasoplegic shock due to metformin. As the already high doses of noradrenalin and vasopressin were considered insufficient, we decided to treat the patient with methylene blue. Subsequently, 250 mg of methylene blue (2 mg/kg) was administered intravenously over 5 min. The noradrenalin dose could be reduced from 1.2 μg/kg/min to 0.5 μg/kg/min within 15 min, indicating rapid shock reversal, which was maintained at 0.5 μg/kg/min for 6 h without additional intervention. A second bolus of methylene blue 2 mg/kg was then administered in an attempt to further reduce noradrenalin levels. This allowed the noradrenalin dose to be lowered to 0.25 μg/kg/min (Fig. 1).

The patient remained stable for the next 24 h. Lactate levels decreased from a maximum of 29 mmol/L to 4.4 mmol/L, indicating metformin clearance and improvement of shock. However, the next day, lactate levels began to increase again while still on hemodialysis. She developed severe liver test abnormalities, with alanine aminotransferase (ASAT) of 10518 U/L and aspartate aminotransferase (ALAT) of 4171 U/L, and developed progressive shock again. A computed tomography (CT) scan of both the thorax and abdomen showed extensive necrosis of the liver. As there were no curative options, treatment was switched to palliative care and she passed away. Permission for post-mortem examination was not obtained. However, her next of kin signed informed consent for publication.

3. Discussion

We presented a case of severe vasoplegic shock due to metformin toxicity, which was treated with methylene blue in addition to conventional treatment, resulting in rapid shock resolution.

Severe metformin poisoning can lead to metabolic acidosis with hyperlactatemia (metformin associated lactic acidosis, or MALA), glucose derangement (both hyperglycemia and hypoglycemia) and shock. Treatment consists of enhancement of drug elimination via hemodialysis and supportive care. In a scoping review, Juneja et al. summarize the symptomology, clinical interventions and outcomes of 242 patients with metformin poisoning [2]. MALA, defined as lactate levels above 5 mmol/L with concurrent acidosis, was found in 92.6 % of patients and 68.6 % required renal replacement therapy. In patients with acute ingestion, they report a median ingested dose of 42.5 g, mean serum levels of 108.7 mg/L and a mortality of 19.3 %. They did not report any use of methylene blue.

The mechanism of hyperlactatemia in metformin toxicity mainly follows two pathways: the inhibition of mitochondrial glycerol 3-phosphate dehydrogenase (mGPD) and the inhibition of mitochondrial respiratory chain complex 1 (mRCC1) of the electron transport chain [3]. Inhibition of mGPD causes a decrease in gluconeogenesis, which reduces the production of glucose from pyruvate and results in the conversion of pyruvate to lactate. Inhibition of mRCC1 impairs oxidative phosphorylation, leading to mitochondrial dysfunction. This increases the amount of reduced nicotinamide adenine dinucleotide (NADH), which enhances the conversion of pyruvate into lactate. The mechanism for metformin induced vasoplegia is most likely mediated by nitric oxide (NO). Metformin has been shown to increase adenosine monophosphate-activated

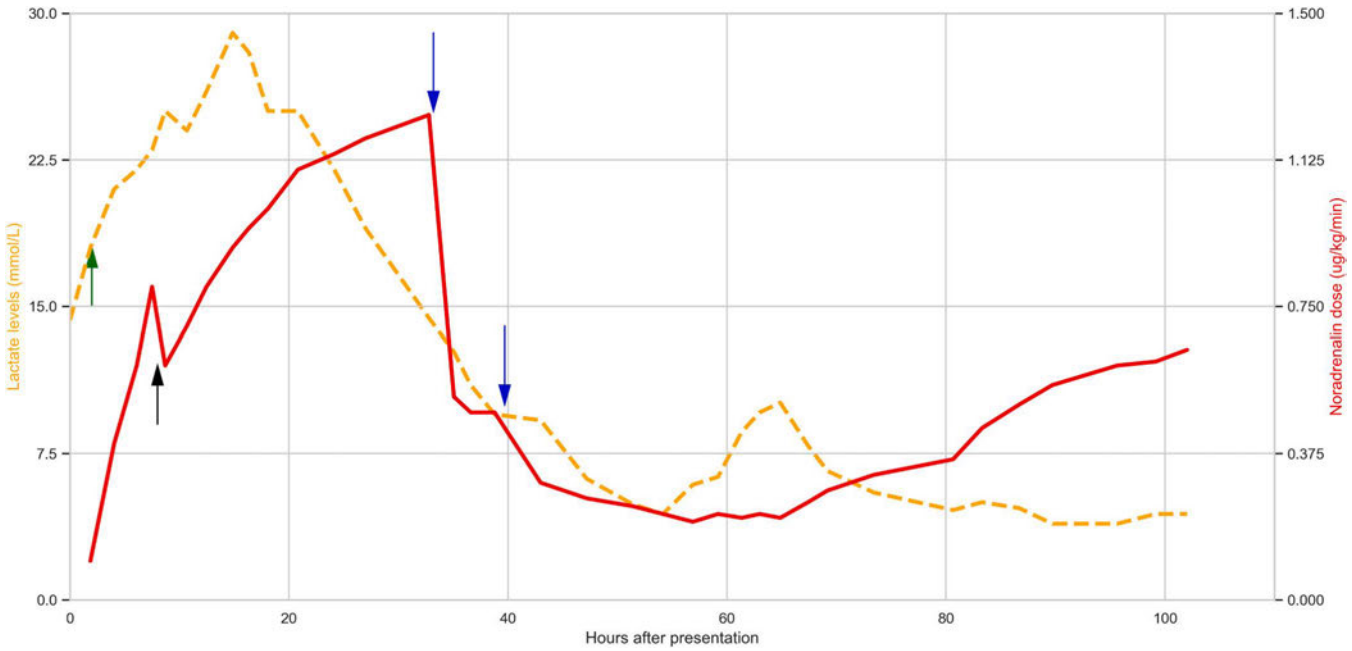

Fig. 1. The course of serum lactate (orange dashed line, left y-axis) and noradrenalin dose (red solid line, right y-axis). The green arrow (arrow 1) indicates the initiation of continuous hemodialysis. The black arrow (arrow 2) indicated the addition of vasopressin and hydrocortisone to noradrenalin. The blue arrows (arrows 3 and 4) indicate a bolus of methylene blue 2 mg/kg intravenously. As noradrenalin levels could be rapidly decreased after the first methylene blue injection, the first blue arrow therefore also indicates the start of shock reversal.

protein kinase phosphorylation, which activates endothelial nitric oxide synthase (eNOS) and increases NO bioactivity, leading to increased NO levels and subsequent vasodilation [4]. NO-mediated vasoplegia contributes to hyperlactatemia in several ways: first, it leads to shock which causes systemic tissue hypoxia; second, NO itself can cause mitochondrial dysfunction which may increase the production of lactic acid via a mechanism similar to sepsis induced lactic acidosis.

Methylene blue is a commonly used synthetic dye, but is also used in medicine to reverse methemoglobinemia. In toxicology, it is therefore known to reverse the effects of sodium nitrite poisoning [5]. However, methylene blue also reduces NO production, by directly inhibiting NO synthase, but also by binding to the iron heme-moiety of soluble guanylate cyclase, thus competitively blocking the target enzyme of NO [6,7]. This reduces NO-mediated vasodilation. Therefore, methylene blue has been used in cases where NO-mediated vasoplegia is suspected, such as in sepsis and poisoning with beta-blockers and calcium channel blockers [8,9].

Methylene blue as rescue therapy for metformin toxicity has only been described in literature in a few case reports. Graham et al. [10] described a case of 44 year old man who ingested 35 g of metformin and developed severe lactic acidosis and shock. He received daily hemodialysis and methylene blue (2 mg/kg bolus with a continuous infusion of 0.25 mg/kg/h for 20 h). He was weaned off vasopressors after 2 days of ICU admission and made a full recovery. Plumb et al. [11] described a case of a 66 year old woman presenting with severe lactic acidosis due to an accidental metformin overdose of unknown quantity, also successfully treated with renal replacement therapy and methylene blue (2 mg/kg loading dose and continuous infusion of 2 mg/kg/h for 12 h). Tallman et al. [12] used va-ECMO as the mainstay of their treatment in addition to conventional treatment, but also describe a beneficial effect of methylene blue on the patient's blood pressure.

Other than by reducing NO levels, methylene blue may also have a direct positive effect on hyperlactatemia in metformin poisoning. It can act as an alternative electron carrier by accepting electrons from NADH and subsequently delivering them to ubiquinone or cytochrome c, therefore bypassing the electron transport chain impediment at mRCC1, which is impaired in severe metformin poisoning [2]. Therefore, it may also improve MALA. In our patient, this effect could not have been distinguished from the effect of hemodialysis on lactate clearance.

Methylene blue works within minutes and has a maximum effect in 30–60 min after administration. The recommended dose is 1–2 mg/kg intravenously, with a maximum of 7 mg/kg. Approximately 75 % of methylene blue is excreted by the kidneys, either unchanged or as leucomethylene blue. It has a terminal half-life of approximately 25 h [13]. Due to the long half-life of methylene blue, we decided that continuous infusion would not have any benefits over repeated boluses, but would increase the chance of exceeding the recommended dose.

The side effects of methylene blue are mild. They include short-term blue discoloration of the skin, urine and feces, which also occurred in our patient. Other side effects include gastro-intestinal side effects such as nausea and diarrhea. Methylene blue should be administered with caution in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency, as it can induce hemolytic anemia. In patients with serotonergic co-medication, methylene blue could increase the risk of developing serotonergic syndrome. In both cases, the risk should be weighed against the potential benefits. In doses that exceed the recommended maximum dose of 7 mg/kg, methylene blue can itself induce the formation of methemoglobinemia.

Our patient presented with a severe metformin overdose. She ingested 82.5 g (660 mg/kg), which is double the median dose described in the literature. The metformin level sampled approximately 4 h after ingestion was 622.9 mg/L, which is 6 times the average metformin levels in toxicologic literature [2]. Despite continuous hemodialysis being initiated early, lactate levels continued to rise until 16 h after presentation. Lactate levels served as a treatment efficacy marker: when lactate levels started to decrease, this indicated that metformin levels themselves were also decreasing [14,15]. We therefore hypothesized that metformin-induced NO production would also decrease. This is why, in contrast to the use of methylene blue in sepsis in which NO production is ongoing, we expected a positive treatment effect of methylene blue in our patient. The effect of methylene blue was immediate and persistent.

Despite being stable for 24 h after the first injection of methylene blue, the patient developed progressive shock again. It is unlikely that

this was caused by metformin toxicity, since our patient had been treated with continuous hemodialysis for more than 48 h, given that the half-life for metformin during continuous hemodialysis is approximately 4 h [14]. Therefore, we did not repeat methylene blue as we suspected other causes for the shock. A CT scan showed extensive liver necrosis, which has not been described in metformin toxicity. Considering the known side effects of methylene blue, none of which include liver necrosis or exacerbation of shock, it is unlikely that methylene blue itself contributed to the patient's worsening condition. Acetaminophen levels 4 h after ingestion were 29 mg/L, which is below the toxic threshold, and liver panel at presentation was normal, ruling out acetaminophen toxicity as a cause. A potential interaction between acetaminophen and simvastatin as a CYP3A4 inducer was considered highly unlikely. As CK levels remained low and no hepatotoxic medication was administered in our ICU, we therefore hypothesize that the severity of the initial shock with high vasopressor doses may have compromised hepatic blood flow, resulting in liver ischemia and subsequent necrosis. This observation further highlights the potential value of methylene blue to reduce vasopressor need in vasoplegic shock. As methylene blue allowed for a rapid reduction in noradrenalin dose in our case, early application could have potentially mitigated the harmful effects of prolonged high-dose vasopressor therapy, such as impaired hepatic blood flow leading to liver necrosis.

4. Conclusion

Our patient presented with a metabolic acidosis with hyperlactatemia and a severe vasoplegic shock after a massive metformin overdose. Although scarcely described, methylene blue proved to be a highly effective therapy of vasoplegic shock, with an immediate and persistent effect, allowing a rapid reduction of noradrenalin. As methylene blue has only a few side effects, it is important for clinicians to consider methylene blue when treating patients with refractory shock due to severe metformin overdose.

Previous presentation

None.

Funding

None.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data Availability

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

References

[1] D.P. Calello, K.D. Liu, T.J. Wiegand, et al., Extracorporeal treatment for metformin poisoning: systematic review and recommendations from the extracorporeal treatments in poisoning workgroup, Crit. Care Med. 43 (2015) 1716–1730.
[2] D. Juneja, P. Nasa, R. Jain, Metformin toxicity: a meta-summary of case reports, World J. Diabetes 13 (2022) 654–664.
[3] G.S. Wang, C. Hoyte, Review of biguanide (metformin) toxicity, J. Intensive Care Med. 34 (2019) 863–876.
[4] B.J. Davis, Z. Xie, B. Viollet, M. Zou, Activation of the AMP-activated kinase by antidiabetes drug metformin stimulates nitric oxide synthesis in vivo and endothelial nitric oxide synthase, Diabetes (2006) 55.
[5] J.D. Workum, L.L.A. Bisschops, M.J.W. Van Den Berg, Auto-intoxication with 'suicide powder', Ned. Tijdschr. Geneeskd. (2019) 163.
[6] B. Mayer, F. Brunner, K. Schmidt, Novel actions of methylene blue, Eur. Heart J. 14 Suppl. I (1993) 22–26.
[7] B. Mayer, F. Brunner, K. Schmidt, Inhibition of nitric oxide synthesis by methylene blue, Biochem. Pharm. 45 (1993) 367–374.
[8] E.S.H. Kwok, D.W. Howes, Use of methylene blue in sepsis: a systematic review, J. Intensive Care Med. 21 (2006) 359–363.
[9] N. Aggarwal, Y. Kupfer, C. Seneviratne, S. Tessler, Methylene blue reverses recalcitrant shock in β-blocker and calcium channel blocker overdose, BMJ Case Rep. (2013) 2013.
[10] R.E. Graham, M. Cartner, J. Winearls, Case report: a severe case of vasoplegic shock following metformin overdose successfully treated with methylene blue as a last line therapy, BMJ Case Rep. (2015) 2015.
[11] B. Plumb, A. Parker, P. Wong, Feeling blue with metformin-associated lactic acidosis, BMJ Case Rep. 2013 (2013), bcr2013008855.
[12] C. Ives Tallman, Y. Zhang, N. Black, K. Lynch, M. Fayed, P. Armenian, Refractory vasodilatory shock secondary to metformin overdose supported with VA ECMO, Toxicol. Rep. 9 (2022) 64–67.
[13] Methylthioninium chloride: summary of product characteristics, 2022.
[14] P. Ayoub, P.O. Hétu, M. Cormier, et al., Toxicokinetics of metformin during hemodialysis, Anu. Psicol. 47 (2017) 759–762.
[15] M. Prikis, E.L. Mesler, V.L. Hood, W.J. Weise, When a friend can become an enemy! Recognition and management of metformin-associated lactic acidosis, Kidney Int. 72 (2007) 1157–1160.

FDA - Adverse Event Reporting System (FAERS)
FOIA Case Report Information

Case ID: 22844011

Case Information:

Case Type : Expedited (15-Day) **eSub:** Y **HP:** **Country:** NL **Event Date:** **Outcomes:** DE , LT , HO , OT **Application Type:** ANDA

FDA Rcvd Date: 21-Aug-2023 **Mfr Rcvd Date:** 06-Aug-2023 **Mfr Control #:** NL-Indicus Pharma-000969 **Application #:** 079148

Patient Information:

Age: 55 YR **Sex:** Female **Weight:**

Suspect Products:

#	Product Name:	Compounded Drug ?	Dose/Frequency	Route	Dosage Text	Start Date	End Date	Indication(s)
1	METFORMIN		165 Dosage Form /	Oral				10042464
2	SEMAGLUTIDE		30 Dosage Form /	Oral				10042464

#	Product Name:	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler	OTC
1	METFORMIN		Not Applicable	NA					
2	SEMAGLUTIDE		Not Applicable	NA					

Device Products:

#	Brand Name / Common Device Name / Product Code	Similar Device?	Malfunction ?	Device Lot#	Device Usage/ Operator of Device	Remedial Action	Device Problem	Manufacturer Name
1	//	No			/			
2	//	No			/			

Event Information:

Preferred Term (MedDRA Version: v.26.1)	ReC
Intentional overdose	
Lactic acidosis	
Distributive shock	

Case ID: 22844011

Hypoglycaemia

Suicide attempt

Event/Problem Narrative:

This literature report (Workum JD, Keyany A, Jaspers TCC. Methylene blue as treatment for vasoplegic shock in severe metformin overdose: A case report. Toxicol Rep. 2023 Jul 17;11:141-144) concerns a 55-year-old adult female patient (weight: 125 kg) who attempted suicide by severe overdose of oral metformin and oral semaglutide and experienced hypoglycemia and died due to metformin associated lactic acidosis and severe vasoplegic shock. This case concerns a patient with body mass index of 46 kg/m2 presented to the emergency department (ED) after ingestion of 165 tablets of metformin 500 mg (82.5 g, or 660 mg/kg), 20 tablets of acetaminophen 500 mg (10 g, or 80 mg/kg), 38 tablets of simvastatin 40 mg (1520 mg, or 12 mg/kg) and 30 tablets of semaglutide 14 mg (420 mg or 3.4 mg/kg) as a suicide attempt. Immediately after ingestion, she alerted the emergency services herself and presented within 1 h of ingestion. In the ED she was alert and cooperative. Her medical history comprised of earlier suicide attempts with chronic depression and type II diabetes. Her initial vital signs were normal: she had a normal respiratory rate and an oxygen saturation of 95 percent without supplemental oxygen, blood pressure was 122/51 mmHg with a normal sinus rhythm of 89/min, and she was alert with a Glasgow Coma Scale of 15. Glucose was mildly elevated (18.4 mmol/L). Her body temperature was 35.7 degrees C. Initial blood gas analysis showed a pH of 7.19, a pCO2 of 5.6 kPa, bicarbonate of 16 mmol/L, base excess of -11.8 and lactate levels of 9.5 mmol/L. Liver panel, coagulation and creatine kinase (CK) levels were normal. Serum creatinine was 90 micromol/L. Laboratory results during admission were hemoglobin (normal values: 8.5-11 mmol/ L) day 0 8.5, day 1 7.2, day 2 6.8, day 3 6.6, day 4 6.3; hematocrit; (normal values: 0.40-0.54), day 0 0.43, day 1 0.37, day 2 0.32, day 3 0.32, day 4 0.32; white blood cells (normal values: 4-11 10*9/L) day 0 5.3, day 1 36.7, day 2 24.2, day 3 18.7, day 4 20.0; platelets (normal values: 150-450 10*9/L) day 0 152, day 1 244, day 2 146, day 4 85; glucose (normal values: 3.9-6.1 mmol/L), day 0 18.4, day 1 5.6, day 2 8.0, day 3 10.8, day 4 8.1; urea (normal values: 2.5-7.8 mmol/L) day 0 3.8, day 1 0.9, day 2 1.3, day 3 4.3, day 4 4.7; creatinine (normal values: 45-90 micromol/L) day 0 90, day 1 60, day 2 51, day 3 122, day 4 136; glomerular filtration rate (GFR) (CKD-EPI) (normal values: 90-120 mL/min/1.73 m2) day 0 62, day 1 greater than 90, day 2 greater than 90, day 3 43, day 4 38; sodium (normal values: 135-145 mmol/L) day 0 139, day 1 142, day 2 137, day 3 139, day 4 136; potassium (normal values: 3.5-5.1 mmol/L) day 0 5.2, day 1 3.2, day 2 4.3, day 3 4.5, day 4 4.5; magnesium (normal values: 0.7-1.0 mmol/ L) day 0 0.8, day 1 0.67, day 2 0.71, day 3 1.16, day 4 1.35; phosphate (normal values: 0.8-1.5 mmol/L) day 0 1.02, day 1 1.17, day 2 0.50, day 3 1.85, day 4 1.51; ionized calcium (normal values: 1.05-1.3 mmol/L) day 0 1.01, day 1 0.88, day 2 0.89, day 3 0.87, day 4 0.96; albumin (normal values: 35-50 g/L) day 0 38, day 3 25; total bilirubin (normal values: 3-22 micromol/L) day 0 11, day 1 12, day 2 26, day 3 78, day 4 112; alkaline phosphatase (normal values: 40-150 U/L) day 0 107, day 1 90, day 2 80, day 3 139, day 4 831; gamma-glutamyl transferase (GGT) (normal values: 10-60 U/L) day 0 40, day 1 38, day 2 34, day 3 71, day 4 111; aspartate aminotransferase (ASAT) (normal values: 10-40 U/L) day 0 52, day 1 224, day 2 805, day 3 3100, day 4 10518; alanine aminotransferase (ALAT) (normal values: 10-45 U/L) day 0 52, day 1 99, day 2 148, day 3 757, day 4 4171; lactate dehydrogenase (LDH) (normal values: 125-220 U/L) day 0 176, day 1 428, day 2 782, day 3 2799, day 4 7896; pH (arterial) (normal values 7.35-7.45) day 0 7.19, day 1 7.10, day 2 7.43, day 3 7.36, day 4 7.27; pO2 (arterial) (normal values: 11-13 kPa) day 0 14.3, day 1 12.7, day 2 9.5, day 3 11.3, day 4 9.6; pCO2 (arterial) (normal values: 4.7-6.0 kPa) day 0 5.6, day 1 6.2, day 2 4.9, day 3 4.9, day 4 6.0; bicarbonate (arterial) (normal values: 22-26 mmol/L) day 0 16, day 1 14.6, day 2 24.3, day 3 20.5, day 4 20.6; base excess (arterial) (normal values: -2 to +2mmol/L) day 0 -11.8, day 1 -14.6, day 2 0.1, day 3 -4.4, day 4 -6; lactate (arterial) (normal values: 0.5-1.6 mmol/L) day 0 9.5, day 1 25.0, day 2 9.2, day 3 7.9, day 4 4.4. Due to the expected severity of the intoxication and the early presentation, she was treated with activated charcoal and immediately admitted to the intensive care unit (ICU) for continuous hemodialysis as the severe lactic acidosis indicated a severe metformin overdose. After admission to the ICU, she deteriorated rapidly. She became tachypneic and was intubated for exhaustion. She developed rapid onset shock, which required continuous fluid resuscitation, noradrenalin (rapidly increasing up to 1.2 microgram/kg/min) and vasopressin (0.03 IE/min). Hydrocortisone was added because of the refractory nature of the shock. Continuous hemodialysis was initiated within 3 h after presentation. Arterial blood gas and lactate levels were monitored every two hours as a marker for resolution of the metformin overdose. She became hypoglycemic, most likely due to co-ingestion of metformin and semaglutide, for which a continuous 50 percent glucose infusion was started. Four hours post-ingestion, approximately three hours after presentation but prior to the initiation of hemodialysis, both acetaminophen and metformin levels were drawn. Acetaminophen levels 4 h after ingestion were 29 mg/L, so treatment with N-acetylcysteine was withheld. Metformin levels were drawn with the intent of retrospective analysis, as the results took one week to complete. Results revealed a level of 622.9 mg/L. However, as these findings were not available during the initial treatment, they had no bearing on

medical decision making. Using bedside ultrasonography in conjunction with invasive hemodynamic monitoring using a pulse index continuous cardiac output device (PiCCO), cardiogenic, obstructive, and hypovolemic shock were excluded. Causes of distributive shock other than vasoplegia, such as septic shock and anaphylaxis, were considered unlikely due to the clinical presentation and otherwise normal appearance. As there was no cardiogenic component to the shock, venoarterial extracorporeal membrane oxygenation (va-ECMO) was not considered to be of added value. Therefore, the current condition was considered severe vasoplegic shock due to metformin. As the already high doses of noradrenalin and vasopressin were considered insufficient, the authors decided to treat the patient with methylene blue. Subsequently, 250 mg of methylene blue (2 mg/kg) was administered intravenously over 5 min. The noradrenalin dose could be reduced from 1.2 microgram/kg/min to 0.5 microgram/kg/ min within 15 min, indicating rapid shock reversal, which was maintained at 0.5 microgram/kg/min for 6 h without additional intervention. A second bolus of methylene blue 2 mg/kg was then administered in an attempt to further reduce noradrenalin levels. This allowed the noradrenalin dose to be lowered to 0.25 microgram/kg/min. The patient remained stable for the next 24 h. Lactate levels decreased from a maximum of 29 mmol/L to 4.4 mmol/L, indicating metformin clearance and improvement of shock. However, the next day, lactate levels began to increase again while still on hemodialysis. She developed severe liver test abnormalities, with alanine aminotransferase (ASAT) of 10518 U/L and aspartate aminotransferase (ALAT) of 4171 U/ L and developed progressive shock again. A computed tomography (CT) scan of both the thorax and abdomen showed extensive necrosis of the liver. As there were no curative options, treatment was switched to palliative care and she passed away. Permission for post-mortem examination was not obtained. However, her next of kin signed informed consent for publication. The authors presented a case of severe vasoplegic shock due to metformin toxicity, which was treated with methylene blue in addition to conventional treatment, resulting in rapid shock resolution. Severe metformin poisoning can lead to metabolic acidosis with hyperlactatemia (metformin associated lactic acidosis, or MALA), glucose derangement (both hyperglycemia and hypoglycemia) and shock. This patient presented with a severe metformin overdose. She ingested 82.5 g (660 mg/kg), which is double the median dose described in the literature. The metformin level sampled approximately 4 h after ingestion was 622.9 mg/L, which is 6 times the average metformin levels in toxicologic literature. Despite continuous hemodialysis being initiated early, lactate levels continued to rise until 16 h after presentation. Lactate levels served as a treatment efficacy marker: when lactate levels started to decrease, this indicated that metformin levels themselves were also decreasing. Therefore hypothesized that metformin-induced NO production would also decrease. This is why, in contrast to the use of methylene blue in sepsis in which NO production is ongoing, they expected a positive treatment effect of methylene blue in this patient. The effect of methylene blue was immediate and persistent. Despite being stable for 24 h after the first injection of methylene blue, the patient developed progressive shock again. It is unlikely that this was caused by metformin toxicity, since this patient had been treated with continuous hemodialysis for more than 48 h, given that the half-life for metformin during continuous hemodialysis is approximately 4 h. Therefore, the authors did not repeat methylene blue as they suspected other causes for the shock. A CT scan showed extensive liver necrosis, which has not been described in metformin toxicity. Considering the known side effects of methylene blue, none of which include liver necrosis or exacerbation of shock, it is unlikely that methylene blue itself contributed to the patients worsening condition. Acetaminophen levels 4 h after ingestion were 29 mg/L, which is below the toxic threshold, and liver panel at presentation was normal, ruling out acetaminophen toxicity as a cause. A potential interaction between acetaminophen and simvastatin as a CYP3A4 inducer was considered highly unlikely. As CK levels remained low and no hepatotoxic medication was administered in ICU, therefore the authors hypothesize that the severity of the initial shock with high vasopressor doses may have compromised hepatic blood flow, resulting in liver ischemia and subsequent necrosis. This observation further highlights the potential value of methylene blue to reduce vasopressor need in vasoplegic shock. As methylene blue allowed for a rapid reduction in noradrenalin dose in this case, early application could have potentially mitigated the harmful effects of prolonged high-dose vasopressor therapy, such as impaired hepatic blood flow leading to liver necrosis. In conclusion, this patient presented with a metabolic acidosis with hyperlactatemia and a severe vasoplegic shock after a massive metformin overdose. Although scarcely described, methylene blue proved to be a highly effective therapy of vasoplegic shock, with an immediate and persistent effect, allowing a rapid reduction of noradrenalin. As methylene blue has only a few side effects, it is important for clinicians to consider methylene blue when treating patients with refractory shock due to severe metformin overdose. The reporter considered case to be serious as the patient was hospitalized due to life-threatening and medically significant conditions resulting in death. Medical review comment: The causality is assessed as possible for attempted suicide by severe overdose of oral metformin and experienced hypoglycemia and died due to fatal events with lactic acidosis and severe vasoplegic shock based on reasonable temporal association. However, the other co-suspect drug semaglutide confounds the causality.

Relevant Medical History:

FDA - Adverse Event Reporting System (FAERS)
FOIA Case Report Information

Case ID: 22844011

Disease/Surgical Procedure	Start Date	End Date	Continuing?
Type II diabetes mellitus			Yes
Chronic depression			Yes
Unsuccessful suicide			No

Medical History Product(s)	Start Date	End Date	Indications	Events

Relevant Laboratory Data:

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail
10061384	622.9	mg/L			N
10047939	5.3	10*9/L	4	11	N
10004544	20.6	mmol/L	22	26	N
10017687	38	U/L	10	60	N
10041263	142	mmol/L	135	145	N
10035766	12.7	kPa	11	13	N
10065594	cardiogenic, obstructive, and hypovolemic shock w				Y
10004544	14.6	mmol/L	22	26	N
10018414	10.8	mmol/L	3.9	6.1	N
10001546	4171	U/L	10	45	N
10023649	9.5	mmol/L	0.5	1.6	N
10035766	14.3	kPa	11	13	N
10023653	7896	U/L	125	220	N
10001546	757	U/L	10	45	N
10019299	89	{beats}/min			N
10036439	4.3	mmol/L	3.5	5.1	N

Case ID: 22844011

10040230	90	mmol/L	45	90	N
10036439	4.5	mmol/L	3.5	5.1	N
10035766	9.5	kPa	11	13	N
10003476	224	U/L	10	40	N
10019481	7.2	mmol/L	8.5	11	N
10019481	6.8	mmol/L	8.5	11	N
10018414	18.4	mmol/L	3.9	6.1	N
10035766	11.3	kPa	11	13	N
10059961	-6				N
10023649	9.2	mmol/L	0.5	1.6	N
10018414	8	mmol/L	3.9	6.1	N
10047939	18.7	10*9/L	4	11	N
10003476	52	U/L	10	40	N
10004544	24.3	mmol/L	22	26	N
10023653	176	U/L	125	220	N
10034928	1.02	mmol/L	0.8	1.5	N
10017687	71	U/L	10	60	N
10034928	0.5	mmol/L	0.8	1.5	N
10001558	38	g/L	35	50	N
10019481	6.6	mmol/L	8.5	11	N
10001546	52	U/L	10	45	N
10036439	5.2	mmol/L	3.5	5.1	N
10041263	137	mmol/L	135	145	N
10035525	244	10*9/L	150	450	N
10018355	38	mL/min/{1.73_m2}	90	120	N
10018355	90	mL/min/{1.73_m2}	90	120	N
10017687	40	U/L	10	60	N
10001546	99	U/L	10	45	N
10018355	62	mL/min/{1.73_m2}	90	120	N

Case ID: 22844011

10046346	1.3	mmol/L	2.5	7.8	N
10018355	43	mL/min/{1.73_m2}	90	120	N
10025430	0.71	mmol/L	0.7	1	N
10001546	148	U/L	10	45	N
10019481	8.5	mmol/L	8.5	11	N
10040230	122	mmol/L	45	90	N
10059961	-14.6				N
10005906	35.7	Cel			N
10059944	4.9	kPa	4.7	6	N
10019422	0.43		0.4	0.54	N
10046346	0.9	mmol/L	2.5	7.8	N
10019422	0.32		0.4	0.54	N
10059961	--4.4				N
10025430	0.8	mmol/L	0.7	1	N
10022929	0.88	mmol/L	1.05	1.3	N
10022929	0.87	mmol/L	1.05	1.3	N
10019481	6.3	mmol/L	8.5	11	N
10040230	136	mmol/L	45	90	N
10057557	cardiogenic, obstructive, and hypovolemic shock w				Y
10057825	showed extensive necrosis of the liver				N
10059944	5.6	kPa	4.7	6	N
10047939	20	10*9/L	4	11	N
10059944	6.2	kPa	4.7	6	N
10019422	0.32		0.4	0.54	N
10011334	were normal				N
10023653	428	U/L	125	220	N

FDA - Adverse Event Reporting System (FAERS)
FOIA Case Report Information

Case ID: 22844011

10025430	0.67	mmol/L	0.7	1	N
10061384	29	mg/L			N
10022929	1.01	mmol/L	1.05	1.3	N
10004696	112	umol/L	3	22	N
10036439	4.5	mmol/L	3.5	5.1	N
10063590	7.27	[pH]	7.35	7.45	N
10036439	3.2	mmol/L	3.5	5.1	N
10046346	4.3	mmol/L	2.5	7.8	N
10035525	152	10*9/L	150	450	N
10046346	4.7	mmol/L	2.5	7.8	N
10003476	805	U/L	10	40	N
10047939	24.2	10*9/L	4	11	N
10023653	782	U/L	125	220	N
10059944	4.9	kPa	4.7	6	N
10063590	7.19	[pH]	7.35	7.45	N
10003476	10518	U/L	10	40	N
10004544	16	mmol/L	22	26	N
10059961	-11.8				N
10004696	12	umol/L	3	22	N
10022929	0.89	mmol/L	1.05	1.3	N
10063590	7.1	[pH]	7.35	7.45	N
10019422	0.37		0.4	0.54	N
10004696	11	umol/L	3	22	N
10017687	34	U/L	10	60	N
10040230	60	mmol/L	45	90	N
10035766	9.6	kPa	11	13	N
10023649	25	mmol/L	0.5	1.6	N
10023649	4.4	mmol/L	0.5	1.6	N
10041263	139	mmol/L	135	145	N

Case ID: 22844011

10058476	15				N
10017687	111	U/L	10	60	N
10046346	3.8	mmol/L	2.5	7.8	N
10035525	146	10*9/L	150	450	N
10001674	107	U/L	40	150	N
10011334	remained low				N
10041263	139	mmol/L	135	145	N
10004696	26	umol/L	3	22	N
10003476	3100	U/L	10	40	N
10025430	1.35	mmol/L	0.7	1	N
10001674	139	U/L	40	150	N
10018414	8.1	mmol/L	3.9	6.1	N
10034928	1.17	mmol/L	0.8	1.5	N
10063590	7.36	[pH]	7.35	7.45	N
10063590	7.43	[pH]	7.35	7.45	N
10023649	7.9	mmol/L	0.5	1.6	N
10001674	831	U/L	40	150	N
10023653	2799	U/L	125	220	N
10047939	36.7	10*9/L	4	11	N
10004544	36.7	mmol/L	22	26	N
10025430	1.16	mmol/L	0.7	1	N
10001674	80	U/L	40	150	N
10004696	78	umol/L	3	22	N
10040230	51	mmol/L	45	90	N
10034928	1.85	mmol/L	0.8	1.5	N
10018414	5.6	mmol/L	3.9	6.1	N
10059944	6	kPa	4.7	6	N
10023649	29	mmol/L	0.5	1.6	N
10001558	25	g/L	35	50	N

FDA - Adverse Event Reporting System (FAERS)
FOIA Case Report Information

Case ID: 22844011

10022929	0.96	mmol/L	1.05	1.3	N
10019422	0.32		0.4	0.54	N
10033316	95	%			N
10059961	0.1	mmol/L			N
10005894	46	kg/m2			N
10001674	90	U/L	40	150	N
10053876	showed extensive necrosis of the liver				N
10038709	normal				N
10041263	136	mmol/L	135	145	N
10035525	85	10*9/L	150	450	N
10018355	90	mL/min/{1.73_m2}	90	120	N
10034928	1.51	mmol/L	0.8	1.5	N

Concomitant Products:

#	Product Name:	Dose/Frequency	Route	Dosage Text	Start Date	End Date	Indication(s)	Interval 1st Dose to Event
1	SIMVASTATIN	38 Dosage Form /	Oral				10042464	
2	ACETAMINOPHEN	20 Dosage Form /	Oral				10042464	

Reporter Source:

Study report?: No **Sender organization:** INDICUS **503B Compounding Outsourcing Facility?:**

Literature Text: Workum JD, Keyany A, Jaspers TCC. Methylene blue as treatment for vasoplegic shock in severe metformin overdose: A case report. Toxicol Rep. 2023 Jul 17;11:141-144.

FDA - Adverse Event Reporting System (FAERS)
FOIA Case Report Information

Case ID: 22844498

Case Information:

Case Type : Expedited (15-Day) **eSub:** Y **HP:** **Country:** NL **Event Date:** **Outcomes:** DE , LT , HO , OT **Application Type:** ANDA

FDA Rcvd Date: 21-Aug-2023 **Mfr Rcvd Date:** 06-Aug-2023 **Mfr Control #:** NL-Inventia-000656 **Application #:** 201991

Patient Information:

Age: 55 YR **Sex:** Female **Weight:** 125 KG

Suspect Products:

#	Product Name:	Compounded Drug ?	Dose/Frequency	Route	Dosage Text	Start Date	End Date	Indication(s)
1	METFORMIN HYDROCHLORIDE		165 Dosage Form /	Oral				10042464
2	SEMAGLUTIDE		30 Dosage Form /	Oral				10042464

#	Product Name:	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler	OTC
1	METFORMIN HYDROCHLORIDE		Not Applicable	NA					
2	SEMAGLUTIDE		Not Applicable	NA					

Device Products:

#	Brand Name / Common Device Name / Product Code	Similar Device?	Malfunction ?	Device Lot#	Device Usage/ Operator of Device	Remedial Action	Device Problem	Manufacturer Name
1	//	No			/			
2	//	No			/			

Event Information:

Preferred Term (MedDRA Version: v.26.1)	ReC
Intentional overdose	

Case ID: 22844498

Lactic acidosis

Distributive shock

Hypoglycaemia

Suicide attempt

Event/Problem Narrative:

This literature report was received by a physician from the Netherland (Workum JD, Keyany A, Jaspers TCC. Methylene blue as treatment for vasoplegic shock in severe metformin overdose: A case report. Toxicol Rep. 2023 Jul 17;11:141-144) concerns a 55-year-old adult female patient (weight: 125 kg) who attempted suicide by severe overdose of oral metformin and oral semaglutide and experienced hypoglycemia and died due to metformin associated lactic acidosis and severe vasoplegic shock. This case concerns a patient with body mass index of 46 kg/m2 presented to the emergency department (ED) after ingestion of 165 tablets of metformin 500 mg (82.5 g, or 660 mg/kg), 20 tablets of acetaminophen 500 mg (10 g, or 80 mg/kg), 38 tablets of simvastatin 40 mg (1520 mg, or 12 mg/kg) and 30 tablets of semaglutide 14 mg (420 mg or 3.4 mg/ kg) as a suicide attempt. Immediately after ingestion, she alerted the emergency services herself and presented within 1 h of ingestion. In the ED she was alert and cooperative. Her medical history comprised of earlier suicide attempts with chronic depression and type II diabetes. Her initial vital signs were normal: she had a normal respiratory rate and an oxygen saturation of 95 percent without supplemental oxygen, blood pressure was 122/51 mmHg with a normal sinus rhythm of 89/min, and she was alert with a Glasgow Coma Scale of 15. Glucose was mildly elevated (18.4 mmol/ L). Her body temperature was 35.7 degrees C. Initial blood gas analysis showed a pH of 7.19, a pCO2 of 5.6 kPa, bicarbonate of 16 mmol/L, base excess of -11.8 and lactate levels of 9.5 mmol/L. Liver panel, coagulation and creatine kinase (CK) levels were normal. Serum creatinine was 90 micromol/L. Laboratory results during admission were hemoglobin (normal values: 8.5-11 mmol/ L) day 0 8.5, day 1 7.2, day 2 6.8, day 3 6.6, day 4 6.3; hematocrit; (normal values: 0.40-0.54), day 0 0.43, day 1 0.37, day 2 0.32, day 3 0.32, day 4 0.32; white blood cells (normal values: 4-11 10*9/L) day 0 5.3, day 1 36.7, day 2 24.2, day 3 18.7, day 4 20.0; platelets (normal values: 150-450 10*9/L) day 0 152, day 1 244, day 2 146, day 4 85; glucose (normal values: 3.9-6.1 mmol/L), day 0 18.4, day 1 5.6, day 2 8.0, day 3 10.8, day 4 8.1; urea (normal values: 2.5-7.8 mmol/L) day 0 3.8, day 1 0.9, day 2 1.3, day 3 4.3, day 4 4.7; creatinine (normal values: 45-90 micromol/L) day 0 90, day 1 60, day 2 51, day 3 122, day 4 136; glomerular filtration rate (GFR) (CKD-EPI) (normal values: 90-120 mL/min/1.73 m2) day 0 62, day 1 greater than 90, day 2 greater than 90, day 3 43, day 4 38; sodium (normal values: 135-145 mmol/L) day 0 139, day 1 142, day 2 137, day 3 139, day 4 136; potassium (normal values: 3.5-5.1 mmol/L) day 0 5.2, day 1 3.2, day 2 4.3, day 3 4.5, day 4 4.5; magnesium (normal values: 0.7-1.0 mmol/ L) day 0 0.8, day 1 0.67, day 2 0.71, day 3 1.16, day 4 1.35; phosphate (normal values: 0.8-1.5 mmol/L) day 0 1.02, day 1 1.17, day 2 0.50, day 3 1.85, day 4 1.51; ionized calcium (normal values: 1.05-1.3 mmol/L) day 0 1.01, day 1 0.88, day 2 0.89, day 3 0.87, day 4 0.96; albumin (normal values: 35-50 g/L) day 0 38, day 3 25; total bilirubin (normal values: 3-22 micromol/L) day 0 11, day 1 12, day 2 26, day 3 78, day 4 112; alkaline phosphatase (normal values: 40-150 U/L) day 0 107, day 1 90, day 2 80, day 3 139, day 4 831; gamma-glutamyl transferase (GGT) (normal values: 10-60 U/L) day 0 40, day 1 38, day 2 34, day 3 71, day 4 111; aspartate aminotransferase (ASAT) (normal values: 10-40 U/L) day 0 52, day 1 224, day 2 805, day 3 3100, day 4 10518; alanine aminotransferase (ALAT) (normal values: 10-45 U/L) day 0 52, day 1 99, day 2 148, day 3 757, day 4 4171; lactate dehydrogenase (LDH) (normal values: 125-220 U/L) day 0 176, day 1 428, day 2 782, day 3 2799, day 4 7896; pH (arterial) (normal values 7.35-7.45) day 0 7.19, day 1 7.10, day 2 7.43, day 3 7.36, day 4 7.27; pO2 (arterial) (normal values: 11-13 kPa) day 0 14.3, day 1 12.7, day 2 9.5, day 3 11.3, day 4 9.6; pCO2 (arterial) (normal values: 4.7-6.0 kPa) day 0 5.6, day 1 6.2, day 2 4.9, day 3 4.9, day 4 6.0; bicarbonate (arterial) (normal values: 22-26 mmol/L) day 0 16, day 1 14.6, day 2 24.3, day 3 20.5, day 4 20.6; base excess (arterial) (normal values: -2 to +2mmol/L) day 0 -11.8, day 1 -14.6, day 2 0.1, day 3 -4.4, day 4 -6; lactate (arterial) (normal values: 0.5-1.6 mmol/L) day 0 9.5, day 1 25.0, day 2 9.2, day 3 7.9, day 4 4.4. Due to the expected severity of the intoxication and the early presentation, she was treated with activated charcoal and immediately admitted to the intensive care unit (ICU) for continuous hemodialysis as the severe lactic acidosis indicated a severe metformin overdose. After admission to the ICU, she deteriorated rapidly. She became tachypneic and was intubated for exhaustion. She developed rapid onset shock, which required continuous fluid resuscitation, noradrenalin (rapidly increasing up to 1.2 microgram/kg/min) and vasopressin (0.03 IE/min). Hydrocortisone was added because of the refractory nature of the shock. Continuous hemodialysis was initiated within 3 h after presentation. Arterial blood gas and lactate levels were monitored every two hours as a marker for resolution of the metformin overdose. She became hypoglycemic, most likely due to co-ingestion of metformin and semaglutide, for which a continuous 50 percent glucose infusion

was started. Four hours post-ingestion, approximately three hours after presentation but prior to the initiation of hemodialysis, both acetaminophen and metformin levels were drawn. Acetaminophen levels 4 h after ingestion were 29 mg/L, so treatment with N-acetylcysteine was withheld. Metformin levels were drawn with the intent of retrospective analysis, as the results took one week to complete. Results revealed a level of 622.9 mg/L. However, as these findings were not available during the initial treatment, they had no bearing on medical decision making. Using bedside ultrasonography in conjunction with invasive hemodynamic monitoring using a pulse index continuous cardiac output device (PiCCO), cardiogenic, obstructive, and hypovolemic shock were excluded. Causes of distributive shock other than vasoplegia, such as septic shock and anaphylaxis, were considered unlikely due to the clinical presentation and otherwise normal appearance. As there was no cardiogenic component to the shock, venoarterial extracorporeal membrane oxygenation (va-ECMO) was not considered to be of added value. Therefore, the current condition was considered severe vasoplegic shock due to metformin. As the already high doses of noradrenalin and vasopressin were considered insufficient, the authors decided to treat the patient with methylene blue. Subsequently, 250 mg of methylene blue (2 mg/kg) was administered intravenously over 5 min. The noradrenalin dose could be reduced from 1.2 microgram/kg/min to 0.5 microgram/kg/ min within 15 min, indicating rapid shock reversal, which was maintained at 0.5 microgram/kg/min for 6 h without additional intervention. A second bolus of methylene blue 2 mg/kg was then administered in an attempt to further reduce noradrenalin levels. This allowed the noradrenalin dose to be lowered to 0.25 microgram/kg/min. The patient remained stable for the next 24 h. Lactate levels decreased from a maximum of 29 mmol/L to 4.4 mmol/L, indicating metformin clearance and improvement of shock. However, the next day, lactate levels began to increase again while still on hemodialysis. She developed severe liver test abnormalities, with alanine aminotransferase (ASAT) of 10518 U/L and aspartate aminotransferase (ALAT) of 4171 U/ L and developed progressive shock again. A computed tomography (CT) scan of both the thorax and abdomen showed extensive necrosis of the liver. As there were no curative options, treatment was switched to palliative care and she passed away. Permission for post-mortem examination was not obtained. However, her next of kin signed informed consent for publication. The authors presented a case of severe vasoplegic shock due to metformin toxicity, which was treated with methylene blue in addition to conventional treatment, resulting in rapid shock resolution. Severe metformin poisoning can lead to metabolic acidosis with hyperlactatemia (metformin associated lactic acidosis, or MALA), glucose derangement (both hyperglycemia and hypoglycemia) and shock. This patient presented with a severe metformin overdose. She ingested 82.5 g (660 mg/kg), which is double the median dose described in the literature. The metformin level sampled approximately 4 h after ingestion was 622.9 mg/L, which is 6 times the average metformin levels in toxicologic literature. Despite continuous hemodialysis being initiated early, lactate levels continued to rise until 16 h after presentation. Lactate levels served as a treatment efficacy marker: when lactate levels started to decrease, this indicated that metformin levels themselves were also decreasing. Therefore hypothesized that metformin-induced NO production would also decrease. This is why, in contrast to the use of methylene blue in sepsis in which NO production is ongoing, they expected a positive treatment effect of methylene blue in this patient. The effect of methylene blue was immediate and persistent. Despite being stable for 24 h after the first injection of methylene blue, the patient developed progressive shock again. It is unlikely that this was caused by metformin toxicity, since this patient had been treated with continuous hemodialysis for more than 48 h, given that the half-life for metformin during continuous hemodialysis is approximately 4 h. Therefore, the authors did not repeat methylene blue as they suspected other causes for the shock. A CT scan showed extensive liver necrosis, which has not been described in metformin toxicity. Considering the known side effects of methylene blue, none of which include liver necrosis or exacerbation of shock, it is unlikely that methylene blue itself contributed to the patients worsening condition. Acetaminophen levels 4 h after ingestion were 29 mg/L, which is below the toxic threshold, and liver panel at presentation was normal, ruling out acetaminophen toxicity as a cause. A potential interaction between acetaminophen and simvastatin as a CYP3A4 inducer was considered highly unlikely. As CK levels remained low and no hepatotoxic medication was administered in ICU, therefore the authors hypothesize that the severity of the initial shock with high vasopressor doses may have compromised hepatic blood flow, resulting in liver ischemia and subsequent necrosis. This observation further highlights the potential value of methylene blue to reduce vasopressor need in vasoplegic shock. As methylene blue allowed for a rapid reduction in noradrenalin dose in this case, early application could have potentially mitigated the harmful effects of prolonged high-dose vasopressor therapy, such as impaired hepatic blood flow leading to liver necrosis. In conclusion, this patient presented with a metabolic acidosis with hyperlactatemia and a severe vasoplegic shock after a massive metformin overdose. Although scarcely described, methylene blue proved to be a highly effective therapy of vasoplegic shock, with an immediate and persistent effect, allowing a rapid reduction of noradrenalin. As methylene blue has only a few side effects, it is important for clinicians to consider methylene blue when treating patients with refractory shock due to severe metformin overdose. The reporter considered case to be serious as the patient was hospitalized due to life-threatening and medically significant conditions resulting in death. Medical review comment: Based on the available information, a 55 year-old female patient who developed events lactic acidosis, vasodilatory shock, hypoglycemia and reported drug overdose while receiving metformin for suicide attempt. Patient died due to lactic acidosis, vasodilatory shock. Information regarding diabetes history also confounding factor for

the events. However, role of another co-suspect drug semaglutide could not be excluded. Hence the reported case falls under the possible category of WHO-UMC causality assessment system.

Relevant Medical History:

Disease/Surgical Procedure	Start Date	End Date	Continuing?
Type II diabetes mellitus			Yes
Chronic depression			Yes
Unsuccessful suicide			No

Medical History Product(s)	Start Date	End Date	Indications	Events

Relevant Laboratory Data:

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail
10061384	622.9	mg/L			N
10047955	5.3	10*9/L	4	11	N
10047955	36.7	10*9/L	4	11	N
10047955	24.2	10*9/L	4	11	N
10047955	18.7	10*9/L	4	11	N
10047955	20.0	10*9/L	4	11	N
10035525	152	10*9/L	150	450	N
10035525	244	10*9/L	150	450	N
10035525	146	10*9/L	150	450	N
10035525	85	10*9/L	150	450	N
10018414	18.4	mmol/L	3.9	6.1	N
10018414	5.6	mmol/L	3.9	6.1	N
10018414	8.0	mmol/L	3.9	6.1	N
10018414	10.8	mmol/L	3.9	6.1	N
10018414	8.1	mmol/L	3.9	6.1	N

Case ID: 22844498

10046346	3.8	mmol/L	2.5	7.8	N
10046346	0.9	mmol/L	2.5	7.8	N
10046346	1.3	mmol/L	2.5	7.8	N
10046346	4.3	mmol/L	2.5	7.8	N
10046346	4.7	mmol/L	2.5	7.8	N
10019481	8.5	mmol/L	8.5	11	N
10019481	7.2	mmol/L	8.5	11	N
10019481	6.8	mmol/L	8.5	11	N
10019481	6.6	mmol/L	8.5	11	N
10019481	6.3	mmol/L	8.5	11	N
10011358	90	umol/L	45	90	N
10011358	60	umol/L	45	90	N
10011358	51	umol/L	45	90	N
10011358	122	umol/L	45	90	N
10011358	136	umol/L	45	90	N
10018355	62	mL/min/{1.73_m2}	90	120	N
10018355	90	mL/min/{1.73_m2}	90	120	N
10018355	90	mL/min/{1.73_m2}	90	120	N
10018355	43	mL/min/{1.73_m2}	90	120	N
10018355	38	mL/min/{1.73_m2}	90	120	N
10041263	139	mmol/L	135	145	N
10041263	142	mmol/L	135	145	N
10041263	137	mmol/L	135	145	N
10041263	139	mmol/L	135	145	N
10041263	136	mmol/L	135	145	N
10036439	5.2	mmol/L	3.5	5.1	N
10036439	3.2	mmol/L	3.5	5.1	N
10036439	4.3	mmol/L	3.5	5.1	N
10036439	4.5	mmol/L	3.5	5.1	N

Case ID: 22844498

10036439	4.5	mmol/L	3.5	5.1	N
10034928	1.02	mmol/L	0.8	1.5	N
10034928	1.17	mmol/L	0.8	1.5	N
10034928	0.50	mmol/L	0.8	1.5	N
10034928	1.85	mmol/L	0.8	1.5	N
10034928	1.51	mmol/L	0.8	1.5	N
10022929	1.01	mmol/L	1.05	1.3	N
10022929	0.88	mmol/L	1.05	1.3	N
10022929	0.89	mmol/L	1.05	1.3	N
10022929	0.87	mmol/L	1.05	1.3	N
10022929	0.96	mmol/L	1.05	1.3	N
10001558	38	g/L	35	50	N
10001558	25	g/L	35	50	N
10004696	11	umol/L	3	22	N
10004696	12	umol/L	3	22	N
10004696	26	umol/L	3	22	N
10004696	78	umol/L	3	22	N
10004696	112	umol/L	3	22	N
10001674	107	U/L	40	150	N
10001674	90	U/L	40	150	N
10001674	80	U/L	40	150	N
10001674	139	U/L	40	150	N
10001674	831	U/L	40	150	N
10017687	40	U/L	10	60	N
10017687	38	U/L	10	60	N
10017687	34	U/L	10	60	N
10017687	71	U/L	10	60	N
10017687	111	U/L	10	60	N
10003476	52	U/L	10	40	N

Case ID: 22844498

10003476	224	U/L	10	40	N
10003476	805	U/L	10	40	N
10003476	3100	U/L	10	40	N
10003476	10518	U/L	10	40	N
10001546	52	U/L	10	45	N
10001546	99	U/L	10	45	N
10001546	148	U/L	10	45	N
10001546	757	U/L	10	45	N
10001546	4171	U/L	10	45	N
10023653	176	U/L	125	220	N
10023653	428	U/L	125	220	N
10023653	782	U/L	125	220	N
10023653	2799	U/L	125	220	N
10023653	7896	U/L	125	220	N
10063590	7.19	[pH]	7.35	7.45	N
10063590	7.10	[pH]	7.35	7.45	N
10063590	7.43	[pH]	7.35	7.45	N
10063590	7.36	[pH]	7.35	7.45	N
10063590	7.27	[pH]	7.35	7.45	N
10035766	14.3	kPa	11	13	N
10035766	12.7	kPa	11	13	N
10035766	9.5	kPa	11	13	N
10035766	11.3	kPa	11	13	N
10035766	9.6	kPa	11	13	N
10059944	5.6	kPa	4.7	6.0	N
10059944	6.2	kPa	4.7	6.0	N
10059944	4.9	kPa	4.7	6.0	N
10059944	4.9	kPa	4.7	6.0	N
10059944	6.0	kPa	4.7	6.0	N

Case ID: 22844498

10004544	16	mmol/L	22	26	N
10004544	14.6	mmol/L	22	26	N
10004544	24.3	mmol/L	22	26	N
10004544	20.5	mmol/L	22	26	N
10004544	20.6	mmol/L	22	26	N
10059961	-11.8				N
10059961	-14.6				N
10059961	0.1	mmol/L			N
10059961	-4.4				N
10059961	-6				N
10023649	9.5	mmol/L	0.5	1.6	N
10023649	25.0	mmol/L	0.5	1.6	N
10023649	9.2	mmol/L	0.5	1.6	N
10023649	7.9	mmol/L	0.5	1.6	N
10023649	4.4	mmol/L	0.5	1.6	N
10065594	cardiogenic, obstructive, and hypovolemic shock w				Y
10057557	cardiogenic, obstructive, and hypovolemic shock w				Y
10057825	showed extensive necrosis of the liver				N
10011334	were normal				N
10011334	remained low				N
10053876	showed extensive necrosis of the liver				N
10005894	46	kg/m2			N
10033316	95	%			N

FDA - Adverse Event Reporting System (FAERS)
FOIA Case Report Information

Case ID: 22844498

10038709	normal				N
10005906	35.7	Cel			N
10019299	89	{beats}/min			N
10058476	15				N
10061384	29	mg/L			N
10019422	0.43		0.40	0.54	N
10019422	0.37		0.40	0.54	N
10019422	0.32		0.40	0.54	N
10019422	0.32		0.40	0.54	N
10019422	0.32		0.40	0.54	N
10025430	0.8	mmol/L	0.7	1.0	N
10025430	0.67	mmol/L	0.7	1.0	N
10025430	0.71	mmol/L	0.7	1.0	N
10025430	1.16	mmol/L	0.7	1.0	N
10025430	1.35	mmol/L	0.7	1.0	N

Concomitant Products:

#	Product Name:	Dose/Frequency	Route	Dosage Text	Start Date	End Date	Indication(s)	Interval 1st Dose to Event
1	SIMVASTATIN	38 Dosage Form /	Oral				10042464	
2	ACETAMINOPHEN	20 Dosage Form /	Oral				10042464	

Reporter Source:

Study report?: No **Sender organization:** INVENTIA HEALTHCARE **503B Compounding Outsourcing Facility?:**

Literature Text: Workum JD, Keyany A, Jaspers TCC. Methylene blue as treatment for vasoplegic shock in severe metformin overdose: A case report. Toxicol Rep. 2023 Jul 17;11:141-144.

FDA - Adverse Event Reporting System (FAERS)
FOIA Case Report Information

Case ID: 22852516

Case Information:

Case Type : Expedited (15-Day) **eSub:** Y **HP:** Y **Country:** US **Event Date:** **Outcomes:** DE **Application Type:**

FDA Rcvd Date: 23-Aug-2023 **Mfr Rcvd Date:** 10-Aug-2023 **Mfr Control #:** US-NOVOPROD-1104167 **Application #:** 209637

Patient Information:

Age: **Sex:** Male **Weight:**

Suspect Products:

#	Product Name:	Compounded Drug ?	Dose/Frequency	Route	Dosage Text	Start Date	End Date	Indication(s)
1	Ozempic		/	Subcutaneous	UNK			Product used for unknown indication

#	Product Name:	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler	OTC
1	Ozempic		Unknown	NA				NOVO NORDISK	

Device Products:

#	Brand Name / Common Device Name / Product Code	Similar Device?	Malfunction ?	Device Lot#	Device Usage/ Operator of Device	Remedial Action	Device Problem	Manufacturer Name
1	Ozempic//	No			/Other		Adverse Event Without Identified Device or Use Problem	Novo Nordisk A/S

Event Information:

Preferred Term (MedDRA Version: v.26.1) **ReC**

Completed suicide

Event/Problem Narrative:

FDA - Adverse Event Reporting System (FAERS)
FOIA Case Report Information

Case ID: 22852516

This serious Spontaneous case from the UNITED STATES was reported by a Health Care Professional as "committed suicide(Completed suicide)" with an unspecified onset date, and concerned a Male patient who was treated with Ozempic (SEMAGLUTIDE) from unknown start date for "Product used for unknown indication", Medical history was not provided. On an unknown date patient committed suicide. It was unknown whether autospy was performed Batch Number for Ozempic has been requested Action taken to Ozempic was Not reported. The outcome for the event "committed suicide(Completed suicide)" was Fatal. Company comment: Suicide is assessed as an unlisted event according to the NovoNordisk current CCDS information on Ozempic The information regarding event and therapy dates, indication for use of the suspect product, complete medical history (psychological disorder), social habits, past history of attempt to suicide, family history, socioeconomic conditions, relevant investigation reports are unavailable which limits the medical assessment of the case This single case report is not considered to change the current knowledge of the safety profile of Ozempic

Relevant Medical History:

Disease/Surgical Procedure	Start Date	End Date	Continuing?

Medical History Product(s)	Start Date	End Date	Indications	Events

Relevant Laboratory Data:

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail

Concomitant Products:

#	Product Name:	Dose/Frequency	Route	Dosage Text	Start Date	End Date	Indication(s)	Interval 1st Dose to Event

Reporter Source:

Study report?: No **Sender organization:** NOVO NORDISK **503B Compounding Outsourcing Facility?:**

Literature Text:

FDA - Adverse Event Reporting System (FAERS)
FOIA Case Report Information

Case ID: 22856052

Case Information:

Case Type : Expedited (15-Day) **eSub:** Y **HP:** N **Country:** NL **Event Date:** **Outcomes:** DE , HO , OT **Application Type:** ANDA

FDA Rcvd Date: 23-Aug-2023 **Mfr Rcvd Date:** 18-Aug-2023 **Mfr Control #:** NL-PERRIGO-23NL009161 **Application #:** 070608

Patient Information:

Age: 55 YR **Sex:** Female **Weight:** 125 KG

Suspect Products:

#	Product Name:	Compounded Drug ?	Dose/Frequency	Route	Dosage Text	Start Date	End Date	Indication(s)
1	Paracetamol		20 Dosage Form /	Unknown	20 tablets of acetaminophen 500 mg (10 g, or 80 mg/kg)			Product used for unknown indication
2	RYBELSUS		30 Dosage Form /	Oral	30 tablets of semaglutide 14 mg (420 mg or 3.4 mg/ kg)			Product used for unknown indication
3	SIMVASTATIN		40 Mg Milligram(S) /	Oral	40 mg (1520 mg, or 12 mg/kg)			Product used for unknown indication
4	METFORMIN		165 Dosage Form /	Oral	165 tablets of 500 mg			Product used for unknown indication

#	Product Name:	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler	OTC
1	Paracetamol		Not Applicable	NA				PERRIGO	
2	RYBELSUS		Not Applicable	NA					
3	SIMVASTATIN		Not Applicable	NA					
4	METFORMIN		Not Applicable	NA					

Device Products:

FDA - Adverse Event Reporting System (FAERS)
FOIA Case Report Information

Case ID: 22856052

#	Brand Name / Common Device Name / Product Code	Similar Device?	Malfunction ?	Device Lot#	Device Usage/ Operator of Device	Remedial Action	Device Problem	Manufacturer Name
1	//	No			/			
2	//	No			/			
3	//	No			/			
4	//	No			/			

Event Information:

Preferred Term (MedDRA Version: v.26.1)	ReC
Hypoglycaemia	
Intentional overdose	
Completed suicide	
Hepatic necrosis	
Lactic acidosis	
Distributive shock	
Toxicity to various agents	

Event/Problem Narrative:

Hypoglycaemia, Intentional overdose, Completed suicide, Hepatic necrosis, Lactic acidosis, Distributive shock, Toxicity to various agents This Regulatory Authority-Literature case was reported by a Other Health Professional and received through EMA on 14-AUG-2023. A Female patient of 55 Years-old experienced Hypoglycaemia, Intentional overdose, Completed suicide after receiving Paracetamol for product used for unknown indication. Relevant medical history included Suicide attempt, Chronic depression, Type II diabetes mellitus. No concomitant drugs were reported. The action taken with the suspect drug was Unknown.
At the time of reporting the outcome of the events were Unknown for Hypoglycaemia and Fatal for Intentional overdose, Completed suicide. Cause of death: Intentional overdose, Completed suicide. Co-suspects are: Rybelsus; SIMVASTATIN; METFORM. EMA MC received on 18-AUG-2023: WWID NL-SANDOZ-SDZ2023NL009965. Reporter Other Health Professional changed into Physician and Consumer/non HCP. AEs added: Hepatic necrosis, Lactic acidosis, Distributive shock, Toxicity to various agents Action with Paracetamol and other suspects changed into N/A. Dosage regimens updated. Relevant tests updated. Literature reference updated. Cause of death: Intentional overdose, Completed suicide, Hepatic necrosis, Lactic acidosis, Distributive shock, Toxicity to various agents.

Relevant Medical History:

Disease/Surgical Procedure	Start Date	End Date	Continuing?
Suicide attempt			No

FDA - Adverse Event Reporting System (FAERS)
FOIA Case Report Information

Case ID: 22856052

Depression			Yes	
Type 2 diabetes mellitus			Yes	
Medical History Product(s)	**Start Date**	**End Date**	**Indications**	**Events**

Relevant Laboratory Data:

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail
ALANINE AMINOTRANSFERASE	99	U/L	10	45	N
ALANINE AMINOTRANSFERASE	4171	U/L	10	45	N
ALANINE AMINOTRANSFERASE	52	U/L	10	45	N
ALANINE AMINOTRANSFERASE	757	U/L	10	45	N
ALANINE AMINOTRANSFERASE	148	U/L	10	45	N
ASPARTATE AMINOTRANSFERASE	10518	U/L	10	40	N
ASPARTATE AMINOTRANSFERASE	52	U/L	10	40	N
ASPARTATE AMINOTRANSFERASE	3100	U/L	10	40	N
ASPARTATE AMINOTRANSFERASE	224	U/L	10	40	N
ASPARTATE AMINOTRANSFERASE	805	U/L	10	40	N
BASE EXCESS					Y
BASE EXCESS					Y
BASE EXCESS					Y
BASE EXCESS					Y
BASE EXCESS					Y
BLOOD ALBUMIN	25	g/l	35	50	N
BLOOD ALBUMIN	38	g/l	35	50	N
BLOOD ALKALINE PHOSPHATASE					Y
BLOOD ALKALINE PHOSPHATASE					Y
BLOOD ALKALINE PHOSPHATASE					Y
BLOOD ALKALINE PHOSPHATASE					Y

Case ID: 22856052

BLOOD ALKALINE PHOSPHATASE					Y
BLOOD BICARBONATE	16	mmol/liter	22	26	N
BLOOD BICARBONATE	20.5	mmol/liter	22	26	N
BLOOD BICARBONATE	20.6	mmol/liter	22	26	N
BLOOD BICARBONATE	24.3	mmol/liter	22	26	N
BLOOD BICARBONATE	16	mmol/liter	22	26	N
BLOOD BICARBONATE	14.6	mmol/liter	22	26	N
BLOOD BILIRUBIN	12	umol/l	3	22	N
BLOOD BILIRUBIN	112	umol/l	3	22	N
BLOOD BILIRUBIN	78	umol/l	3	22	N
BLOOD BILIRUBIN	26	umol/l	3	22	N
BLOOD BILIRUBIN	11	umol/l	3	22	N
BLOOD CREATINE PHOSPHOKINASE					Y
BLOOD CREATININE	60	mmol/liter	45	90	N
BLOOD CREATININE	90	mmol/liter	45	90	N
BLOOD CREATININE	51	mmol/liter	45	90	N
BLOOD CREATININE	122	mmol/liter	45	90	N
BLOOD CREATININE	136	mmol/liter	45	90	N
BLOOD CREATININE	90	umol/l			N
BLOOD GASES					Y
BLOOD GLUCOSE	5.6	millimole per litre	3.9	6.1	N
BLOOD GLUCOSE	10.8	millimole per litre	3.9	6.1	N
BLOOD GLUCOSE	8.1	millimole per litre	3.9	6.1	N
BLOOD GLUCOSE	8	millimole per litre	3.9	6.1	N
BLOOD GLUCOSE	18.4	millimole per litre	3.9	6.1	N
BLOOD GLUCOSE	18.4	millimole per litre	3.9	6.1	N
BLOOD LACTATE DEHYDROGENASE	428	U/L	125	220	N
BLOOD LACTATE DEHYDROGENASE	7896	U/L	125	220	N
BLOOD LACTATE DEHYDROGENASE	176	U/L	125	220	N

FDA - Adverse Event Reporting System (FAERS)
FOIA Case Report Information

Case ID: 22856052

BLOOD LACTATE DEHYDROGENASE	2799	U/L	125	220	N
BLOOD LACTATE DEHYDROGENASE	782	U/L	125	220	N
BLOOD LACTIC ACID	7.9	mmol/liter	0.5	1.6	N
BLOOD LACTIC ACID	25	mmol/liter	0.5	1.6	N
BLOOD LACTIC ACID	9.2	mmol/liter	0.5	1.6	N
BLOOD LACTIC ACID	4.4	mmol/liter	0.5	1.6	N
BLOOD LACTIC ACID	9.5	mmol/liter	0.5	1.6	N
BLOOD LACTIC ACID	9.5	mmol/liter	0.5	1.6	N
BLOOD MAGNESIUM	0.67	mmol/liter	0.7	1	N
BLOOD MAGNESIUM	0.8	mmol/liter	0.7	1	N
BLOOD MAGNESIUM	1.35	mmol/liter	0.7	1	N
BLOOD MAGNESIUM	1.16	mmol/liter	0.7	1	N
BLOOD MAGNESIUM	0.71	mmol/liter	0.7	1	N
BLOOD PHOSPHORUS	0.5	mmol/liter	0.8	1.5	N
BLOOD PHOSPHORUS	1.02	mmol/liter	0.8	1.5	N
BLOOD PHOSPHORUS	1.51	mmol/liter	0.8	1.5	N
BLOOD PHOSPHORUS	1.17	mmol/liter	0.8	1.5	N
BLOOD PHOSPHORUS	1.85	mmol/liter	0.8	1.5	N
BLOOD POTASSIUM	4.5	mmol/liter	3.5	5.1	N
BLOOD POTASSIUM	4.3	mmol/liter	3.5	5.1	N
BLOOD POTASSIUM	3.2	mmol/liter	3.5	5.1	N
BLOOD POTASSIUM	5.2	mmol/liter	3.5	5.1	N
BLOOD POTASSIUM	4.5	mmol/liter	3.5	5.1	N
BLOOD PRESSURE MEASUREMENT					Y
BLOOD SODIUM	136	mmol/liter	135	145	N
BLOOD SODIUM	137	mmol/liter	135	145	N
BLOOD SODIUM	139	mmol/liter	135	145	N
BLOOD SODIUM	142	mmol/liter	135	145	N
BLOOD SODIUM	139	mmol/liter	135	145	N

FDA - Adverse Event Reporting System (FAERS)
FOIA Case Report Information

Case ID: 22856052

BLOOD UREA	1.3	mmol/liter	2.5	7.8	N
BLOOD UREA	4.7	mmol/liter	2.5	7.8	N
BLOOD UREA	3.8	mmol/liter	2.5	7.8	N
BLOOD UREA	0.9	mmol/liter	2.5	7.8	N
BLOOD UREA	4.3	mmol/liter	2.5	7.8	N
BODY MASS INDEX	46	kilogram per square metre			N
BODY TEMPERATURE					Y
CALCIUM IONISED	0.96	mmol/liter	1.05	1.3	N
CALCIUM IONISED	1.01	mmol/liter	1.05	1.3	N
CALCIUM IONISED	0.89	mmol/liter	1.05	1.3	N
CALCIUM IONISED	0.88	mmol/liter	1.05	1.3	N
CALCIUM IONISED	0.87	mmol/liter	1.05	1.3	N
COAGULATION TEST					Y
COMA SCALE					Y
COMPUTERISED TOMOGRAM					Y
GAMMA-GLUTAMYLTRANSFERASE	111	U/L	10	60	N
GAMMA-GLUTAMYLTRANSFERASE	40	U/L	10	60	N
GAMMA-GLUTAMYLTRANSFERASE	38	U/L	10	60	N
GAMMA-GLUTAMYLTRANSFERASE	34	U/L	10	60	N
GAMMA-GLUTAMYLTRANSFERASE	71	U/L	10	60	N
GLOMERULAR FILTRATION RATE	43	mL/min/{1.73_m2}	90	120	N
GLOMERULAR FILTRATION RATE	90	mL/min/{1.73_m2}	90	120	N
GLOMERULAR FILTRATION RATE	62	mL/min/{1.73_m2}	90	120	N
GLOMERULAR FILTRATION RATE	38	mL/min/{1.73_m2}	90	120	N
GLOMERULAR FILTRATION RATE	90	mL/min/{1.73_m2}	90	120	N
HAEMATOCRIT					Y
HAEMATOCRIT					Y
HAEMATOCRIT					Y

Case ID: 22856052

HAEMATOCRIT					Y
HAEMATOCRIT					Y
HAEMOGLOBIN	7.2	mmol/liter	8.5	11	N
HAEMOGLOBIN	6.6	mmol/liter	8.5	11	N
HAEMOGLOBIN	8.5	mmol/liter	8.5	11	N
HAEMOGLOBIN	6.3	mmol/liter	8.5	11	N
HAEMOGLOBIN	6.8	mmol/liter	8.5	11	N
LIVER FUNCTION TEST					Y
PCO2	4.9	kPa	4.7	6	N
PCO2	4.9	kPa	4.7	6	N
PCO2	4.9	kPa	4.7	6	N
PCO2	6	kPa	4.7	6	N
PCO2	6.2	kPa	4.7	6	N
PCO2	5.6	kPa	4.7	6	N
PCO2	5.6	kPa	4.7	6	N
PH BODY FLUID					Y
PH BODY FLUID					Y
PH BODY FLUID					Y
PH BODY FLUID					Y
PH BODY FLUID					Y
PLATELET COUNT	152	10 9/L	150	450	N
PLATELET COUNT	244	10 9/L	150	450	N
PLATELET COUNT	85	10 9/L	150	450	N
PLATELET COUNT	146	10 9/L	150	450	N
PO2	14.3	kPa	11	13	N
PO2	11.3	kPa	11	13	N
PO2	9.6	kPa	11	13	N
PO2	9.5	kPa	11	13	N
PO2	12.7	kPa	11	13	N

FDA - Adverse Event Reporting System (FAERS)
FOIA Case Report Information

Case ID: 22856052

PO2	9.5	kPa	11	13	N
PO2	11.3	kPa	11	13	N
PO2	12.7	kPa	11	13	N
RESPIRATORY RATE					Y
SINUS RHYTHM	89	/min			N
WHITE BLOOD CELL COUNT	5.3	10 9/L	4	11	N
WHITE BLOOD CELL COUNT	24.2	10 9/L	4	11	N
WHITE BLOOD CELL COUNT	36.7	10 9/L	4	11	N
WHITE BLOOD CELL COUNT	18.7	10 9/L	4	11	N
WHITE BLOOD CELL COUNT	20	10 9/L	4	11	N

Concomitant Products:

#	Product Name:	Dose/Frequency	Route	Dosage Text	Start Date	End Date	Indication(s)	Interval 1st Dose to Event

Reporter Source:

Study report?: No **Sender organization:** PERRIGO **503B Compounding Outsourcing Facility?:**

Literature Text: Workum JD, Keyany A, Jaspers TCC. Methylene blue as treatment for vasoplegic shock in severe metformin overdose: A case report.. Toxicology Reports.. 2023;11:141-4. doi:10.1016/j.toxrep.2023.07.005

FDA - Adverse Event Reporting System (FAERS)
FOIA Case Report Information

Case ID: 22871187

Case Information:

Case Type : Expedited (15-Day) **eSub:** Y **HP:** Y **Country:** SE **Event Date:** 2023 **Outcomes:** LT **Application Type:**

FDA Rcvd Date: 28-Aug-2023 **Mfr Rcvd Date:** 14-Aug-2023 **Mfr Control #:** SE-NOVOPROD-1103274 **Application #:** 209637

Patient Information:

Age: 14 YR **Sex:** Female **Weight:** 110 KG

Suspect Products:

#	Product Name:	Compounded Drug ?	Dose/Frequency	Route	Dosage Text	Start Date	End Date	Indication(s)
1	Ozempic 0.25 mg		/		0.25 mg	19-Jan-2023		Type 2 diabetes mellitus
2	Ozempic 0.25 mg		/					Obesity

#	Product Name:	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler	OTC
1	Ozempic 0.25 mg		Unknown	NA				NOVO NORDISK	
2	Ozempic 0.25 mg		Unknown	NA				NOVO NORDISK	

Device Products:

#	Brand Name / Common Device Name / Product Code	Similar Device?	Malfunction ?	Device Lot#	Device Usage/ Operator of Device	Remedial Action	Device Problem	Manufacturer Name
1	//	No			/			
2	//	No			/			

Event Information:

Preferred Term (MedDRA Version: v.26.1) **ReC**

Suicidal ideation

Suicide attempt

Event/Problem Narrative:

FDA - Adverse Event Reporting System (FAERS)
FOIA Case Report Information

Case ID: 22871187

This is a serious Spontaneous Regulatory authority case received via Swedish Medical Products Agency (SEMPA) from SWEDEN was reported by a Physician as "Suicidal ideation(Suicidal ideation)" beginning on 2023, "Suicide attempt(Suicide attempt)" beginning on 2023, and concerned a 14 Years old Female patient who was treated with Ozempic 0.25 mg (SEMAGLUTIDE) from (b) (6) for "Type 2 diabetes mellitus", "Morbid obesity", The events Suicidal ideation,Suicide attempt were medically confirmed. Patient's height: 165 cm Patient's weight: 110 kg Patient's BMI: 40.40404040. Dosage Regimens: Ozempic 0.25 mg: (b) (6) (b) (6) to Not Reported; Current Condition: Type 2 diabetes mellitus(duration not reported), Unspecified disturbance of conduct, Autism, ADHD, Self injurious behavior, Morbid obesity. Concomitant products included - HALDOL HALOPERIDOL On an unspecified date (2023), patient had Suicidal ideation and Suicide attempt. Batch Numbers: Ozempic 0.25 mg: not reported Action taken to Ozempic 0.25 mg was Not reported. The outcome for the event "Suicidal ideation(Suicidal ideation)" was Not recovered. The outcome for the event "Suicide attempt(Suicide attempt)" was Not recovered. References included: Reference Type: E2B Report Duplicate Reference ID#: SE-SEMPA-2023-013359 Reference Notes: SEMPA Reference Type: E2B Authority Number Reference ID#: SE-SEMPA-2023-013359 Reference Notes: NO further information available COMPANY COMMENT - Suicidal ideation and suicide attempt are assessed as unlisted events according to the Novo Nordisk current CCDS information on Ozempic. Information on age of the patient, relevant history on mental health and environmental factors influencing suicide attempt are not available. It is difficult to perform thorough medical evaluation on suspected suicide attempt. However, chornic medical conditions like diabetes mellitus and morbid obesity are risk factors for the event. This single case report is not considered to change the current knowledge of the safety profile of Ozempic.

Relevant Medical History:

Disease/Surgical Procedure	Start Date	End Date	Continuing?
Type 2 diabetes mellitus			Yes
Disturbance in social behaviour			Yes
Autism spectrum disorder			Yes
Attention deficit hyperactivity disorder			Yes
Intentional self-injury			Yes
Obesity			Yes

Medical History Product(s)	Start Date	End Date	Indications	Events

Relevant Laboratory Data:

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail

Concomitant Products:

FDA - Adverse Event Reporting System (FAERS)
FOIA Case Report Information

Case ID: 22871187

#	Product Name:	Dose/Frequency	Route	Dosage Text	Start Date	End Date	Indication(s)	Interval 1st Dose to Event
1	HALDOL [HALOPERIDOL]	/		UNK	Dec-2021			

Reporter Source:

Study report?: No

Sender organization: NOVO NORDISK

503B Compounding Outsourcing Facility?:

Literature Text:

FDA - Adverse Event Reporting System (FAERS)
FOIA Case Report Information

Case ID: 22873106

Case Information:

Case Type : Expedited (15-Day) **eSub:** Y **HP:** Y **Country:** NL **Event Date:** **Outcomes:** DE , LT , HO , OT **Application Type:** ANDA

FDA Rcvd Date: 29-Sep-2023 **Mfr Rcvd Date:** 27-Sep-2023 **Mfr Control #:** NL-MYLANLABS-2023M1089200 **Application #:** 090868

Patient Information:

Age: 55 YR **Sex:** Female **Weight:** 125 KG

Suspect Products:

#	Product Name:	Compounded Drug ?	Dose/Frequency	Route	Dosage Text	Start Date	End Date	Indication(s)
1	Methylene Blue		2 Mg/Kg Milligram(S)/ Kilogram /	Intravenous (not otherwise specified)	2 milligram/kilogram,6 hours after first one			Vasoplegia syndrome
2	Methylene Blue		250 Mg Milligram(S) /	Intravenous (not otherwise specified)	250 milligram, 2 mg/kg			

#	Product Name:	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler	OTC
1	Methylene Blue		Not Applicable	NA					
2	Methylene Blue		Not Applicable	NA					

Device Products:

#	Brand Name / Common Device Name / Product Code	Similar Device?	Malfunction ?	Device Lot#	Device Usage/ Operator of Device	Remedial Action	Device Problem	Manufacturer Name
1	//	No			/			
2	//	No			/			
3	//	No			/			
4	//	No			/			
5	//	No			/			

6	//	No	/
7	//	No	/

Event Information:

Preferred Term (MedDRA Version: v.26.1)	ReC
Lactic acidosis	
Distributive shock	
Toxicity to various agents	
Intentional overdose	
Completed suicide	
Hepatic necrosis	
Drug interaction	
Hepatic ischaemia	
Drug abuse	
Hypoglycaemia	
Faeces discoloured	
Condition aggravated	
Skin discolouration	
Chromaturia	

Event/Problem Narrative:

This EVWEB report (Ref. No: NL-SANDOZ-SDZ2023NL009965) originated from Netherlands was downloaded by Viatris on 24-Aug-2023. Follow-up information was downloaded from EVWEB (Ref. No: NL-ORGANON-O2308NLD000287) by Viatris on 25-Aug-2023. Initial and follow up reports were processed together. This case was referenced in an article titled Literature Reference: Jessica D. Workum, Keyany A, Jaspers CCT, Methylene blue as treatment for vasoplegic shock in severe metformin overdose, 2023, A case report. Elsevier Toxicology Reports, 11, 141-144. This initial case, received from physician in the Netherlands, involved a 55-years-old female patient who reportedly took an overdose of simvastatin and metformin film-coated tablet 500 mg in an act of drug abuse and died/completed suicide due to hepatic necrosis, lactic acidosis, distributive shock and toxicity to various agents. Medical history included suicide attempt. Current conditions included depression and type 2 diabetes mellitus. Concomitant medications were not reported. Non-company suspect medications included acetaminophen tablet 500 mg and semaglutide tablet 14 mg. Unknown Date: The patient initiated metformin film-coated tablet at a dose of 165 dosage form (82.5 g, or 660 mg/kg) via oral use and acetaminophen tablet 20 tablets of 500 mg (10 g, or 80 mg/kg) via oral use (dose, frequency, batch number and expiration date were unknown) and semaglutide tablet 30 tablets of semaglutide 14 mg (420 mg or 3.4 mg/ kg) via oral use and simvastatin at a dose of 40 milligram (1520 mg, or 12 mg/kg) via oral use (frequency, batch number and expiration date were unknown) for unknown indication. The patient reportedly took simvastatin and metformin in an act of drug abuse and experienced lactic acidosis, took overdose and multiple drug toxicity / ingestion of 165 tablets of metformin 500 mg (82.5 g, or 660 mg/

kg), 20 tablets of acetaminophen 500 mg (10 g, or 80 mg/kg), 38 tablets of simvastatin 40 mg (1520 mg, or 12 mg/kg) and 30 tablets of semaglutide 14 mg (420 mg or 3.4 mg/ kg, necrosis of the liver, severe vasoplegic shock and completed suicide. The patient was hospitalized in response to the events hepatic necrosis, lactic acidosis, distributive shock, toxicity to various agents, intentional overdose and completed suicide. Date of hospitalization, number of days hospitalized and discharge details were not reported. The events drug abuse, hepatic necrosis, lactic acidosis, distributive shock and completed suicide were considered medically significant. Laboratory data included blood phosphorus was 1.51 millimole per litre, 1.17 millimole per litre, 0.5 millimole per litre, 1.02 millimole per litre, 1.85 millimole per litre (low value: 0.8; high value: 1.5), coma scale was showed 15, Sinus rhythm was 89 per minute, blood pressure measurement was 122/51 mmHg, blood gases was pH of 7.19, blood bilirubin was 26 micromoles per litre, 11 micromoles per litre, 78 micromoles per litre, 112 micromoles per litre, 12 micromoles per litre (low value: 3; high value: 22), blood lactic acid was 7.9 millimole per litre, 9.5 millimole per litre, 4.4 millimole per litre, 25 millimole per litre, 9.2 millimole per litre (low value: 0.5; high value: 1.6), computerised tomogram was both the thorax and abdomen showed extensive necrosis of the liver, blood glucose was 10.8 millimole per litre, 8.1 millimole per litre, 18.4 millimole per litre, 5.6 millimole per litre (low value: 3.9; high value: 6.1), pCO2 5.6 kilopascal, PCO2 was 4.9 kilopascal, 6 kilopascal, 5.6 kilopascal and 6.2 kilopascal, 5.6 kilopascal, 4.9 kilopascal (low value: 4.7; high value: 6), pH body fluid was 7.43, 7.27, 7.10, 7.19, 7.36 (low value: 7.35; high value: 7.45), body temperature was 35.7 degree Celsius, blood glucose was18.4 millimole per, haemoglobin was 8.5 millimole per litre, 7.2 millimole per litre, 6.3 millimole per litre 6.6 millimole per litre, 6.8 millimole per litre (low value: 8.5; high value: 11), blood sodium was 136 millimole per litre, 137 millimole per litre, 139 millimole per litre, 139 millimole per litre, 142 millimole per litre (low value: 135; high value: 145), blood magnesium was 0.67 millimole per litre, 0.71 millimole per litre, 1.35 millimole per litre, 0.8 millimole per litre, 1.16 millimole per litre (low value: 0.7; high value: 1), blood potassium was 3.2 millimole per litre, 4.5 millimole per litre, 5.2 millimole per litre, 4.5 millimole per litre, 4.3 millimole per litre (low value: 3.5; high value: 5.1), blood lactate dehydrogenase was 782 enzyme unit per litre, 2799 enzyme unit per litre, 428 enzyme unit per litre, 7896 enzyme unit per litre, 176 enzyme unit per litre (low value: 125; high value: 220), haematocrit was 0.32, 0.32, 0.37, 0.43, 0.32 (low value: 0.40; high value: 0.54), blood alkaline phosphatase was 139, 80,107, 831 and 90 (low value: 40; high value: 150), white blood cell count was 20 billion per litre, 18.7 billion per litre, 24.2 billion per litre, 36.7 billion per litre, 5.3 billion per litre (low value: 4; high value: 11), blood albumin was 25 gram per litre, 38 gram per litre (low value: 35; high value: 50), glomerular filtration rate was 90 millilitre per minute per 1.73 square metre, 90 millilitre per minute per 1.73 square metre, 38 millilitre per minute per 1.73 square metre, 43 millilitre per minute per 1.73 square metre, 62 millilitre per minute per 1.73 square metre (low value: 90; high value: 120), platelet count was 152 billion per litre, 146 billion per litre, 244 billion per litre, 85 billion per litre (low value: 150; high value: 450), blood bicarbonate was16 millimole per litre, 20.5 millimole per litre, 24.3 millimole per litre, 20.6 millimole per litre, 14.6 millimole per litre, 14.6 millimole per litre, 14.6 millimole per litre (low value: 22; high value: 26), calcium ionised was 0.87 millimole per litre, 0.89 millimole per litre, 0.88 millimole per litre, 0.96 millimole per litre, 1.01 millimole per litre (low value: 1.05; high value: 1.3), blood creatinine was 90 micromole per litre, base excess was 0.1 mmol/L, minus 4.4 mmol/L), minus 14.6 mmol/L, minus 11.8 mmol/L, minus 6 mmol/L (minus 2 to plus 2)), blood creatinine was 51 millimole per litre, 90 millimole per litre, 136 millimole per litre, 122 millimole per litre, 60 millimole per litre (low value: 45; high value: 90), PO2 was 14.3 kilopascal, 9.6 kilopascal,12.7 kilopascal, 9.5 kilopascal and 11.3 kilopascal (low value: 11; high value: 13), gamma-glutamyltransferase was 40 enzyme unit per litre, 111 enzyme unit per litre, 71 enzyme unit per litre, 34 enzyme unit per litre, 34 enzyme unit per litre, 38 enzyme unit per litre (low value: 10; high value: 60), blood urea was 4.3 millimole per litre, 0.9 millimole per litre, 1.3 millimole per litre, 4.7 millimole per litre, 3.8 millimole per litre (low value: 2.5; high value: 7.8), aspartate aminotransferase was 52 enzyme unit per litre, 10518 enzyme unit per litre, 224 enzyme unit per litre, 805 enzyme unit per litre and 3100 enzyme unit per litre (low value: 10; high value: 40), alanine aminotransferase was 757 enzyme unit per litre, 4171 enzyme unit per litre, 148 enzyme unit per litre, 52 enzyme unit per litre, 99 enzyme unit per litre (low value: 10; high value: 45). Unknown Date: The patient died and the cause of death was reported vasodilatory shock, hepatic necrosis, intentional overdose, completed suicide, drug toxicity (severe metformin toxicity) and lactic acidosis. The autopsy was not performed. Follow up information was downloaded from EVWeb (Ref no: NL-NOVOPROD-1101616) by Viatris on 29-Aug-2023 which is significant. Follow up information was downloaded from EVWeb (Ref no: NL-SANDOZ-SDZ2023NL009965) by Viatris on 30-Aug-2023 which is non-significant. Follow up information was downloaded from EVWeb (Ref no: NL-SANDOZ-SDZ2023NL009965) by Viatris on 31-Aug-2023 which is non-significant. Follow up information was downloaded from EVWeb (Ref no: NL-Provepharm SAS-2023000096) by Viatris on 31-Aug-2023 which is significant. All follow-up reports were processed together. The following information was added-reporter detail, laboratory data, event information (new events faeces discoloured, condition aggravated, skin discolouration, chromaturia and hypoglycaemia), product detail (brand name Rybelsus was added for semaglutide, concomitant product detail) A new reporter was added. Current condition included Vasoplegia syndrome. Concomitant medications were hydrocortisone, noradrenaline, Activated charcoal (charcoal, activated), Vasopressin (lypressin) and fluid resuscitation. Non-company suspect medication included Methylene Blue. Unknown Date: The patient initiated methylene blue solution for injection at a dose of 2 milligram/ kilogram via intravenous use (frequency, batch/lot number and expiration date were unknown) for vasoplegic shock and methylene blue solution for injection at

a dose of 250 milligram via intravenous use (frequency, batch/lot number and expiration date were unknown) for vasoplegic shock. The patient experienced blue discoloration of the feces, blue discoloration of the skin, blue discoloration of the urine, hypoglycemic and second shock (progressive shock again). Laboratory data included body mass index was 46 kilogram per square metre. The outcome of events faeces discoloured, condition aggravated, skin discolouration, chromaturia and hypoglycaemia was unknown. Follow up information was downloaded from EVWEB (Reference Number: NL-SANDOZ-SDZ2023NL009965) by Viatris on 04-Sep-2023 which is non-significant and follow-up information was received by Viatris on 31-Aug-2023 (local Ref no: NZ-Adis-3817868-348074) which was significant. Both follow-up reports processed together. The following information was added/updated: Literature information and event details. New events and lab data added, company comment updated. This case was referenced in an article titled: Jessica D. Workum JD, Keyany A, Jaspers CCT, Methylene blue as treatment for vasoplegic shock in severe metformin overdose, A case report. Elsevier Toxicology Reports, 2023, 11, 141-144. Unknown date: The patient developed hypoglycaemia following the drug interaction of metformin and semaglutide; developed liver necrosis following the drug interaction of paracetamol and simvastatin. Additionally, she exhibited lack of efficacy during treatment with norepinephrine, methylthioninium-chloride, hydrocortisone and vasopressin for severe vasoplegic shock [not all routes and dosages stated; durations of treatments to reactions onsets and outcomes not stated]. The woman presented to the emergency room after the ingestion of metformin 165 tablets of 500mg (82.5g, or 660 mg/kg), paracetamol [acetaminophen] 500mg of 20 tablets (10g, or 80mg/kg), simvastatin 40mg of 38 tablets (1520mg, or 12 mg/kg) and semaglutide 14mg of 30 tablets (420mg or 3.4 mg/kg) for suicide attempt (overdose and drug intoxication of metformin, simvastatin, paracetamol and semaglutide). She presented to the emergency department within 1 hour after the ingestion of metformin, simvastatin, paracetamol and semaglutide. In the emergency department, she was cooperative and alert. She had normal respiratory rate, oxygen saturation of 95%, BP was 122/51 mm Hg, sinus rhythm of 89/minutes and she was alert with a Glasgow coma scale of 15. Her glucose was mildly elevated. Body temperature was 35.7 degC. Her initial blood gas analysis revealed pH of 7.19, partial pressure of carbon dioxide of 5.6 kPa, bicarbonate of 16 mmol/L, base excess of 11.8 mmol/L and lactate levels of 9.5 mmol/L. Serum creatinine was 90 micromol/L. She was treated with activated charcoal for intoxication, which was attributed to metformin, simvastatin, paracetamol and semaglutide and immediately admitted to the ICU for continuous haemodialysis as she experienced severe lactic acidosis due to severe metformin overdose. She deteriorated rapidly after admission to the ICU. She experienced tachypnoea and was intubated for exhaustion. She experienced rapid onset shock and for which she needed continuous fluid resuscitation, norepinephrine [noradrenalin] rapidly increasing up to 1.2 microg/kg/min and vasopressin 0.03 IE/min. The treatment of hydrocortisone was added due to the refractory nature of the shock. Within 3 hours after the presentation a continuous haemodialysis was initiated. To mark her resolution of metformin overdose, arterial blood gas and lactate levels were observed every two hours. Due to the co-ingestion of semaglutide and metformin (drug interaction between semaglutide and metformin) she developed hypoglycaemia secondary to the interaction of semaglutide and metformin and for which she started the continuous infusion of glucose 50%. Her paracetamol and metformin levels were decreased approximately three hours after presentation and prior to the initiation of haemodialysis. Four hours after the ingestion, her paracetamol levels were 29 mg/L. Hence, the treatment with acetylcysteine [N-acetylcysteine] was discontinued. Her metformin levels were decreased to 622.9 mg/L. A diagnosis of severe vasoplegic shock was made secondary to metformin. A methylthioninium-chloride [methylene blue] was added to the treatment as a high dose of vasopressin and norepinephrine were insufficient to treat her rapid onset shock (indicating lack of efficacy to vasopressin and norepinephrine). Administered IV bolous methylthioninium-chloride 250mg (2 mg/kg) over 5 minutes. Her dose of norepinephrine was reduced from 1.2 microg/kg/min to 0.5 microg/kg/minutes within 15 minutes. However, despite the treatment with methylthioninium-chloride she had reversal of rapid shock (indicating lack of efficacy to methylthioninium-chloride and hydrocortisone), which was maintained at norepinephrine 0.5 microg/kg/min for 6 hours without additional intervention. For the further reduction of norepinephrine dose, a second bolus of methylthioninium-chloride 2 mg/kg was given. Her norepinephrine dose reduced to 0.25 microg/kg/min. She was stable for 24 hours. Her levels of lactate was decreased from 29 mmol/L to 4.4 mmol/L, which indicated the clearance of metformin and improvement of shock. However, her lactate levels increased again next day while she was on haemodialysis. She experienced severe liver test abnormalities with alanine aminotransferase of 10518 U/L and aspartate aminotransferase of 4171 U/ L. She experienced progressive shock again. A CT scan of both the thorax and abdomen revealed extensive necrosis of the liver. She was diagnose with liver necrosis secondary to the interaction of paracetamol and simvastatin (drug interaction of paracetamol and simvastatin). Also, she developed liver ischaemia due to vasopressin. The events hepatic ischaemia and drug interaction which were considered to be Life Threatening. The events hepatic ischaemia and hypoglycemia which were considered to be medically significant. The patient was hospitalized in response to the events hepatic ischaemia, drug interaction hypoglycaemia, completed suicide, intentional overdose. Follow up information was downloaded from EVWeb (Ref No: NL-NOVOPROD-1101616) by Viatris on 27-Sep-2023 which is significant. The following information was added/updated: Event information (seriousness criteria of hospitalization removed for event Hypoglycemia) and reference number. Company Comment: Serious: Hepatic necrosis (fatal, life threatening), Lactic acidosis (fatal), Distributive shock (fatal), Toxicity to various agents (fatal), Intentional overdose (fatal), Completed suicide (fatal), Drug abuse, Faeces discoloured (NS), Condition aggravated (NS),

Case ID: 22873106

Skin discolouration (NS), Chromaturia (NS), hypoglycaemia, hepatic ischaemia (life threatening) and drug interaction (life threatening) are unlisted events as per company RSI of metformin. Hepatic necrosis (life threatening) is Listed event whereas rest are Unlisted events as per company RSI of Simvastatin. Causality has been assessed as Unassessable for events Hepatic necrosis, lactic acidosis, distributive shock, due to due to lack of information on autopsy details. Causality has been assessed as Unlikely for event Completed suicide as could be explained by confounders of medical history of previous suicide attempts with chronic depression. Causality has been assessed as Possible for rest of the events as the contributory role of the suspect drugs cannot be completely excluded based on the available information. Non company suspects confound the causality.

Relevant Medical History:

Disease/Surgical Procedure	Start Date	End Date	Continuing?
Chronic depression			Yes
Type 2 diabetes mellitus			Yes
Attempted suicide			No
Vasoplegia syndrome			Yes

Medical History Product(s)	Start Date	End Date	Indications	Events

Relevant Laboratory Data:

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail
ALANINE AMINOTRANSFERASE	148	enzyme unit per litre	10	45	N
ALANINE AMINOTRANSFERASE	4171	enzyme unit per litre	10	45	N
ALANINE AMINOTRANSFERASE	99	enzyme unit per litre	10	45	N
ALANINE AMINOTRANSFERASE	52	enzyme unit per litre	10	45	N
ALANINE AMINOTRANSFERASE	757	enzyme unit per litre	10	45	N
ASPARTATE AMINOTRANSFERASE	224	enzyme unit per litre	10	40	N
ASPARTATE AMINOTRANSFERASE	10518	enzyme unit per litre	10	40	N
ASPARTATE AMINOTRANSFERASE	3100	enzyme unit per litre	10	40	N
ASPARTATE AMINOTRANSFERASE	805	enzyme unit per litre	10	40	N
ASPARTATE AMINOTRANSFERASE	52	enzyme unit per litre	10	40	N
BASE EXCESS					Y

Case ID: 22873106

BASE EXCESS					Y
BASE EXCESS					Y
BASE EXCESS					Y
BASE EXCESS					Y
ALBUMIN	25	gram per litre	35	50	N
ALBUMIN	38	gram per litre	35	50	N
ALKALINE PHOSPHATASE					Y
ALKALINE PHOSPHATASE					Y
ALKALINE PHOSPHATASE					Y
ALKALINE PHOSPHATASE					Y
ALKALINE PHOSPHATASE					Y
BICARBONATE	14.6	millimole per litre	22	26	N
BICARBONATE	16	millimole per litre	22	26	N
BICARBONATE	20.5	millimole per litre	22	26	N
BICARBONATE	20.6	millimole per litre	22	26	N
BICARBONATE	24.3	millimole per litre	22	26	N
BILIRUBIN	26	micromole per litre	3	22	N
BILIRUBIN	11	micromole per litre	3	22	N
BILIRUBIN	12	micromole per litre	3	22	N
BILIRUBIN	112	micromole per litre	3	22	N
BILIRUBIN	78	micromole per litre	3	22	N
CREATININE	51	millimole per litre	45	90	N
CREATININE	122	millimole per litre	45	90	N
CREATININE	136	millimole per litre	45	90	N
CREATININE	60	millimole per litre	45	90	N
CREATININE	90	millimole per litre	45	90	N
SERUM CREATININE	90	micromole per litre			N
BLOOD GASES					Y
GLUCOSE	8	millimole per litre	3.9	6.1	N

FDA - Adverse Event Reporting System (FAERS)
FOIA Case Report Information

Case ID: 22873106

GLUCOSE	5.6	millimole per litre	3.9	6.1	N
GLUCOSE	18.4	millimole per litre	3.9	6.1	N
GLUCOSE	8.1	millimole per litre	3.9	6.1	N
GLUCOSE	10.8	millimole per litre	3.9	6.1	N
LACTATE DEHYDROGENASE	176	enzyme unit per litre	125	220	N
LACTATE DEHYDROGENASE	7896	enzyme unit per litre	125	220	N
LACTATE DEHYDROGENASE	428	enzyme unit per litre	125	220	N
LACTATE DEHYDROGENASE	2799	enzyme unit per litre	125	220	N
LACTATE DEHYDROGENASE	782	enzyme unit per litre	125	220	N
LACTATE	25	millimole per litre	0.5	1.6	N
LACTATE	4.4	millimole per litre	0.5	1.6	N
LACTATE	7.9	millimole per litre	0.5	1.6	N
LACTATE	9.2	millimole per litre	0.5	1.6	N
LACTATE	9.5	millimole per litre	0.5	1.6	N
LACTATE					Y
MAGNESIUM	1.16	millimole per litre	0.7	1	N
MAGNESIUM	0.8	millimole per litre	0.7	1	N
MAGNESIUM	1.35	millimole per litre	0.7	1	N
MAGNESIUM	0.67	millimole per litre	0.7	1	N
MAGNESIUM	0.71	millimole per litre	0.7	1	N
PHOSPHATE	1.85	millimole per litre	0.8	1.5	N
PHOSPHATE	1.02	millimole per litre	0.8	1.5	N
PHOSPHATE	0.5	millimole per litre	0.8	1.5	N
PHOSPHATE	1.17	millimole per litre	0.8	1.5	N
PHOSPHATE	1.51	millimole per litre	0.8	1.5	N
POTASSIUM	5.2	millimole per litre	3.5	5.1	N
POTASSIUM	4.5	millimole per litre	3.5	5.1	N
POTASSIUM	4.3	millimole per litre	3.5	5.1	N
POTASSIUM	3.2	millimole per litre	3.5	5.1	N

FDA - Adverse Event Reporting System (FAERS)
FOIA Case Report Information

Case ID: 22873106

POTASSIUM	4.5	millimole per litre	3.5	5.1	N
BLOOD PRESSURE					Y
SODIUM	142	millimole per litre	135	145	N
SODIUM	139	millimole per litre	135	145	N
SODIUM	139	millimole per litre	135	145	N
SODIUM	137	millimole per litre	135	145	N
SODIUM	136	millimole per litre	135	145	N
UREA	4.7	millimole per litre	2.5	7.8	N
UREA	1.3	millimole per litre	2.5	7.8	N
UREA	0.9	millimole per litre	2.5	7.8	N
UREA	3.8	millimole per litre	2.5	7.8	N
UREA	4.3	millimole per litre	2.5	7.8	N
BODY MASS INDEX	46	kilogram per square metre			N
BODY TEMPERATURE	35.7	degree Celsius			N
CALCIUM IONISED	1.01	millimole per litre	1.05	1.3	N
CALCIUM IONISED	0.96	millimole per litre	1.05	1.3	N
CALCIUM IONISED	0.88	millimole per litre	1.05	1.3	N
CALCIUM IONISED	0.89	millimole per litre	1.05	1.3	N
CALCIUM IONISED	0.87	millimole per litre	1.05	1.3	N
GLASGOW COMA SCALE					Y
CT SCAN					Y
DRUG LEVEL	29	milligram per litre			N
DRUG LEVEL	622.9	milligram per litre			N
DRUG LEVEL					Y
GAMMA GLUTAMYL TRANSPEPTIDASE	34	enzyme unit per litre	10	60	N
GAMMA GLUTAMYL TRANSPEPTIDASE	71	enzyme unit per litre	10	60	N
GAMMA GLUTAMYL TRANSPEPTIDASE	40	enzyme unit per litre	10	60	N
GAMMA GLUTAMYL TRANSPEPTIDASE	111	enzyme unit per litre	10	60	N

Case ID: 22873106

GAMMA GLUTAMYL TRANSPEPTIDASE	38	enzyme unit per litre	10	60	N
GLOMERULAR FILTRATION RATE	62	millilitre per minute per 1.73 squa	90	120	N
GLOMERULAR FILTRATION RATE	38	millilitre per minute per 1.73 squa	90	120	N
GLOMERULAR FILTRATION RATE	90	millilitre per minute per 1.73 squa	90	120	N
GLOMERULAR FILTRATION RATE	43	millilitre per minute per 1.73 squa	90	120	N
GLOMERULAR FILTRATION RATE	90	millilitre per minute per 1.73 squa	90	120	N
HAEMATOCRIT					Y
HAEMATOCRIT					Y
HAEMATOCRIT					Y
HAEMATOCRIT					Y
HAEMATOCRIT					Y
HAEMOGLOBIN	7.2	millimole per litre	8.5	11	N
HAEMOGLOBIN	8.5	millimole per litre	8.5	11	N
HAEMOGLOBIN	6.8	millimole per litre	8.5	11	N
HAEMOGLOBIN	6.6	millimole per litre	8.5	11	N
HAEMOGLOBIN	6.3	millimole per litre	8.5	11	N
OXYGEN SATURATION	95	percent			N
PCO2	5.6	kilopascal			N
PCO2	4.9	kilopascal	4.7	6	N
PCO2	6	kilopascal	4.7	6	N
PCO2	6.2	kilopascal	4.7	6	N
PCO2	5.6	kilopascal	4.7	6	N
PCO2	4.9	kilopascal	4.7	6	N
PH					Y
PH					Y

Case ID: 22873106

PH					Y
PH					Y
PH					Y
PLATELET COUNT	85	billion per litre	150	450	N
PLATELET COUNT	244	billion per litre	150	450	N
PLATELET COUNT	146	billion per litre	150	450	N
PLATELET COUNT	152	billion per litre	150	450	N
PO2	14.3	kilopascal	11	13	N
PO2	11.3	kilopascal	11	13	N
PO2	9.6	kilopascal	11	13	N
PO2	9.5	kilopascal	11	13	N
PO2	12.7	kilopascal	11	13	N
RESPIRATORY RATE					Y
SINUS RHYTHM	89	per minute			N
WHITE BLOOD CELLS	5.3	billion per litre	4	11	N
WHITE BLOOD CELLS	36.7	billion per litre	4	11	N
WHITE BLOOD CELLS	24.2	billion per litre	4	11	N
WHITE BLOOD CELLS	18.7	billion per litre	4	11	N
WHITE BLOOD CELLS	20	billion per litre	4	11	N

Concomitant Products:

#	Product Name:	Dose/Frequency	Route	Dosage Text	Start Date	End Date	Indication(s)	Interval 1st Dose to Event
1	Vasopressin	/	Unknown	0.03 IE/min			Vasoplegia syndrome	
2	Hydrocortisone	/	Unknown	UNK			Vasoplegia syndrome	
3	Activated charcoal	/	Unknown	UNK				
4	Noradrenaline	/	Unknown	0 to 1.2 µg/kg/min (increasing rapidely)			Vasoplegia syndrome	

5	Noradrenaline	/	Unknown	0.5 µg/kg/min (15 min after first inj) for 6 h
6	Noradrenaline	/	Unknown	UNK0.25 µg/kg/min. after second 2 mg/kg

Reporter Source:

Study report?: No **Sender organization:** MYLAN **503B Compounding Outsourcing Facility?:**

Literature Text: Jessica D. Workum JD, Keyany A, Jaspers CCT. Methylene blue as treatment for vasoplegic shock in severe metformin overdose. A case report. Elsevier Toxicology Reports. 2023;11:141-144

FDA - Adverse Event Reporting System (FAERS)
FOIA Case Report Information

Case ID: 22910526

Case Information:

Case Type : Expedited (15-Day) **eSub:** Y **HP:** N **Country:** CA **Event Date:** **Outcomes:** DE **Application Type:**

FDA Rcvd Date: 06-Sep-2023 **Mfr Rcvd Date:** 25-Aug-2023 **Mfr Control #:** CA-NOVOPROD-1108849 **Application #:** 209637

Patient Information:

Age: **Sex:** Male **Weight:**

Suspect Products:

#	Product Name:	Compounded Drug ?	Dose/Frequency	Route	Dosage Text	Start Date	End Date	Indication(s)
1	Ozempic		/		UNK			Product used for unknown indication

#	Product Name:	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler	OTC
1	Ozempic		Not Applicable	NA				NOVO NORDISK	

Device Products:

#	Brand Name / Common Device Name / Product Code	Similar Device?	Malfunction ?	Device Lot#	Device Usage/ Operator of Device	Remedial Action	Device Problem	Manufacturer Name
1	Ozempic//	No			/Other		Adverse Event Without Identified Device or Use Problem	Novo Nordisk A/S

Event Information:

Preferred Term (MedDRA Version: v.26.1) **ReC**

Completed suicide

Event/Problem Narrative:

FDA - Adverse Event Reporting System (FAERS)
FOIA Case Report Information

Case ID: 22910526

This serious Spontaneous case from CANADA was reported by a Consumer as "suicide(Suicide)" with an unspecified onset date, and concerned a Male patient who was treated with Ozempic (SEMAGLUTIDE) from unknown start date for "Product used for unknown indication", Patient height, weight, and body mass index were not reported Medical history was not provided. On an unknown date, the patient commited suicide (reason unknown). Autopsy Information was not reported. Batch Numbers: Ozempic: Requested Action taken to Ozempic was Not Applicable.. The outcome for the event "suicide(Suicide)" was Fatal. Company Comment : 'Completed Suicide' was assessed as unlisted according to Novo Nordisk current CCDS on Ozempic.Information on detailed clinical course of events, concomitant medications (benzodiazepines, etc.), complete medical history (previous history of similar episode, treatment with sleep medications, etc.), family history and social/environmental circumstances , onset latency between suspect product exposure and event onset etc preclude comprehensive medical assessment. This single case report is not considered to change the current knowledge of the safety profile of Ozempic.

Relevant Medical History:

Disease/Surgical Procedure	Start Date	End Date	Continuing?

Medical History Product(s)	Start Date	End Date	Indications	Events

Relevant Laboratory Data:

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail

Concomitant Products:

#	Product Name:	Dose/Frequency	Route	Dosage Text	Start Date	End Date	Indication(s)	Interval 1st Dose to Event

Reporter Source:

Study report?: No **Sender organization:** NOVO NORDISK **503B Compounding Outsourcing Facility?:**

Literature Text:

FDA - Adverse Event Reporting System (FAERS)
FOIA Case Report Information

Case ID: 22949407

Case Information:

Case Type : Expedited (15-Day) **eSub:** Y **HP:** **Country:** NL **Event Date:** **Outcomes:** DE , OT **Application Type:** SUN

FDA Rcvd Date: 15-Sep-2023 **Mfr Rcvd Date:** 31-Aug-2023 **Mfr Control #:** NL-SUN PHARMACEUTICAL INDUSTRIES LTD-2023RR-407933 **Application #:** 075967

Patient Information:

Age: 55 YR **Sex:** Female **Weight:** 125 KG

Suspect Products:

#	Product Name:	Compounded Drug ?	Dose/Frequency	Route	Dosage Text	Start Date	End Date	Indication(s)
1	Metformin		82.5 G Gram(S) /	Oral	82.5 gram			Product used for unknown indication
2	Noradrenaline		/	Unknown	rapidly increasing to 1.2 microgram/kg/min			Shock
3	Acetaminophen		10 G Gram(S) /	Oral	10 gram			Product used for unknown indication
4	Simvastatin		1520 Mg Milligram(S) /	Oral	1520 milligram			Product used for unknown indication
5	Semaglutide		420 Mg Milligram(S) /	Oral	420 milligram			Product used for unknown indication
6	Vasopressin		/	Unknown	0.03 IE/min			Shock
7	Hydrocortisone		/	Unknown	UNK			Shock

#	Product Name:	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler	OTC
1	Metformin		Not Applicable	NA				SUN	
2	Noradrenaline		Not Applicable	NA				SUN	

FDA - Adverse Event Reporting System (FAERS)
FOIA Case Report Information

Case ID: 22949407

3	Acetaminophen	Not Applicable	NA		RANBAXY
4	Simvastatin	Not Applicable	NA		SUN
5	Semaglutide	Not Applicable	NA		
6	Vasopressin	Not Applicable	NA		
7	Hydrocortisone	Not Applicable	NA		RANBAXY

Device Products:

#	Brand Name / Common Device Name / Product Code	Similar Device?	Malfunction ?	Device Lot#	Device Usage/ Operator of Device	Remedial Action	Device Problem	Manufacturer Name
1	//	No			/			
2	//	No			/			
3	//	No			/			
4	//	No			/			
5	//	No			/			
6	//	No			/			
7	//	No			/			

Event Information:

Preferred Term (MedDRA Version: v.26.1)	ReC
Suicide attempt	
Vasoplegia syndrome	
Toxicity to various agents	
Lactic acidosis	
Intentional overdose	
Drug ineffective	

Event/Problem Narrative:

This Literature case was reported by a other health professional and concerns a 55 Years old female patient from NETHERLANDS. The Medical History of patient includes depression, suicide attempt and type 2 diabetes mellitus. The patient was started on Company suspect(s): Acetaminophen (PARACETAMOL) Unknown Formulation for an unknown indication, Hydrocortisone (HYDROCORTISONE) Unknown Formulation for Refractory shock, Metformin (METFORMIN) Unknown Formulation for an unknown indication, Noradrenaline (NORADRENALINE) Unknown Formulation for Shock and Simvastatin (SIMVASTATIN) Unknown

FDA - Adverse Event Reporting System (FAERS)
FOIA Case Report Information

Case ID: 22949407

Formulation for an unknown indication. The non-company suspect drug(s) includes Semaglutide (Semaglutide) for an unknown indication and Vasopressin (Vasopressin) for shock. Acetaminophen (PARACETAMOL) Unknown Formulation (Company suspect) was administered at 10 gram Oral use. Hydrocortisone (HYDROCORTISONE) Unknown Formulation (Company suspect) was administered at Unknown Dosage Unknown Route of Admin. Metformin (METFORMIN) Unknown Formulation (Company suspect) was administered at 82.5 gram Oral use. Noradrenaline (NORADRENALINE) Unknown Formulation (Company suspect) was administered at rapidly increasing to 1.2 microgram/kg/min Unknown Route of Admin. Simvastatin (SIMVASTATIN) Unknown Formulation (Company suspect) was administered at 1520 milligram Oral use. Semaglutide (Semaglutide) (non-company suspect) was administered at 420 milligram Oral use. Vasopressin (Vasopressin) (non-company suspect) was administered at 0.03 IE/min Unknown Route of Admin. No Concomitant medications were reported. On unspecified date the patient experienced Suicide attempt (death, medically-significant), Vasoplegia syndrome (death, medically-significant), Toxicity to various agents (death, medically-significant), Lactic acidosis (death, medically-significant), Intentional overdose (death, medically-significant) and Drug ineffective (medically-significant). Action Taken with Metformin (METFORMIN) (Company suspect) was not applicable. The dechallenge was not applicable. The rechallenge was not applicable. Action Taken with Noradrenaline (NORADRENALINE) (Company suspect) was not applicable. The dechallenge was not applicable. The rechallenge was not applicable. Action Taken with Acetaminophen (PARACETAMOL) (Company suspect) was not applicable. The dechallenge was not applicable. The rechallenge was not applicable. Action Taken with Simvastatin (SIMVASTATIN) (Company suspect) was not applicable. The dechallenge was not applicable. The rechallenge was not applicable. Action Taken with Hydrocortisone (HYDROCORTISONE) (Company suspect) was not applicable. The dechallenge was not applicable. The rechallenge was not applicable. Action taken with non-company suspect drug Semaglutide (Semaglutide) and Vasopressin (Vasopressin) was not applicable and not applicable respectively. The outcome(s) of the event(s) was reported as Suicide attempt (Fatal), Vasoplegia syndrome (Fatal), Toxicity to various agents (Fatal), Lactic acidosis (Fatal), Intentional overdose (Fatal) and Drug ineffective (Unknown). On unspecified date, the patient had passed away. The Autopsy was not done. The cause of death was reported as Vasoplegia syndrome, Intentional overdose, Toxicity to various agents, Lactic acidosis. The reporter assessed the causality for the events (Drug ineffective) as Related and for the events (Suicide attempt, Vasoplegia syndrome, Toxicity to various agents, Lactic acidosis and Intentional overdose) as Not Related to Hydrocortisone. The reporter assessed the causality for the events (Drug ineffective) as Related and for the events (Suicide attempt, Vasoplegia syndrome, Toxicity to various agents, Lactic acidosis and Intentional overdose) as Not Related to Noradrenaline. The reporter assessed the causality for the events (Suicide attempt) as Related and for the events (Vasoplegia syndrome, Toxicity to various agents, Lactic acidosis, Intentional overdose and Drug ineffective) as Not Related to Acetaminophen. The reporter assessed the causality for the events (Suicide attempt) as Related and for the events (Vasoplegia syndrome, Toxicity to various agents, Lactic acidosis, Intentional overdose and Drug ineffective) as Not Related to Simvastatin. The reporter assessed the causality for the events (Suicide attempt, Vasoplegia syndrome, Toxicity to various agents, Lactic acidosis and Intentional overdose) as Related and for the events (Drug ineffective) as Not Related to Metformin. The case is linked to (. The case is deemed Serious (Death, Medically Significant). Sun Pharma medical reviewer's assessment: The case is rated as serious. Based on the temporal association between administration of the suspect drugs and onset of the ADRs, causality of Suicide attempt, Vasoplegia syndrome, Toxicity to various agents, Lactic acidosis and Intentional overdose is assessed as related to Metformin. Causality of Suicide attempt is assessed as related to Acetaminophen and Simvastatin and causality of Drug ineffective is assessed as related to Noradrenaline and Hydrocortisone. The adverse event Lactic acidosis is listed among the SPC of Metformin and Noradrenaline . The rest of the adverse events are not listed among the SPCs of the other suspect drugs. Further information will be requested from the authors for a more accurate assessment of the case.

Relevant Medical History:

Disease/Surgical Procedure	Start Date	End Date	Continuing?
Suicide attempt			
Type 2 diabetes mellitus			
Depression			Yes

Medical History Product(s)	Start Date	End Date	Indications	Events

FDA - Adverse Event Reporting System (FAERS)
FOIA Case Report Information

Case ID: 22949407

Relevant Laboratory Data:

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail

Concomitant Products:

#	Product Name:	Dose/Frequency	Route	Dosage Text	Start Date	End Date	Indication(s)	Interval 1st Dose to Event

Reporter Source:

Study report?: No **Sender organization:** RANBAXY **503B Compounding Outsourcing Facility?:**

Literature Text: Workum JD, Keyany A, Jaspers TCC. Methylene blue as treatment for vasoplegic shock in severe metformin overdose: A case report. Toxicology Reports. 2023;11:141-144