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

Date - Time: 26-Sep-2024 16:15:20 EDT

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

Case ID(s) Printed:

22960930	23410623	23449022	23467967
23469335	23720825	23796312	23891676
23961490	23980673	23989873	23999511
24007576			

Total Cases: 13

Total number of Inactive cases: *0

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

Case ID: 22960930

Case Information:

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

FDA Rcvd Date: 08-Jan-2024 **Mfr Rcvd Date:** 28-Dec-2023 **Mfr Control #:** CA-Accord-361536 **Combination Product Report:** No Information **Application #:** 205011

Patient Information:

Age: 37 YR **Sex:** Female **Weight:**

Suspect Products:

#	Product Name:	Compounded Drug ?	Dose/Frequency	Route	Dosage Text	Start Date	End Date	Indication(s)
1	LACOSAMIDE		/	Unknown				10041962
2	LEVETIRACETAM		/	Unknown				10041962
3	AZATHIOPRIN		150.0 Mg Milligram(S) /	Unknown	1 every 1 Days			10054980
4	CLOBAZAM		/	Unknown				10041962
5	Eslicarbazepine		/	Oral				10041962
6	KETAMIN		/	Unknown				10018060
7	LORAZEPAM		/	Unknown				10041962
8	METHYLPREDNISOLONE		/	Unknown				10054980
9	MIDAZOLAM		/	Unknown				10018060
10	Perampanel		/	Oral				10041962
11	PHENOBARBITAL		/	Unknown				10041962
12	PHENYTOIN		/	Unknown				10041962
13	PROPOFOL		/	Unknown				10018060
14	RITUXIMAB		/	Intravenous (not otherwise specified)	1 every 1 weeks			10054980

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15	IMMUNOGLOBULIN HUMAN	/	Intravenous (not otherwise specified)	Immunosuppressant drug therapy, Immunomodulat ory therapy		10054980
16	LAMOTRIGINE	/				10041962
17	VALPROIC ACID	/	Unknown			10041962
18	AZATHIOPRIN	150.0 Mg Milligram(S) /	Unknown	1 every 1 Days		10041962
19	IMMUNOGLOBULIN HUMAN	1 Dosage Form /	Intravenous (not otherwise specified)	IV drip, every 1 Day		10041962
20	KETAMIN	/	Unknown			10041962
21	METHYLPREDNISOLONE	/	Unknown			10041962
22	MIDAZOLAM	/	Unknown			10041962
23	PROPOFOL	/	Unknown			10041962
24	RITUXIMAB	1 Dosage Form /	Intravenous (not otherwise specified)	1 every 1 day, IV drip		10041962

#	Product Name:	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler	OTC
1	LACOSAMIDE		Unknown	NA					
2	LEVETIRACETAM		Unknown	NA					
3	AZATHIOPRIN		Unknown	NA					
4	CLOBAZAM		Unknown	NA					
5	Eslicarbazepine		Unknown	NA					
6	KETAMIN		Unknown	NA					
7	LORAZEPAM		Unknown	NA					
8	METHYLPREDNISOLONE		Unknown	NA					
9	MIDAZOLAM		Unknown	NA					
10	Perampanel		Unknown	NA					
11	PHENOBARBITAL		Unknown	NA					

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12	PHENYTOIN	Unknown	NA
13	PROPOFOL	Unknown	NA
14	RITUXIMAB	Unknown	NA
15	IMMUNOGLOBULIN HUMAN	Unknown	NA
16	LAMOTRIGINE	Unknown	NA
17	VALPROIC ACID	Unknown	NA
18	AZATHIOPRIN	Unknown	NA
19	IMMUNOGLOBULIN HUMAN	Unknown	NA
20	KETAMIN	Unknown	NA
21	METHYLPREDNISOLONE	Unknown	NA
22	MIDAZOLAM	Unknown	NA
23	PROPOFOL	Unknown	NA
24	RITUXIMAB	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			/			
5	//	No			/			
6	//	No			/			
7	//	No			/			
8	//	No			/			
9	//	No			/			
10	//	No			/			

11	//	No	/
12	//	No	/
13	//	No	/
14	//	No	/
15	//	No	/
16	//	No	/
17	//	No	/
18	//	No	/
19	//	No	/
20	//	No	/
21	//	No	/
22	//	No	/
23	//	No	/
24	//	No	/

Event Information:

Preferred Term (MedDRA Version: v.27.0) **ReC**

Drug ineffective

Event/Problem Narrative:

MHPD Health Authority report from a other health professional via the Regulatory Agency (CA-MHPD-E2B_06204721) concerns a 37 years old adult female patient who had drug ineffective after receiving azathioprin, clobazam, eslicarbazepine, Immunoglobulin (human), ketamin, lacosamide, levetiracetam, lorazepam , methylprednisolone, midazolam, perampanel, phenobarbital, phenytoin, propofol, rituximab and valproic acid, all for status epilepticus. Concomitant medications included acyclovir, ceftriaxone, piperacillin sodium w/tazobactam and vancomycin, all for status epilepticus. The patient received azathioprin (150 mg) (1 every 1 days), clobazam (tablet), eslicarbazepine, Immunoglobulin (human), ketamin, lacosamide, levetiracetam, lorazepam, methylprednisolone, midazolam, perampanel, phenobarbital, phenytoin, propofol for route Intravenous (not otherwise specified), rituximab (1 every 1 weeks), and valproic acid, all with batch no: unknown. Patient had drug ineffective. At the time of reporting, the action taken with azathioprin, clobazam, eslicarbazepine, Immunoglobulin (human), ketamin, lacosamide, levetiracetam, lorazepam , methylprednisolone, midazolam, perampanel, phenobarbital, phenytoin, propofol, rituximab and valproic was reported as unknown. The outcome of drug ineffective was reported as unknown. The reporter considered case to be Non-Serious. Medical review comment: The causality is assessed as possible for event drug ineffective with suspect drug lacosamide and levetiracetam based on available information. Version 02 was created as duplicate (CA-MHPD-E2B_06435582) received on 08-Sep-2023. Additional information revealed that, Event drug ineffective upgraded to serious (hospitalization), indication updated for drug Azathioprine, Ketamine, Methylprednisolone, Midazolam, Rituximab, Immunoglobulin Human for Immunosuppressant drug therapy. Added additional Co-suspect drug Lamotrigine for status epilepticus. The reporter considered the case to be serious as the event was involved hospitalization. Duplicate (CA-MHPD-E2B_06435814) received on 08-Sep-2023. Additional information revealed that, Additional seriousness life threatening and other medically significant

was added, updated indication for concomitant medication Piperacillin Sodium/Tazobactam, Vancomycin, Acyclovir and Ceftriaxone for antibiotic therapy, updated indication for co-suspect Ketamine for general anaesthesia. Updated indication for co-suspect Midazolam and Propofol for General anaesthesia. The reporter considered the case to be serious as the event was life threatening and other medically significant. Duplicate (CA-MHPD-E2B_06463107) received on 08-Sep-2023. No new medically significant information was received. Duplicate (CA-MHPD-E2B_06465151) received on 08-Sep-2023. No new medically significant information was received. Medical review comment: The causality is assessed as possible for event drug ineffective with suspect drug lacosamide and levetiracetam based on available information. However, other co-suspect drug also ineffective which confounds the causality. Version 03 has been created as duplicate (CA-MHPD-E2B_06669945) received on 28-Dec-2023. Additional information revealed that, Brand name of suspect drug eslicarbazepine has been added as Aptiom and dosage form has been added as tablets and route of administration has been added as oral. Duplicate (CA-MHPD-E2B_06689009) received on 28-Dec-2023. Additional information revealed that, Additional regimen of suspect drug azathioprine at the dose of 150mg for status epilepticus has been added. Additional regimen of suspect drug immunoglobulin human and rituximab at the dose of 1 dosage form intravenous drip for status epilepticus have been added. Additional regimen of suspect drug ketamine, methylprednisolone, midazolam for status epilepticus have been added. Brand name for suspect drug perampanel has been added as Fycompa and route of administration has been added as oral. Medical review comment: No changes were made in previous medical review comment.

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
1	ACYCLOVIR	/	Unknown				10067768	
2	CEFTRIAXONE	/	Unknown				10067768	
3	PIPERACILLIN SODIUM W/ TAZOBACTAM SO	/	Unknown				10067768	
4	VANCOMYCIN	/	Unknown				10067768	

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FOIA Case Report Information

Case ID: 22960930

Reporter Source:

Study report?: No

Sender organization: ACCORD

503B Compounding Outsourcing Facility?:

Literature Text:

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

Case ID: 23410623

Case Information:

Case Type : Expedited (15-Day) **eSub:** Y **HP:** Y **Country:** CH **Event Date:** 18-Oct-2023 **Outcomes:** LT , HO **Application Type:** ANDA

FDA Rcvd Date: 17-Jan-2024 **Mfr Rcvd Date:** 08-Jan-2024 **Mfr Control #:** CH-FreseniusKabi-FK202400617 **Combination Product Report:** No **Application #:** 206223

Patient Information:

Age: 85 YR **Sex:** Male **Weight:** 84 KG

Suspect Products:

#	Product Name:	Compounded Drug ?	Dose/Frequency	Route	Dosage Text	Start Date	End Date	Indication(s)
1	Remifentanil Hydrochloride		/	Intravenous (not otherwise specified)		18-Oct-2023	18-Oct-2023	10073800
2	PROPOFOL		/	Intravenous (not otherwise specified)		18-Oct-2023	18-Oct-2023	10073800
3	CEFUROXIM FRESENIUS		1.5 G Gram(S) /	Intravenous (not otherwise specified)	2x 1.5 g (7:50 and 13:55)	18-Oct-2023	18-Oct-2023	10049086
4	Iomeron		/	Intravenous (not otherwise specified)		18-Oct-2023	18-Oct-2023	10050062
5	Atracurium		/	Intravenous (not otherwise specified)		18-Oct-2023	18-Oct-2023	10073800
6	Dexamethasonum		/	Intravenous (not otherwise specified)	IN TOTAL	18-Oct-2023	18-Oct-2023	10073800
7	Fentanyl		/	Intravenous (not otherwise specified)	9 x 0.1 mg	18-Oct-2023	18-Oct-2023	10073800
8	Heparin		/	Intravenous (not otherwise specified)	1.25 x 7500 IU	18-Oct-2023	18-Oct-2023	10073800

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9	Ketamin	/	Intravenous (not otherwise specified)	1.8 x 40 mg	18-Oct-2023	18-Oct-2023	10073800	
10	Morphine	/	Intravenous (not otherwise specified)	IN TOTAL	18-Oct-2023	18-Oct-2023	10073800	

#	Product Name:	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler	OTC
1	Remifentanil Hydrochloride	1 Day	Not Applicable	NA	Unknown			UNKNOWN	
2	PROPOFOL	1 Day	Not Applicable	NA	Unknown			UNKNOWN	
3	CEFUROXIM FRESENIUS	1 Day	Not Applicable	NA	Unknown				
4	Iomeron		Not Applicable	NA	Unknown				
5	Atracurium		Not Applicable	NA	Unknown				
6	Dexamethasonum		Not Applicable	NA	Unknown				
7	Fentanyl		Not Applicable	NA	Unknown				
8	Heparin		Not Applicable	NA	Unknown				
9	Ketamin		Not Applicable	NA	Unknown				
10	Morphine		Not Applicable	NA	Unknown				

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			/			

Case ID: 23410623

8	//	No	/
9	//	No	/
10	//	No	/

Event Information:

Preferred Term (MedDRA Version: v.27.0)	**ReC**
Anaphylactic shock	
Hypokalaemia	

Event/Problem Narrative:

Anaphylactic shock (anaphylactic shock, anaphylactic shock) Hypokalaemia (hypokalaemia, hypokalaemia) Country of occurrence: Switzerland. Case reference number FK202400617 is a spontaneous case received on 08/Jan/2024 from pharmacist that refers to a 85-years-old, male patient with a body weight of 84 kilograms and a body height of 170 centimeters. The patient's medical history included popliteal artery aneurysm, arterial hypertension, hypercholesteraemia, diastasis recti abdominis, basal cell carcinoma, squamous cell carcinoma, arrhythmia sinus, av block first degree, nicotine dependence, alcohol use and right femoro-popliteal bypass surgery. Concomitant medication included ass cardio (oral), acicutan (oral), valsartan (oral, unknown therapy start date through(b)(6)****** and oral, (b)(6)******through 01/Nov/2023), atorvastatin (oral, (b)(6)***** through 01/Nov/2023), noradrenalin [norepinephrine hydrochloride] (intravenous, on(b)(6)******), ephedrine (intravenous, on(b)(6)******), ringer acetate [calcium chloride;potassium chloride] (intravenous, on (b)(6)*****) and ringer lactat [calcium chloride;potassium chloride;sodium lactate] (intravenous on(b)(6)******). On (b)(6)*****, the patient received intravenous CEFUROXIM FRESENIUS (lot number unknown) for antibacterial prophylaxis, REMIFENTANYL (manufacturer and lot unknown), for general anaesthesia and PROPOFOL (manufacturer and lot number unknown) given for induction of anesthesia. Additionally, as co-suspect medication he received intravenous Iomeron for angiography, Atracurium, Dexamethasonum, Fentanyl, Heparin, Ketamin and Morphine for anaesthesia general. On(b)(6)******, patient developed anaphylactic shock and hypokalaemia. Action taken with the suspect drugs was unknown. Relevant tests/laboratory data were included: tryptase (7.8 microgram per litre), potassium (3.3 millimole per litre), heart rate (unknown), blood pressure (unknown). The outcome for the event anaphylactic shock was resolving and for hypokalaemia unknown. The case was considered to be serious, due to life threatening condition. Translation of the Verbatim: This 85-year-old male patient (weight: 84 kg; height: 170 cm) with right popliteal artery aneurysm was admitted for in-patient right femoro-popliteal bypass surgery. Preoperatively, the patient reported no symptoms or abnormalities whatsoever, and there were no acute signs of infection or B symptoms.Following uneventful induction of anaesthesia on (b)(6)****, the patient experienced an increasingly unstable circulation (tachycardia, hypotension) starting about 15 minutes into the procedure, with increasing vasoactive drug requirements (up to 60 mcg noradrenaline [norepinephrine]). An emergency transthoracic echocardiogram revealed no cardiac abnormalities to account for his symptoms. Apart from the severe circulatory instability, the patient also had an exanthem on the trunk, swelling of the face, throat and tongue, and increasing peripheral oedema (DD angioedema). Intraoperative tryptase was 7.8 mcg/L and hence normal (reference range unknown). Suspected anaphylaxis either in response to perioperative administration (on (b)(6)****) of Cefuroxim Fresenius 2 x 1.5 g IV (at 7:50am and 1:55pm) or in response to repeated administration of the contrast material Iomeron® (iomeprol, dose/dosing interval unknown) as part of a computed tomography scan/angiogram prompted treatment of the symptoms with Tavegyl® (clemastine) 2 g [Note from translator: should possibly be mg] IV, Solu-Medrol® (methylprednisolone) 125 mg IV and epinephrine 0.5 mg IM and 0.1 mg via Perfusor over 3 hours, and noradrenaline (norepinephrine). Fluids (10 L in total) and one unit of packed red cells were administered intraoperatively to manage hypovolaemia and replace blood loss. Perioperatively, the norepinephrine Perfusor and the epinephrine Perfusor delivered up to a maximum of 40 mL/h and 15 mL/h, respectively. Following initial stabilisation, tachycardia increased again at the end of surgery; epinephrine and the packed red cell transfusion were therefore stopped. Postoperatively, the patient was admitted to the intensive care unit. In the ICU, the patient presented with haemodynamic instability including an elevated heart rate (130-140 bmp) and low blood pressure (97/57 mmHg). The ECG showed no evidence of higher grade block or acute ischaemia. During the anaphylactic shock, troponin was elevated (trop 62; no unit or reference range reported) but stable over time, with no evidence of acute coronary syndrome. Rattling breath

sounds bilat prompted treatment with inhaled Atrovent (ipratropium). Steroid dosing with Solu-Medrol 125 mg IV was continued in the ICU until (b)(6)**** before switching to Spiricort (prednisolone) 50 mg on(b)(6)*****. In addition, the patient remained intubated until (b)(6)****.Hypokalaemia ((b)(6)****: 3.3 mmol/L, reference unknown) was managed with IV potassium until (b)(6)****. On(b)(6)*****, the patient was haemodynamically stable and moved to a regular ward and, later on, he was discharged home o his usual domestic environment. Additional medication until onset of the ADRs: •ASS Cardio (acetylsalicylic acid) 100 mg PO once daily •Acicutan® (acitretin) 10 mg PO once daily •Valsartan 80 mg PO once daily, withheld from(b)(6) through (b)(6)****, and from 01/11/2023 •Atorvastatin 20 mg PO once daily In addition, the following medications were administered by the anaesthesia team as part of the anaesthesia protocol: •Norepinephrine IV via Perfusor •Ephedrine 2 x 6 mg IV •Atracurium IV via Perfusor •Dexamethasone 4 mg IV •Fentanyl 9 x 0.1 mg IV •Heparin 1.25 x 7500 IU IV •Ketamine 1.8 x 40 mg IV •Propofol 633 mcg IV •Remifentanil 40 ng IV •Morphine 10 mg IV administered 3 hours before the event. The following concomitant and secondary diagnoses are known: arterial hypertension, hypercholesterolaemia, diastasis recti abdominis, H/O multiple basal cell carcinomas and moderately differentiated squamous cell carcinomas. Sinus arrhythmia with first-degree AV block (first diagnosed on (b)(6)****). Nicotine abuse (2 pack years, stopped about 2 months previously), alcohol consumption (not more than 1 glass of beer/wine per day).No further relevant information about this case is available to us Post-marketing experience includes very rare reports of angioedema, eczema, circulatory collapse or shock, laryngeal oedema and pharyngeal oedema. In clinical studies, tachycardia, hypotension and skin rash were rare (0.01-0.1%) and erythema an uncommon (0.1-1%) adverse event following intravascular administration. Hypokalaemia is not listed as a known ADR.The WHO pharmacovigilance database lists 1,128 cases of “Anaphylactic shock (PT)” and 686 cases of “Anaphylactic reaction (PT)” in a total of 49,996 individual Case Safety Reports received for iomeprol since 1994. It should be noted that, due to the nature of the spontaneous reporting system, WHO database case reports do not necessarily show an actual causal relationship to medication exposure.The Swiss Product Information of Noradrenalin Sintetica (one of the available norepinephrine brands) lists tachycardia as a known ADR from post-marketing experience (no frequency reported), typically as a consequence of overdose or too-rapid intravenous administration. Anaphylactic reactions or hypokalaemia are not explicitly listed under adverse drug reactions.According to the Swiss Product Information of Ephedrin Streuli® (one of the available ephedrine brands), anaphylactic reactions or hypokalaemia are not explicitly listed under adverse drug reactions.According to the Swiss Product Information of Atracurium Labatec® IV (one of the available atracurium brands), the administration of atracurium may very rarely be associated with anaphylactic/anaphylactoid reactions. Patients treated with atracurium and one or more anaesthetics have very rarely been observed to develop severe anaphylactoid or anaphylactic reactions. ADRs listed as common (1-10%) include typically mild, temporary arterial hypotension and flushing as consequences of histamine release. Hypokalaemia is not explicitly mentioned.According to the Swiss Product Information of Dexamethason Galepharm (one of the available dexamethasone brands), treatment with this medication may be associated with serious anaphylactic reactions accompanied by arrhythmias, bronchospasm, blood pressure increase or decrease and/or circulatory failure (no frequency reported). Increased potassium excretion (no frequency reported) is also listed under ADRs.The Swiss Product Information of Heparin Sintetica (one of the available heparin brands) lists allergic reactions accompanied by symptoms such as erythema, bronchospasm and drop in blood pressure among the rare adverse events and anaphylactic shock among the very rare adverse events. Uncommon adverse reactions include local tissue reactions such as induration and redness. Hypokalaemia is not explicitly mentioned.The Swiss Product Information of Ketamin Sintetica (one of the available ketamine brands) lists anaphylactic reactions as rare ADRs. Tachycardia and erythema are listed as common adverse events, and hypotension is documented as an uncommon adverse event. Hypokalaemia is not explicitly mentioned.According to the Swiss Product Information of Propofol Labatec (one of the available propofol brands), the administration of propofol may very rarely be associated with anaphylaxis, angioedema, bronchospasm, erythema and hypotension. Hypotension may commonly occur. Hypokalaemia is not explicitly mentioned.According to the Swiss Product Information of Fentanyl-Mepha IV (one of the available fentanyl brands), clinical studies of intravenous fentanyl reported uncommon events of allergic reactions (anaphylaxis, bronchospasm). From post-marketing experience, there have been very rare reports of hypersensitivity reactions including anaphylactic shock and anaphylactoid reactions. Tachycardia and hypotension are listed as common ADRs. Hypokalaemia is not explicitly mentioned.According to the Swiss Product Information of Remifentanil Fresenius (one of the available remifentanil brands), there have been rare reports of allergic reactions including anaphylaxis for patients who received remifentanil together with one or more anaesthetics. Arrhythmias are listed as known ADRs of unknown frequency. Settings in which tachycardia may occur include tachycardia as a withdrawal symptom upon abrupt discontinuation after prolonged exposure. Hypotension is a very common ADR (12%). Hypokalaemia is not explicitly mentioned.According to the Swiss Product Information of Morphin HCL Streuli® (one of the available morphine brands), there have been uncommon reports of hypersensitivity reactions such as exanthem and oedema. Histamine release may give rise to anaphylactic reactions. Settings in which tachycardia may occur include tachycardia as a withdrawal symptom. Low blood pressure is listed as a rare ADR and may be a sign of both morphine intoxication and opioid analgesic-induced adrenal insufficiency. Facial flushing is also listed as a rare adverse drug reaction. Hypokalaemia is not explicitly mentioned.According to the Swiss Product Information of Valsartan axapharm (one of the available valsartan brands),

hypersensitivity reactions may occur very rarely. Common ADRs include orthostatic hypotension in heart failure patients, and hypotension has been reported uncommonly (more frequently in heart failure patients). Very rare skin and subcutaneous tissue ADRs include angioedema, exanthem and rash. An overdose with Valsartan axapharm may produce pronounced hypotension which might lead to a reduced level of consciousness, circulatory collapse and/or shock. Hypokalaemia is not explicitly mentioned.There is a temporal relationship between the use of Cefuroxim Fresenius, Iomeron®, atracurium, dexamethasone, heparin, ketamine, propofol, fentanyl, remifentanil, morphine and the occurrence of intraoperative anaphylactic shock. There is also a temporal relationship between dosing with norepinephrine, ephedrine, valsartan and the onset of symptoms. While most of the symptoms are also documented in the Product Information of valsartan, the aetiological role of valsartan appears less likely because it had presumably already been taken for a prolonged period of time without any complications. The reported symptoms are not explicitly listed for ephedrine and norepinephrine was continued for some time, during which symptoms improved. The aetiological role of these products also appears rather unlikely. A temporal relationship cannot be assessed for ASS Cardio, Acicutan® and atorvastatin because information about exposure periods is missing.The improvement in symptoms after recovery from anaesthesia and discontinuation of Cefuroxim Fresenius and Iomeron® constitutes a positive dechallenge (despite pharmacological intervention).Which or which combination of the intraoperatively administered medications ultimately caused the symptoms cannot be definitively identified because of their simultaneous administration.In summary, based on the temporal relationship, the documentation in the Product Information and in the databases, the positive dechallenge, the absence of evidence in support of non-pharmacological causes (risk factors, endogenous causes), we assess the causal relationship between the use of Cefuroxim Fresenius, Iomeron®, atracurium, dexamethasone, heparin, ketamine, propofol, fentanyl, remifentanil, morphine and the occurrence of intraoperative anaphylactic shock as formally possible for each suspected medication and as formally probable overall in accordance with WHO/CIOMS criteria.

Relevant Medical History:

Disease/Surgical Procedure	Start Date	End Date	Continuing?
Popliteal artery aneurysm			
Arterial hypertension			
Hypercholesteraemia			
Diastasis recti abdominis			
Basal cell carcinoma			
Squamous cell carcinoma			
Arrhythmia sinus	17-Oct-2023		
AV block first degree	17-Oct-2023		
Nicotine dependence		Aug-2023	
Alcohol use			
Femoropopliteal artery bypass			

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

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

Case ID: 23410623

Relevant Laboratory Data:

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail
10063240	7.8	ug/L			
10036439	3.3	mmol/L			

Concomitant Products:

#	Product Name:	Dose/Frequency	Route	Dosage Text	Start Date	End Date	Indication(s)	Interval 1st Dose to Event
1	ASS Cardio	/	Oral				10070592	
2	Acicutan	/	Oral				10070592	
3	Valsartan	/	Oral			18-Oct-2023	10070592	
4	Valsartan	/	Oral		21-Oct-2023	01-Nov-2023		
5	Atorvastatin	/	Oral		21-Oct-2023	01-Nov-2023	10070592	
6	Noradrenalin	/	Intravenous (not otherwise specified)		18-Oct-2023	18-Oct-2023	10073800	
7	Ephedrine	/	Intravenous (not otherwise specified)	2 x 6 mg	18-Oct-2023	18-Oct-2023	10073800	
8	Ringer Acetat	/	Intravenous (not otherwise specified)	6x 1000 mL	18-Oct-2023	18-Oct-2023	10073800	
9	Ringer Lactat	/	Intravenous (not otherwise specified)	5 x 1000 mL	18-Oct-2023	18-Oct-2023	10073800	

Reporter Source:

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

Literature Text:

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

Case ID: 23449022

Case Information:

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

FDA Rcvd Date: 28-Jan-2024 **Mfr Rcvd Date:** 16-Jan-2024 **Mfr Control #:** US-ENDO PHARMACEUTICALS INC-2024-000335 **Combination Product Report:** No **Application #:** 016812

Patient Information:

Age: 49 YR **Sex:** Female **Weight:** 104 KG

Suspect Products:

#	Product Name:	Compounded Drug ?	Dose/Frequency	Route	Dosage Text	Start Date	End Date	Indication(s)
1	KETALAR		30 Mg Milligram(S) /	Intravenous (not otherwise specified)	30 milligram, Unknown			10039897
2	KETALAR		70 Mg Milligram(S) /	Intravenous (not otherwise specified)	70 milligram, Unknown (titrated to dissociation after receiving ketamine 30mg)			

#	Product Name:	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler	OTC
1	KETALAR		Unknown	NA				PAR	
2	KETALAR		Unknown	NA				PAR	

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			/			

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

Case ID: 23449022

Event Information:

Preferred Term (MedDRA Version: v.27.0)	ReC
Stress cardiomyopathy	
Pulmonary oedema	
Delirium	
Apnoea	

Event/Problem Narrative:

A domestic literature report was received from United States, Citation: McMurray M, Orthober R, Huecker M. Ketamine's love story with the heart: A Takotsubo twist. American Journal of Emergency Medicine. 2024; 1-3, concerning a 49-year-old female, who experienced stress cardiomyopathy, pulmonary oedema, delirium, and apnoea while using ketamine for sedation. Medical history included anxiety and hypertension. On an unknown date, the patient presented to an urban, level I trauma center emergency department by ambulance after a motor vehicle collision. Her initial vital signs included a blood pressure (BP) of 116/70 mmHg, 76 beats per minute, 13 breaths per minute, and oxygen saturation of 100% on room air. She was alert and oriented with benign trauma exam other than a closed deformity of her left wrist. A bedside cardiac ultrasound for trauma was unremarkable. Left wrist radiographs demonstrated a comminuted, displaced distal radius fracture. Concomitant medication included diazepam. On an unknown date, after the patient received diazepam, she received 30 mg of intravenous (IV) ketamine, followed by another 70 mg titrating to dissociation (unknown frequency). Systolic BP was 194 mmHg just after onset of sedation and peaked at 236 mmHg 20 minutes later. After successful reduction, she had intermittent periods of apnea and began to desaturate to 83% on nasal cannula. She became significantly agitated and was then cyanotic on non-rebreather mask. Clinicians began bag valve mask ventilation. A bedside echocardiogram demonstrated diminished ejection fraction and lung B-lines suggestive of pulmonary edema. Chest radiograph showed bilateral pulmonary edema. An electrocardiogram (ECG) demonstrated sinus tachycardia, a new conduction delay, new T wave inversions in leads I and aVL, and minimal ST segment elevation. BiPAP was considered due to persistent hypoxia but intubated due to delirium. Pan scan imaging after sedation found no other traumatic injuries, but revealed dense consolidations throughout bilateral lung fields. The patient received 40 mg of IV furosemide and was admitted to the medical intensive care unit with emergent cardiology consultation. High sensitivity troponin peaked at 3155 ng/L. A consultative echocardiogram on the same day demonstrated an ejection fraction of 32%, akinetic mid left ventricle, and severe hypokinesis of the left ventricular apex concerning for Takotsubo cardiomyopathy. She was extubated on hospital day 1. Cardiac catheterization on hospital day 4 revealed non-obstructive coronary arteries and an improved ejection fraction (55-60%). After operative fixation of her left radius fracture, she was discharged home on day 9. She had an unremarkable outpatient follow up with cardiology but had no echocardiogram to determine full resolution. At the time of report, the action taken with ketamine was unknown. The outcome of the events of stress cardiomyopathy and pulmonary oedema was recovering and the outcome of the events of delirium and apnoea was recovered. A copy of the literature article is attached.

Relevant Medical History:

Disease/Surgical Procedure	Start Date	End Date	Continuing?
Sedation			Yes
Anxiety			Yes
Hypertension			Yes

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

Case ID: 23449022

Motor vehicle accident

Distal radius fracture 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
HIGH SENSITIVE TROPONIN	High sensitivity troponin peaked at 3155 ng/l				N

Concomitant Products:

#	Product Name:	Dose/Frequency	Route	Dosage Text	Start Date	End Date	Indication(s)	Interval 1st Dose to Event
1	DIAZEPAM	2.5 Mg Milligram(S) /	Intravenous (not otherwise specified)	2.5 milligram, Unknown			10039897	

Reporter Source:

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

Literature Text: McMurray M, Orthober R, Huecker M.. Ketamine's love story with the heart: A Takotsubo twist. American Journal of Emergency Medicine. 2024;1-3

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Ketamine's love story with the heart: A Takotsubo twist

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Takotsubo
Cardiomyopathy
Sedation

ABSTRACT

Introduction: Ketamine is a dissociative anesthetic with *N*-methyl-D-aspartate and glutamate receptor antagonist properties. It has been the most popular agent to facilitate emergency department procedures for three decades. Considered a safe and effective option for procedural sedation, ketamine has rapid onset, short effective sedation time, and a low risk profile. Ketamine's sympathomimetic effects could theoretically induce stress-related cardiac dysfunction, including cardiomyopathy. A review of the literature demonstrates one prior report of stress (Takotsubo) cardiomyopathy after ketamine sedation.

Case report: In this case report, we present a case of Takotsubo cardiomyopathy after ketamine sedation for distal radius fracture reduction. The patient presented hemodynamically normal with an unremarkable cardiac ultrasound and progressed to hypoxia from bilateral pulmonary edema, eventually requiring intubation. Inpatient evaluation revealed elevated high sensitivity troponin, non-obstructive coronary arteries on catheterization, and echocardiogram findings of Takotsubo cardiomyopathy. She received operative fixation of her radius fracture by orthopedics and was discharged home on hospital day 9. She had an unremarkable follow up with cardiology but had no echocardiogram to determine full resolution.

Conclusion: Although ketamine has robust evidence of safety and efficacy, physicians should be aware of the potential complications of its sympathomimetic effects, from hypertension and tachycardia to overt Takotsubo cardiomyopathy.

1. Introduction

Ketamine is a dissociative anesthetic and analgesic with *N*-methyl-D-aspartate and glutamate receptor antagonist and partial mu opioid receptor agonist properties [1]. It has been the most popular agent to facilitate emergency department (ED) procedures for three decades [2]. Ketamine provides different results based on dosing: the analgesic, "sub dissociative" dose of 0.1–0.3 mg/kg IV can be increased to 1-2 mg/kg for dissociative anesthesia [1].

Although adverse effects rarely occur, complications include laryngospasm, respiratory depression, and emergence reactions [2,3]. Some experts recommend avoiding ketamine in patients with coronary artery disease (CAD), congestive heart failure, and hypertension due to inhibition of catecholamine reuptake and increase in oxygen demand [4]. A literature review demonstrated one case report describing stress (Takotsubo) cardiomyopathy after ketamine sedation for a wrist fracture [5].

Takotsubo cardiomyopathy is a temporary regional systolic dysfunction of the left ventricle occurring in absence of acute coronary occlusion [6]. It commonly afflicts post-menopausal women undergoing intense physical or emotional stress [7]. Mayo Clinic diagnostic criteria include transient hypokinesis or akinesis of the left ventricle, absence of significant CAD, and new electrocardiogram (ECG) abnormalities or elevated troponin [8]. It generally resolves spontaneously, but patients may experience complications like arrhythmias, cardiogenic shock, and death [6].

2. Case report

A 49-year-old (104 kg) female with past medical history of anxiety and hypertension presented to our urban, level I trauma center ED by ambulance after a motor vehicle collision. Her initial vital signs included a blood pressure of 116/70 mmHg, 76 beats per minute, 13 breaths per minute, and oxygen saturation of 100% on room air. She was alert and oriented with benign trauma exam other than a closed deformity of her left wrist. A bedside cardiac ultrasound for trauma was unremarkable. Left wrist radiographs demonstrated a comminuted, displaced distal radius fracture. She received 2.5 mg of intravenous (IV) diazepam,

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0735-6757/

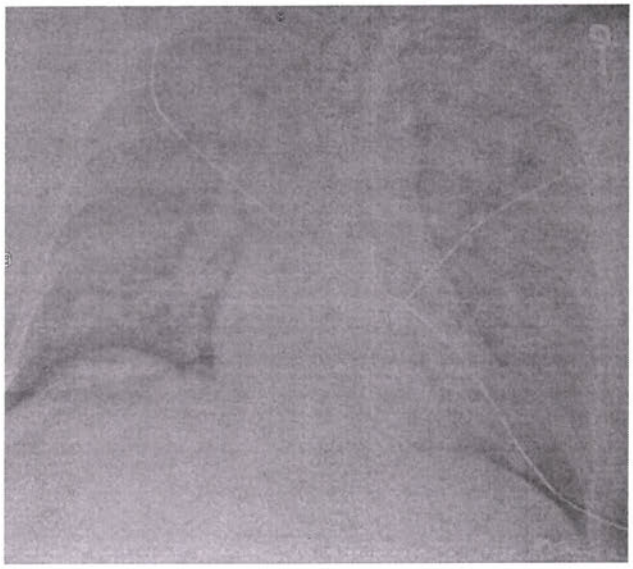

Fig. 1. Demonstrates heavy bilateral diffuse patchy airspace opacities consistent with pulmonary edema.

then 30 mg of IV ketamine, followed by another 70 mg titrating to dissociation. Systolic blood pressure was 194 mmHg just after onset of sedation and peaked at 236 mmHg twenty minutes later. After successful reduction, she had intermittent periods of apnea and began to desaturate to 83% on nasal cannula. She became significantly agitated and was then cyanotic on non-rebreather mask. Clinicians began bag valve mask ventilation. A bedside echocardiogram demonstrated diminished ejection fraction and lung B-lines suggestive of pulmonary edema. Chest radiograph showed bilateral pulmonary edema (Fig. 1). An ECG demonstrated sinus tachycardia, a new conduction delay, new T wave inversions in leads I and aVL, and minimal ST segment elevation (Fig. 2). The team considered BiPAP due to persistent hypoxia but intubated due to delirium.

Pan scan imaging after sedation found no other traumatic injuries, but revealed dense consolidations throughout bilateral lung fields. The patient received 40 mg of IV furosemide and was admitted to the medical ICU with emergent cardiology consultation. High sensitivity troponin peaked at 3155 ng/L. A consultative echocardiogram on the same day demonstrated an ejection fraction of 32%, akinetic mid left ventricle, and severe hypokinesis of the left ventricular apex concerning for Takotsubo cardiomyopathy. She was extubated on hospital day 1. Cardiac catheterization on hospital day 4 revealed non-obstructive coronary arteries and an improved ejection fraction (55–60%). After operative fixation of her left radius fracture, she was discharged home on day 9. She had an unremarkable outpatient follow up with cardiology but had no echocardiogram to determine full resolution.

3. Discussion

We report a case of Takotsubo cardiomyopathy after approximately 1 mg/kg of IV ketamine sedation. Despite initially normal hemodynamics and cardiac ultrasound, she developed left ventricular dysfunction and pulmonary edema. Previous research suggests that ketamine's sympathomimetic activity may lead to increased myocardial oxygen demand and ischemia. In one small study, 9.7% of patients developed myocardial ischemia on ECG after ketamine [9].

The patient developed altered mental status, hypertension, and hypoxia during sedation. The treatment team considered differential diagnoses of acute coronary syndrome, systolic heart failure, hypertensive emergency, and pulmonary embolism. Her initial ECG did not meet STEMI criteria and subsequent pan scan imaging did not reveal hemorrhage or pulmonary embolism. Pulmonary edema on bedside echocardiogram and chest imaging pointed towards acute heart failure. Inpatient evaluation confirmed Takotsubo cardiomyopathy.

The incidence of Takotsubo cardiomyopathy is uncertain but may comprise 1–2% of patients with suspected acute coronary syndrome [6]. Thus, clinicians should exclude coronary occlusion with angiography [10]. The (primarily supportive) treatment of Takotsubo involves diuresis with or without vasopressor support, along with intubation when needed. Although ketamine remains a safe drug, physicians should be aware of the potential complications of its sympathomimetic effects.

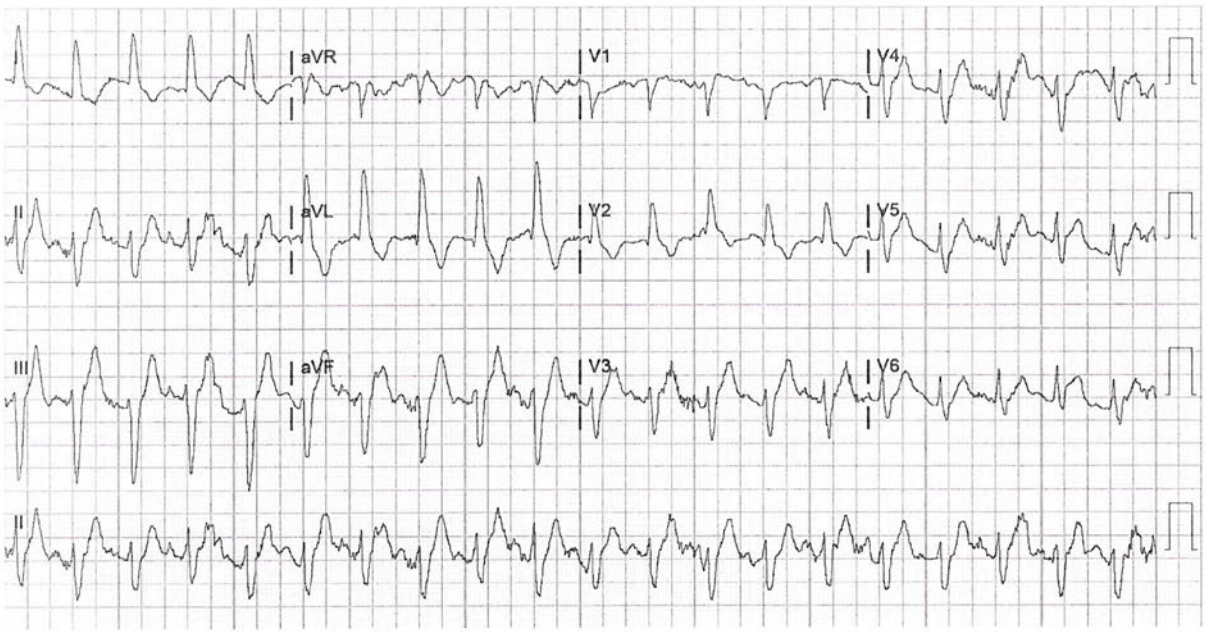

Fig. 2. Demonstrates sinus tachycardia with a conduction delay and T-wave inversions in leads I and aVL.

CRediT authorship contribution statement

Mitchell McMurray: Writing – review & editing, Writing – original draft, Conceptualization. **Raymond Orthober:** Writing – original draft, Conceptualization. **Martin Huecker:** Writing – review & editing, Writing – original draft.

Declaration of competing interest

The authors have no declarations or statements of interest and this research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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

Case ID: 23467967

Case Information:

Case Type : Expedited (15-Day) **eSub:** Y **HP:** Y **Country:** FR **Event Date:** 05-Nov-2023 **Outcomes:** LT **Application Type:**

FDA Rcvd Date: 01-Feb-2024 **Mfr Rcvd Date:** 29-Jan-2024 **Mfr Control #:** FR-ABBVIE-5612999 **Combination Product Report:** No Information **Application #:** 020551

Patient Information:

Age: 73 YR **Sex:** Female **Weight:** 66 KG

Suspect Products:

#	Product Name:	Compounded Drug ?	Dose/Frequency	Route	Dosage Text	Start Date	End Date	Indication(s)
1	NIMBEX		14 Mg Milligram(S) /	Intravenous (not otherwise specified)		05-Nov-2023	05-Nov-2023	10002321
2	Ketalar		20 Mg Milligram(S) /	Intravenous (not otherwise specified)		05-Nov-2023	05-Nov-2023	10002321
3	Etomidate		20 Mg Milligram(S) /	Intravenous (not otherwise specified)		05-Nov-2023	05-Nov-2023	10002321
4	Dexamethasone		8 Mg Milligram(S) /	Intravenous (not otherwise specified)		05-Nov-2023	05-Nov-2023	10002321

#	Product Name:	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler	OTC
1	NIMBEX	1 Day	Yes	NA				ABBVIE	
2	Ketalar	1 Day	Yes	NA				UNKNOWN	
3	Etomidate	1 Day	Yes	NA				UNKNOWN	
4	Dexamethasone	1 Day	Yes	NA				UNKNOWN	

Device Products:

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

Case ID: 23467967

#	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.27.0) **ReC**

Bronchospasm

Hypotension

Event/Problem Narrative:

Event Description ---------- Case received on 29 Jan 2024 from EMA with the reference number of FR-AFSSAPS-ST2024000168. Spontaneous report from France by a physician of 73 years old female with events of Bronchospasm, and Hypotension with Cisatracurium Besilate Solution for Injection. The patient had a relevant medical history of Chronic renal failure, Pneumococcal meningitis, Arterial hypertension, Auricular fibrillation, Type II diabetes mellitus, Acute oedema of lung, unspecified, and Anxiodepressive syndrome. On 2023-11-05, the patient experienced Bronchospasm. On 2023-11-05, the patient experienced Hypotension. On 2023-11-05, Bronchospasm recovered/resolved. On 2023-11-05, Hypotension recovered/resolved. Ketalar, Etomidate, and Dexamethasone were also considered suspect. Causalities ---------- The reporter's causality for the event(s) of Bronchospasm and Hypotension with Etomidate (Etomidate) was Not Provided The reporter's causality for the event(s) of Bronchospasm and Hypotension with Ketalar (Ketamine hydrochloride) was Not Provided The reporter's causality for the event(s) of Bronchospasm and Hypotension with Cisatracurium Besilate Solution for Injection was Not Provided The reporter's causality for the event(s) of Bronchospasm and Hypotension with Dexamethasone (Dexamethasone acetate) was Not Provided Patient Medical History ---------- Acute oedema of lung, unspecified Anxiodepressive syndrome Arterial hypertension Auricular fibrillation Chronic renal failure Pneumococcal meningitis Type II diabetes mellitus Primary reporter contact for lot number information was not available.

Relevant Medical History:

Disease/Surgical Procedure	Start Date	End Date	Continuing?
Chronic renal failure			No
Pneumococcal meningitis			No
Arterial hypertension			No
Auricular fibrillation			No
Type II diabetes mellitus			No

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

Case ID: 23467967

Acute oedema of lung, unspecified	No
Anxiodepressive syndrome	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

Concomitant Products:

#	Product Name:	Dose/Frequency	Route	Dosage Text	Start Date	End Date	Indication(s)	Interval 1st Dose to Event
1	Amoxicilline	/					10057097	
2	Sufenta	/					10057097	
3	Diprivan	/					10057097	

Reporter Source:

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

Literature Text:

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

Case ID: 23469335

Case Information:

Case Type : Expedited (15-Day) **eSub:** Y **HP:** Y **Country:** US **Event Date:** 2022 **Outcomes:** DE **Application Type:** NDANDA

FDA Rcvd Date: 02-Feb-2024 **Mfr Rcvd Date:** 16-Jan-2024 **Mfr Control #:** US-ENDO PHARMACEUTICALS INC-2024-000724 **Combination Product Report:** No **Application #:** 016812

Patient Information:

Age: 38 YR **Sex:** Male **Weight:**

Suspect Products:

#	Product Name:	Compounded Drug ?	Dose/Frequency	Route	Dosage Text	Start Date	End Date	Indication(s)
1	KETALAR		/	Unknown	UNK Unknown, Unknown			10070592
2	METHAMPHETAMINE [METAMFETAMINE]		/	Unknown	UNK Unknown, Unknown			10070592

#	Product Name:	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler	OTC
1	KETALAR		Not Applicable	NA				PAR	
2	METHAMPHETAMINE [METAMFETAMINE]		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:

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

Case ID: 23469335

Preferred Term (MedDRA Version: v.27.0) **ReC**

Drug abuse

Event/Problem Narrative:

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:** ENDO **503B Compounding Outsourcing Facility?:**

Literature Text: Gummin DD, Mowry JB, Beuhler MC, Spyker DA, Rivers LJ, Feldman R, et al.. 2022 Annual Report of the National Poison Data System (NPDS) from America's Poison Centers: 40th Annual Report. Clinical Toxicology. 2023;61 (10):717-939

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

Case ID: 23720825

Case Information:

Case Type : Non-Expedited **eSub:** Y **HP:** N **Country:** US **Event Date:** **Outcomes:** **Application Type:** NDANDA

FDA Rcvd Date: 09-Apr-2024 **Mfr Rcvd Date:** 24-Oct-2023 **Mfr Control #:** US-ENDO PHARMACEUTICALS INC-2023-005567 **Combination Product Report:** No **Application #:** 016812

Patient Information:

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

Suspect Products:

#	Product Name:	Compounded Drug ?	Dose/Frequency	Route	Dosage Text	Start Date	End Date	Indication(s)
1	KETALAR		/	Parenteral	UNK Unknown, Unknown			10070592

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

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			/			

Event Information:

Preferred Term (MedDRA Version: v.27.0) **ReC**

Malaise

Event/Problem Narrative:

A United States spontaneous report was received from Novartis, concerning a 49-year-old female, who experienced malaise while using ketamine for an unknown indication. Medical history included procedure done on 17-Oct and 18-Oct (unknown year of procedure). Concomitant medications were not reported. On an

Case ID: 23720825

unknown date, the patient started treatment with ketamine infusions at an unknown dose and frequency. The patient reported that she was feeling sick after ketamine infusions. At the time of report, the action taken with ketamine was unknown. The outcome of event malaise was unknown.

Relevant Medical History:

Disease/Surgical Procedure	Start Date	End Date	Continuing?
Surgery			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

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:** ENDO **503B Compounding Outsourcing Facility?:**

Literature Text:

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

Case ID: 23796312

Case Information:

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

FDA Rcvd Date: 30-Apr-2024 **Mfr Rcvd Date:** 16-Apr-2024 **Mfr Control #:** US-ENDO PHARMACEUTICALS INC-2024-001834 **Combination Product Report:** No **Application #:** 016812

Patient Information:

Age: 35 YR **Sex:** Female **Weight:**

Suspect Products:

#	Product Name:	Compounded Drug ?	Dose/Frequency	Route	Dosage Text	Start Date	End Date	Indication(s)
1	KETALAR		0.35 Mg/Kg Milligram(S)/Kilogram /	Intravenous bolus	0.35 milligram/kilogram, Unknown (in 0.9% sodium chloride, induction)			10068084
2	KETALAR		0.25 Mg/Kg Milligram(S)/Kilogram /	Intravenous (not otherwise specified)	0.25 milligram/kilogram, Infusion after induction (in 0.9% sodium chloride)			

#	Product Name:	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler	OTC
1	KETALAR		Unknown	NA				PAR	
2	KETALAR		Unknown	NA				PAR	

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			/			

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

Case ID: 23796312

2 // No /

Event Information:

Preferred Term (MedDRA Version: v.27.0) **ReC**

Anaphylactic shock

Event/Problem Narrative:

A domestic literature report was received from United States, Citation: Chia C, Calhoun K, Curatolo M, Kooner P. Ketamine-Induced Anaphylactic Shock During Prophylactic Mastectomy. Understanding the Complexity of Pain from Diverse Perspectives. 14-17-Apr-2024, The Journal of Pain. 2024; 25(4): 34, concerning a 35-year-old female, who experienced anaphylactic shock while using ketamine for anesthesia procedure. Medical history included bilateral prophylactic mastectomy, which was aborted midway. Concomitant medications included cefazolin, propofol, rocuronium, ketamine, lidocaine, and fentanyl. The patient enrolled in the Ketamine Analgesia for Long-lasting Pain relief After Surgery (KALPAS) study and consented to receiving ketamine in 0.9% sodium chloride vs only 0.9% sodium chloride intraoperatively. On an unknown date, she received 0.35mg/kg bolus of study drug ketamine (unknown frequency) and began a 0.25mg/kg ketamine infusion after induction. Within one hour of receiving the medication, the patient experienced anaphylactic shock (onset date unknown) as she developed widespread urticaria, hypercarbia, bronchospasm and refractory hypotension, which was treated with phenylephrine, epinephrine, dexamethasone, and diphenhydramine. The surgery was aborted midway, and the patient required intensive care unit admission overnight. Allergy testing revealed a positive intradermal test for ketamine, indicating IgE mediated anaphylaxis to ketamine. She tested negative for all other medications delivered in the operating room, suggesting that ketamine infusion could result in life-threatening anaphylaxis. At the time of this report, the action taken with ketamine was unknown. The outcome of the event of anaphylactic shock was unknown. A copy of the literature article is attached.

Relevant Medical History:

Disease/Surgical Procedure	Start Date	End Date	Continuing?
Prophylactic mastectomy			No
Anesthesia procedure			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: 23796312

#	Product Name:	Dose/Frequency	Route	Dosage Text	Start Date	End Date	Indication(s)	Interval 1st Dose to Event
1	CEFAZOLIN	/	Unknown	UNK Unknown, Unknown			10068084	
2	PROPOFOL	/	Unknown	UNK Unknown, Unknown			10068084	
3	ROCURONIUM	/	Unknown	UNK Unknown, Unknown			10068084	
4	LIDOCAINE	/	Unknown	UNK Unknown, Unknown			10068084	
5	FENTANYL	/	Unknown	UNK Unknown, Unknown			10068084	

Reporter Source:

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

Literature Text: Chia C, Calhoun K, Curatolo M, Kooner P.. Ketamine-Induced Anaphylactic Shock During Prophylactic Mastectomy. The Journal of Pain. 2024;25 (4):34

department's pain management goals, and patient satisfaction surveys show an opportunity for improvement. The aim of this project was to implement the National Comprehensive Cancer Network's (NCCN) pain management algorithm to promote evidence-based pain management and improve patient-stated pain scores. This project targeted patients on one solid tumor service who were not being treated by palliative care, were not in the intensive care unit, and did not receive continuous analgesic infusions. Nurses and providers were educated on the project's purpose and the published algorithm. Once educated, providers utilized the algorithm on eligible patients. The algorithm was available in multiple accessible formats: printed booklets in the office, a QR code for online access, and printed paper versions. Implementation was monitored weekly by chart audits of patients who reported pain on admission. Audit data included pain score on admission, lowest pain score within 48 hours, and algorithm utilization. Pain was categorized as mild (1-4), moderate (5-7), and severe (8-10). In eight weeks, 30 eligible patients reported pain on admission, and 23 (76%) received care according to the algorithm. All 23 patients who received pain management via algorithm reported at least one pain category decrease within 48 hours. The educational session has increased awareness of the pain management algorithm as a helpful resource. Preliminary data suggests that implementing the NCCN's pain management algorithm may effectively manage pain in this population.

Investigation of Inflammation in Fibromyalgia After a Lipopolysaccharide-Induced Immune Response

Matthew McDaniel, Indonesia A. Jordan, Sophia Fox, and Jarred Younger; University of Alabama at Birmingham, Department of Psychology

Fibromyalgia (FM) is a debilitating chronic pain disorder characterized by widespread musculoskeletal pain. The exact cause of FM is unknown, but current research suggests that an overactive immune response may be involved. The purpose of this study was to examine pathophysiological responses to a low-level immune insult, using in-vivo administration of lipopolysaccharide (LPS). Thirteen women with FM and 13 age-matched healthy controls (HC) completed the study. Blood samples were collected before participants received 0.3ng/kg or 0.4ng/kg endotoxin and 3 hours after. We conducted a mixed analysis of variance (ANOVA) with time as the within-subjects factor (pre-LPS, post-LPS) and the study group as the between-subject factor (FM, HC). LPS dosage was included as another between-subjects factor. A statistical significance threshold of $p < 0.05$ was used for all analyses. We found no significant interactions with IL-6 or TNF-α outcomes, but we did find a significant group-by-time interaction with CRP ($F [1,22] = 4.068$, $p = .032$). An abnormally sensitized reaction to low-level immune insults may be involved in the symptoms of FM. This study is not sufficient to conclusively establish whether fibromyalgia involved irregular inflammatory reactions. Our results suggest further research into immune responses in FM is warranted. This trial was registered at clinicaltrials.gov (NCT04263454) and funded by the American Fibromyalgia Syndrome Association.

Ketamine-Induced Anaphylactic Shock During Prophylactic Mastectomy

Catherine Chia, Kristine Calhoun, Michele Curatolo, and Preetma Kooner; Department of Anesthesiology & Pain Medicine, University of Washington

Ketamine is a commonly used intravenous (IV) anesthetic and postoperative analgesic. Known side effects include sedation, hallucinations, and confusion, but anaphylaxis to ketamine is not generally known as a typical complication. We present the case of a 35-year-old woman undergoing bilateral prophylactic mastectomy that developed intraoperative anaphylaxis to first exposure of ketamine. A literature search using PubMed and key words "ketamine", "anaphylaxis", and "anaphylactic shock" was conducted along with a description of the clinical case. The patient enrolled in the Ketamine Analgesia for Long-lasting Pain relief After Surgery (KALPAS) study and consented to receiving ketamine in 0.9% sodium chloride vs only 0.9% sodium chloride intraoperatively. The literature search of ketamine-induced anaphylaxis yielded only 4 cases. The patient received a 0.35mg/kg bolus of study drug and began a 0.25mg/kg ketamine infusion after induction. She also received cefazolin, propofol, rocuronium, ketamine, lidocaine, and fentanyl intraoperatively. Within one hour of receiving the medications the patient developed widespread urticaria, hypercarbia, bronchospasm, and refractory hypotension, which was treated with phenylephrine, epinephrine, dexamethasone, and diphenhydramine. The surgery was aborted midway, and the patient required ICU admission overnight. Allergy testing revealed a positive intradermal test for ketamine, indicating IgE mediated anaphylaxis to ketamine. She tested negative for all other medications delivered in the OR, suggesting that ketamine infusion can result in life-threatening anaphylaxis. This trial is registered at clinicaltrials.gov (NCT05037123). Funded by National Institutes of Health (1UG3CA261067-01).

Long-Term Safety and Efficacy of Esreboxetine for the Treatment of Fibromyalgia

Lesley M. Arnold, Philip J. Mease, Zachariah Thomas, Allen Moton, and Herriot Tabuteau; University of Cincinnati College of Medicine, Cincinnati, Ohio

Several unmet needs exist for fibromyalgia treatment including long-term efficacy. Esreboxetine is an extended-release, potent and highly-selective norepinephrine reuptake inhibitor under investigation for fibromyalgia. Esreboxetine has demonstrated efficacy and safety in placebo-controlled fibromyalgia trials ranging in duration from 8-14 weeks (Arnold, 2010; Arnold, 2012). This open-label study evaluated long-term treatment of flexibly dosed esreboxetine (4-10 mg) in adult patients with fibromyalgia. At baseline, all participants (N=572; 91% female) had a score ≥40 on the 100-mm pain visual analogue scale (VAS) and met the 1990 American College of Rheumatology fibromyalgia criteria. The median duration of treatment was 140 days; 265 participants received treatment for more than 6 months and 77 were treated for more than 1 year. Discontinuations due to adverse events (AEs) occurred in 35.3% of participants (all causality) and mainly occurred early in treatment. AEs were mostly mild-to-moderate in severity, and the most common (>10%) AEs were dry mouth, constipation, insomnia, headache, hyperhidrosis, nausea, and dizziness. Pain was improved at all timepoints. At Week 2, the mean VAS decrease was −10.2 (baseline score=70.4). Further improvements were noted with continued treatment: -15.8 (Week 4;n=447), -23.2 (Week 8;n=370), -28.6 (Week 32;n=242), -31.2 (Week 44;n=143). Similar improvement trends were reported on the Fibromyalgia Impact Questionnaire (FIQ): mean FIQ decrease was -18.27 at Week 32. These results demonstrate the efficacy and safety of esreboxetine for the treatment of fibromyalgia and support the continued development of esreboxetine as a promising treatment for fibromyalgia. This study was supported by Axsome Therapeutics and Pfizer.

Mean of Daily Versus Single Week Recall-Based Pain Quality Assessments in Painful Chemotherapy-induced Peripheral Neuropathy (CIPN) Trials: Implications for Assay Sensitivity

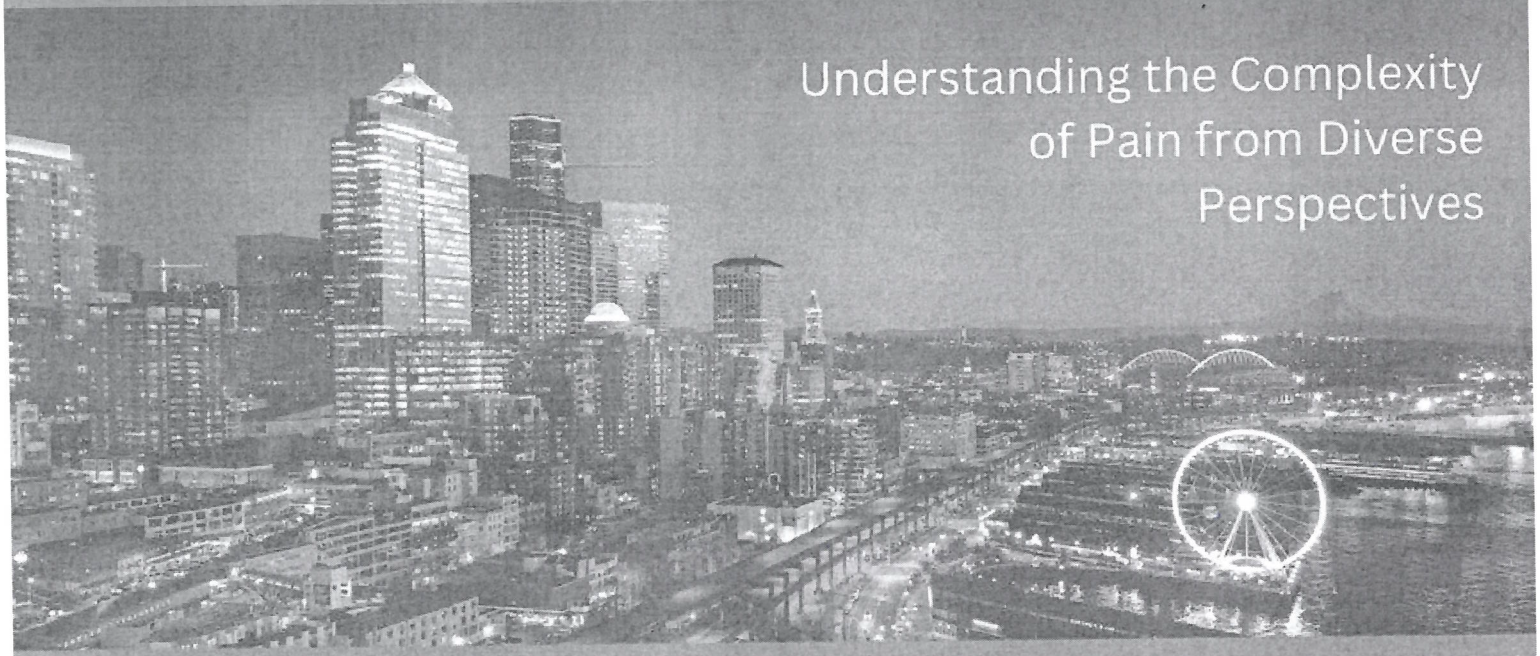
Madelaine S. Rangel, Soroush Besharat, Michael B. Sohn, Brian Burnette, Lori Francar, Carla Jorgensen, Karen Mustian, Gary Morrow, Michael P. Mc Dermott, Mark Jensen, and Jennifer S. Gewandter; University of Rochester School of Medicine and Dentistry

Patients with neuropathic pain present with different pain qualities. Each is usually assessed using single ratings in randomized clinical trials (RCTs). To our knowledge, no studies have investigated whether means of daily pain quality assessments would provide better assay sensitivity (i.e., more sensitive to treatment effects) than single week recall-based assessments. This secondary analysis used data from participants who reported ³4 out of 10 severity for hot/burning pain, sharp/shooting pain, and/or cramping at baseline in a RCT of transcutaneous electrical nerve stimulation for CIPN (N=88). Participants rated the severity of different pain qualities using 0-10 numeric rating scales daily for a week and a single-week recall-based outcome at baseline and endpoint. Effect sizes (differences in mean pain between placebo and active at endpoint) for the mean of the daily assessments and the single week recall assessments were computed using ANCOVAs. The sample sizes that would be required in future clinical trials to detect the observed effect sizes were calculated (alpha=0.5, power=80%). The effect sizes were greater for the mean of daily outcomes than the single week recall outcome in all cases except for sharp/shooting pain. For hot/burning pain and cramping, the projected sample sizes for the mean ratings were 114 and 126 fewer participants per group than with the week recall outcome. For sharp/shooting pain, the week recall outcome had a slightly lower (22 participants) projected sample size requirement than the mean outcome. Daily pain quality assessments may provide improved assay sensitivity than week recall-based assessments. Funded by NIH (R21CA235389; UG1CA189961; K24NS126861).

USASP
US Association for the Study of Pain

2024 Annual Meeting

April 14-17, 2024 I Seattle, Washington



Understanding the Complexity of Pain from Diverse Perspectives

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

Case ID: 23891676

Case Information:

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

FDA Rcvd Date: 24-May-2024 **Mfr Rcvd Date:** 14-May-2024 **Mfr Control #:** US-ENDO USA, INC.-2024-002186 **Combination Product Report:** No **Application #:** 016812

Patient Information:

Age: 68 YR **Sex:** Female **Weight:**

Suspect Products:

#	Product Name:	Compounded Drug ?	Dose/Frequency	Route	Dosage Text	Start Date	End Date	Indication(s)
1	KETALAR		/	Intravenous drip	12.5 ug/kg/min, Infusion (received approximately 18 mg)			10018061

#	Product Name:	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler	OTC
1	KETALAR		Yes	NA				PAR	

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			/			

Event Information:

Preferred Term (MedDRA Version: v.27.0) **ReC**

Arteriospasm coronary

Event/Problem Narrative:

Case ID: 23891676

A domestic literature report was received from the United States, Citation: Perez RK, Lighthall G. Profound Coronary Vasospasm Associated with Intraoperative Ketamine Administration: A Case Report. A and A Practice. 2024 May; 18(5): 1-4, concerning a 68-year-old female who experienced arteriospasm coronary while using ketamine for general anesthesia. Medical history included hypertension, hyperlipidemia, anxiety, current tobacco use (which she has reduced), gastroesophageal reflux, allergies to mold and lisinopril (cough), a knee replacement 3 years before, and bilateral mastectomies at age 21 year. She had a longstanding history of atypical chest pain since 2009, and several emergency department (ED) visits for chest pain, but without any interventions. She described her symptoms as "like indigestion," which lasted around 15 minutes when experiencing stress. She denied ever feeling chest pressure or pain. A coronary angiography was negative for coronary artery disease (CAD) or other pathology. Ultimately, the patient was diagnosed with anxiety and was prescribed alprazolam for symptom relief. An electrocardiogram (ECG) demonstrated inferior Q waves which led to a cardiology consultation. A cardiac perfusion scan showed a subtle degree of reversible hypoperfusion in the basal inferior wall. A transthoracic echocardiogram (TTE) showed a normal left and right ventricular size and function, mild left ventricular hypertrophy, and mild-moderate eccentric mitral valve regurgitation. A coronary computed tomography (CT) scan revealed no atherosclerotic disease. She was counseled on smoking cessation and was prescribed isosorbide mononitrate, hydrochlorothiazide, losartan and atorvastatin (historical medications) as her symptoms resolved, and she stopped filling these prescriptions. Additional historical medication included alprazolam. Concomitant medications included albuterol, fluticasone, pantoprazole, and famotidine. The patient was scheduled for breast implant revisions. Her pre-operative evaluation did not reveal any current symptoms or concerns for cardiac disease. She denied any recent episodes of chest pain, dyspnea on exertion, or palpitations. Her 12-lead ECG was normal. She denied any difficulties with prior anesthetics. The patient was induced with the following anesthesia medications: midazolam, lidocaine, fentanyl, propofol, and rocuronium, which was uneventful. After intubation, her blood pressure and heart rate increased, and were treated with propofol and additional fentanyl. Maintenance of anesthesia was continued with sevoflurane, and she also received dexamethasone, cefazolin, ephedrine, and glycopyrrolate before incision. Vital signs and ST segment analysis were unremarkable throughout this period and well into the surgery. Approximately 40 minutes into the case, a ketamine-propofol infusion was started at a ratio of 12.5 µg/ kg/min of ketamine per 50 µg/kg/min of propofol. The patient had received approximately 18mg of ketamine. Twenty minutes later, a brief 2.6 mm ST elevation appeared in leads II and III and resolved about a minute later. Transient ST changes of a similar magnitude returned a minute later and approximately 10 minutes later. The surgeons were notified, the infusion was stopped, and a 12-lead ECG was requested. Approximately 75 minutes into the case, the patient developed a 5.5 mm ST segment elevation in leads II and III, and a 2.7 mm elevation in lead V with an associated decrease in heart rate (nadir 40 beats per minute) and blood pressure (nadir mean arterial pressure of 42). Blood pressure was stabilized with multiple 10 µg boluses of epinephrine and 1 unit of vasopressin. An arterial line was placed, a 12-lead ECG and a transesophageal echocardiogram (TEE) were performed. The surgeons were informed of the serious nature of the events and the need for an expedited closure. Interventional cardiology was notified and came to assess the patient. An orogastric tube was placed and 325 mg of crushed aspirin in a water suspension was administered. After a discussion with the surgeons, 5000 units of heparin was given intravenously. A TEE revealed a moderately reduced left ventricular inferior wall function. Five minutes later, the ST elevations again resolved, and blood pressure and heart rate returned to normal. At this time, a 12-lead ECG was obtained. A few minutes later, she again developed significant ST segment changes, and the decision was made to proceed to cardiac catheterization and coronary angiography began 15 minutes later. Coronary angiography revealed diffuse vasospasm of a codominant right coronary artery which improved with intracoronary nitroglycerin. No significant obstructive lesions were found. The patient was transferred to the intensive care unit (ICU) for monitoring. Her postoperative TTE was unchanged from prior, and her ICU course was uneventful. She was started on oral diltiazem (60 mg twice daily) and was discharged to the medicine ward for further medication adjustment on postoperative day 1. Follow up was performed 6 months later and she remained well with her symptoms managed on her new regimen of isosorbide mononitrate 120 mg/day and sustained release diltiazem 240 mg/day. At the time of this report, the action taken with ketamine was drug withdrawn. The outcome of the event of arteriospasm coronary was recovered. A copy of the literature article is attached.

Relevant Medical History:

Disease/Surgical Procedure	Start Date	End Date	Continuing?
Hypertension			Yes

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

Case ID: 23891676

Hyperlipidemia		Yes
Anxiety		Yes
Cigarette smoker		Yes
Gastroesophageal reflux		Yes
Knee replacement	2019	No
Mastectomy bilateral		No
Chest pain	2009	Yes
Allergy to molds		Yes
Drug allergy		Yes
Disease risk factor		Yes

Medical History Product(s)	Start Date	End Date	Indications	Events
ISOSORBIDE MONONITRATE				
HYDROCHLOROTHIAZIDE				
LOSARTAN				
ATORVASTATIN				
ALPRAZOLAM			10002855	

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
1	PROPOFOL	/	Intravenous drip	50 ug/kg/min, Infusion			10018061	
2	PROPOFOL	170 Mg Milligram(S) /	Unknown	170 milligram, Unknown (induction)			10005750	

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

Case ID: 23891676

3	PROPOFOL	/	Unknown	UNK Unknown, Unknown (for blood pressure and heart rate increase)	10019303
4	ALBUTEROL [SALBUTAMOL]	/	Unknown	UNK Unknown, Unknown	10057097
5	FLUTICASONE	/	Unknown	UNK Unknown, Unknown	10057097
6	PANTOPRAZOLE	/	Unknown	UNK Unknown, Unknown	10057097
7	FAMOTIDINE	/	Unknown	UNK Unknown, Unknown	10057097
8	MIDAZOLAM	2 Mg Milligram(S) /	Unknown	2 milligram, Unknown (induction)	10018061
9	LIDOCAINE	20 Mg Milligram(S) /	Unknown	20 milligram, Unknown (induction)	10018061
10	FENTANYL	100 Ug Microgram(S) /	Unknown	100 microgram, Unknown (induction)	10018061
11	FENTANYL	/	Unknown	UNK Unknown (for blood pressure and heart rate increase)	10005750
12	FENTANYL	/			10019303
13	ROCURONIUM	70 Mg Milligram(S) /	Unknown	70 milligram, Unknown (induction)	10018061
14	SEVOFLURANE	/	Unknown	UNK Unknown, Unknown	10054468
15	DEXAMETHASONE	4 Mg Milligram(S) /	Unknown	4 milligram, Unknown	10057097
16	CEFAZOLIN	2 G Gram(S) /	Unknown	2 gram, Unknown	10057097
17	EPHEDRINE	5 Mg Milligram(S) /	Unknown	5 milligram, Unknown	10057097

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

Case ID: 23891676

18	GLYCOPYRROLATE	0.1 Mg Milligram(S) /	Unknown	0.1 milligram, Unknown		10057097

Reporter Source:

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

Literature Text: Perez RK, Lighthall G. Profound Coronary Vasospasm Associated with Intraoperative Ketamine Administration: A Case Report. A and A Practice. 2024;18(5):1-4

2024-002186

CASE REPORT

Profound Coronary Vasospasm Associated with Intraoperative Ketamine Administration: A Case Report

Richard K. Perez, MD,* and Geoffrey Lighthall, MD, PhD*†

We report a case of a 62-year-old woman with a decade-long history of atypical chest pain resulting in a largely negative cardiac workup, who developed significant angiographically demonstrated coronary vasospasm thought to be due to a small dose of intravenous ketamine. In patients with a history of atypical chest pain despite a reassuring cardiac evaluation, providers should carefully consider medications that may precipitate coronary vasospasm and be prepared to treat it accordingly. (A&A Practice. 2024;18:e01786.)

Vasospastic angina, previously referred to as Prinzmetal's angina, is often a diagnosis of exclusion but accounts for the majority of nonobstructive coronary disease in patients undergoing invasive evaluations.[1] Patients with vasospastic angina are often younger compared to patients with angina related to coronary artery disease (CAD), and the prevalence is similar between men and women.[1,2] Cigarette smoking is the only shared major risk factor for both atherosclerotic cardiovascular disease and coronary vasospasm.[3] Possible mechanisms underlying coronary vasospasm include endothelial dysfunction, autonomic and sympathetic tone imbalance, and an allergic reaction.[2,4,5] The institutional review board in our medical center does not require approval for case reports. Written Health Insurance Portability and Accountability Act authorization has been obtained from the patient for the publication of this case report. This manuscript adheres to the Enhancing the QUAlity and Transparency Of health Research (EQUATOR) guideline.

CASE DESCRIPTION

A 68-year-old woman with hypertension, hyperlipidemia, anxiety, current tobacco use, gastroesophageal reflux, a knee replacement 3 years before, and bilateral mastectomies at age 21 years was scheduled for breast implant revisions. She had a longstanding history of atypical chest pain since 2009, and several emergency department visits for chest pain, but without any interventions. She described her symptoms as "like indigestion," which lasted around 15 minutes when experiencing stress. She denied ever feeling chest pressure or pain. She underwent coronary angiography, which was negative for CAD or other pathology. Ultimately, the patient was diagnosed with anxiety and was prescribed alprazolam for symptom relief. An electrocardiogram (ECG) obtained before her knee replacement in 2019 demonstrated inferior Q waves which led to a cardiology consultation. A cardiac perfusion scan showed a subtle degree of reversible hypoperfusion in the basal inferior wall. A transthoracic echocardiogram (TTE) showed a normal left and right ventricular size and function, mild left ventricular hypertrophy, and mild-moderate eccentric mitral valve regurgitation. A follow-up coronary computed tomography scan revealed no atherosclerotic disease. She was counseled on smoking cessation and was prescribed isosorbide mononitrate, hydrochlorothiazide, losartan, and atorvastatin. In the year before our encounter, her symptoms resolved, and she stopped filling these prescriptions.

Her preoperative evaluation did not reveal any current symptoms or concerns for cardiac disease. Her medications were albuterol, fluticasone, pantoprazole, and famotidine. The patient denied any recent episodes of chest pain, dyspnea on exertion, or palpitations. She reported current but reduced cigarette smoking frequency. Her 12-lead ECG revealed normal sinus rhythm without significant ST segment abnormalities (Figure 1 A). The patient's stated allergies were mold and lisinopril (cough) and she denied any difficulties with prior anesthetics. Fasting was verified, and she was deemed appropriate for surgery.

A plan for balanced general anesthesia was discussed and agreed on. Induction with 2 mg of midazolam, 20 mg of lidocaine, 100 μg of fentanyl, 170 mg of propofol, and 70 mg of rocuronium was uneventful (Figure 2). After intubation, her blood pressure and heart rate increased, and were treated with propofol and additional fentanyl. Maintenance of anesthesia was continued with 2% sevoflurane. The patient also received 4 mg of dexamethasone, 2 g of cefazolin, 5 mg of ephedrine, and 0.1 mg of glycopyrrolate before incision. Vital signs and ST segment analysis were unremarkable throughout this period and well into the surgery. Approximately 40 minutes into the case, a ketamine-propofol infusion was started at a ratio of 12.5 μg/kg/min of ketamine per 50 μg/kg/min of propofol. Twenty minutes later, a brief 2.6 mm ST elevation appeared in leads II and III and resolved about a minute later. Transient ST changes of a similar magnitude returned a minute later and approximately 10 minutes later. The surgeons were notified, the infusion was stopped, and we requested a 12-lead

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Funding: None.

The authors declare no conflicts of interest.

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DOI: 10.1213/XAA.0000000000001786

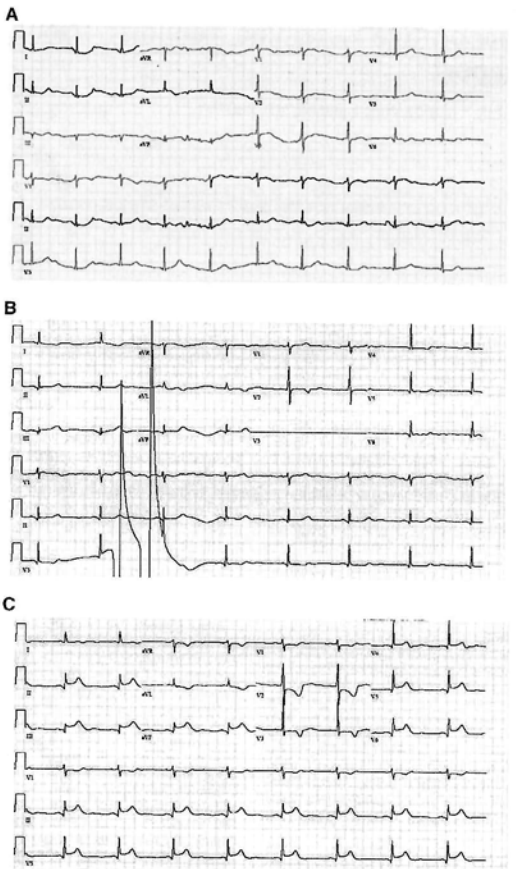

Figure 1. Intraoperative 12-lead electrocardiograms. A, Preoperative 12-lead electrocardiogram revealing normal sinus rhythm and no significant ST changes. B, A 12-lead electrocardiogram obtained after the third episode of ST segment changes. Prominent findings include a heart rate in the high 40 seconds as well as lateral T-wave inversions. C, A 12-lead electrocardiogram obtained approximately 2 minutes after the Figure 1B electrocardiogram showing the fourth episode of coronary vasospasm. Prominent findings include ST segment elevations in the inferior and lateral leads.

ECG machine. Approximately 75 minutes into the case, the patient developed a 5.5 mm ST segment elevation in leads II and III, and a 2.7 mm elevation in lead V with an associated decrease in heart rate (nadir 40 beats per minute) and blood pressure (nadir mean arterial pressure of 42). Blood pressure was stabilized with multiple 10 µg boluses of epinephrine

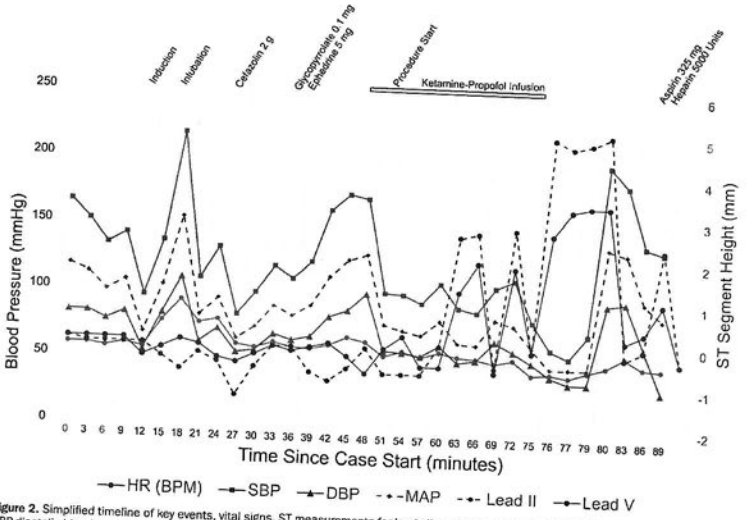

Figure 2. Simplified timeline of key events, vital signs, ST measurements for leads II and V during the case. BPM indicates beats per minutes; DBP, diastolic blood pressure; MAP, mean arterial pressure; SBP, systolic blood pressure.

and 1 unit of vasopressin. Additional help was obtained for arterial line placement, 12-lead ECG acquisition, and to perform a transesophageal echocardiogram (TEE). The surgeons were informed of the serious nature of the events and the need for an expedited closure. Interventional cardiology was notified and came to assess the patient. An orogastric tube was placed and 325 mg of crushed aspirin in a water suspension was administered. After a discussion with the surgeons, 5000 units of heparin was given intravenously. A TEE revealed a moderately reduced left ventricular inferior wall function. Five minutes later, the ST elevations again resolved, and blood pressure and heart rate returned to normal. At this time, a 12-lead ECG was obtained (Figure 1B). A few minutes later, she again developed significant ST segment changes (Figure 1C), and the decision was made to proceed to cardiac catheterization and coronary angiography began 15 minutes later.

Coronary angiography revealed diffuse vasospasm of a codominant right coronary artery (Figure 3) which improved with intracoronary nitroglycerin. No significant obstructive lesions were found. The patient was transferred to the intensive care unit (ICU) for monitoring. Her postoperative TTE was unchanged from prior, and her ICU course was uneventful. She was started on oral diltiazem (60 mg twice daily) and was discharged to the medicine ward for further medication adjustment on postoperative day 1. We followed up 6 months later and she remains well with her symptoms managed on her new regimen of isosorbide mononitrate 120 mg/d and sustained release diltiazem 240 mg/d.

DISCUSSION

Vasospasm results from an interaction between the vascular endothelium and other endogenous or exogenous triggers. Potential triggers in our patient include autonomic

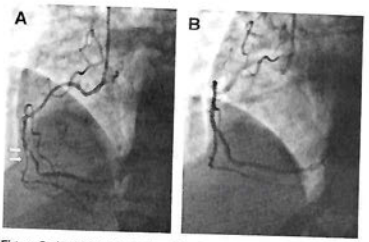

Figure 3. Angiographic studies showing obstruction of the midsegment of the right coronary artery (arrows) both before (A) and after (B) vasospasm was relieved by the administration of intracoronary nitroglycerin.

and sympathetic tone imbalance, factors related to surgical stress, and an allergic reaction.[2,5] Allergic angina, also known as Kounis syndrome, is a multi-system inflammatory reaction associated with coronary vasospasm. Various known triggers include certain foods, latex, and medications like antibiotics.[6,7] It is possible that our patient may have had an allergic reaction to cefazolin, though it is less likely given that the onset of the ST segment elevations was approximately 40 minutes after administration. Based on the timing of the vasospasm, ketamine may have been the trigger as the infusion was started approximately 20 minutes before the first ST segment elevation, and the ST segment elevation events subsided 20 minutes after the infusion termination. Ketamine allergy is rare,[8] and we did not encounter any issues or signs of anaphylaxis or an anaphylactoid reaction, though corticosteroids were given at the beginning of the case and could have masked some of these clinical signs. Ketamine is a N-methyl D-aspartate channel antagonist with excellent anesthetic and analgesic properties but is known to increase sympathetic tone. Therefore, although the patient only received ~18 mg of ketamine, this may have increased sympathetic tone enough to have an additive effect on the underlying surgical stress to trigger the events.[4]

This case highlights the presence of a significant comorbidity that was never definitively characterized or identified. The patient's previous medications controlled her vasospastic events, but it was discontinued more than a year before the events described here. The uneventful knee surgery and the negative cardiac workup were likely reassuring findings that dissuaded further preoperative evaluation for her atypical chest pain. The connection between prior and current events became quite clear when a diagnosis was finally made after thirteen years of negative findings. For the preoperative evaluation, perhaps the best lesson is to allow time for open-ended discussion of health concerns and other major health events that may be obscured by previous evaluations and to avoid anchoring bias. We present this case to alert anesthesiologists to the presence of coronary vasospasm, possible triggers, and the need to consider this diagnosis in patients who report chest pain despite the absence of obstructive arterial lesions or other known causes. In our case, we were fortunate to have had the resources available to obtain a rapid diagnosis and treatment. When there are uncertainties and delays in diagnostic evaluation and treatment, we believe that aspirin administration (crushed and applied to the oral mucosa (preferred option) or rectally) and anticoagulation to the degree tolerable remains appropriate for treatment of possible intraoperative myocardial infarction. Additionally, when a patient presents with a history of atypical chest pain, regardless of how well managed their symptoms are, the use of sympathomimetic medications outside of what is necessary for hemodynamic support should be carefully considered.

DISCLOSURES

Name: Richard K. Perez, MD.
Contribution: This author helped care for the patient, reviewed the literature, and drafted the article.
Name: Geoffrey Lighthall, MD, PhD.
Contribution: This author helped care for the patient, reviewed the literature, and drafted the article.
This manuscript was handled by: BobbieJean Sweitzer, MD, FACP.

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

Case ID: 23961490

Case Information:

Case Type : Expedited (15-Day) **eSub:** Y **HP:** Y **Country:** CH **Event Date:** 20-May-2024 **Outcomes:** HO , OT **Application Type:**

FDA Rcvd Date: 11-Jun-2024 **Mfr Rcvd Date:** 07-Jun-2024 **Mfr Control #:** CH-PFIZER INC-202400189186 **Combination Product Report:** No Information **Application #:** 074549

Patient Information:

Age: 51 YR **Sex:** Male **Weight:**

Suspect Products:

#	Product Name:	Compounded Drug ?	Dose/Frequency	Route	Dosage Text	Start Date	End Date	Indication(s)
1	Ketalar		2 Mg Milligram(S) /	Intravenous (not otherwise specified)	2 mg, single	20-May-2024	20-May-2024	Analgesia
2	KETALGIN [METHADONE HYDROCHLORIDE]		1 Dosage Form /	Oral	Chronic therapy, dosage not known			Drug abuse
3	MORPHINE HCL		3 Mg Milligram(S) /	Intravenous (not otherwise specified)	3 mg, single	20-May-2024	20-May-2024	Analgesia
4	DORMICUM [MIDAZOLAM]		1 Mg Milligram(S) /	Intravenous (not otherwise specified)	1 mg, single, a single administration; IN TOTAL	20-May-2024	20-May-2024	Analgesia
5	PALEXIA		150 Mg Milligram(S) /	Oral	150 mg, daily 50mg-0-0-100mg	May-2024	22-May-2024	Analgesia

#	Product Name:	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler	OTC
1	Ketalar	1 Day	Not Applicable	NA				PFIZER	

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

Case ID: 23961490

2	KETALGIN [METHADONE HYDROCHLORIDE]			NA	NA
3	MORPHINE HCL	1	Day	Not Applicable	NA
4	DORMICUM [MIDAZOLAM]	1	Day	Not Applicable	NA
5	PALEXIA			Yes	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			/			

Event Information:

Preferred Term (MedDRA Version: v.27.0) **ReC**

Toxicity to various agents

Respiratory arrest

Event/Problem Narrative:

This is a spontaneous report received from a Physician from Regulatory Authority. Regulatory number: CH-SM-2024-13514 (Swissmedic). A 51-year-old male patient received ketamine HCl (KETALAR), from (b) (6) at 2 mg single, intravenous for analgesic therapy; methadone hydrochloride (KETALGIN [METHADONE HYDROCHLORIDE]) at 1 DF (chronic therapy, dosage not known), oral for drug abuse; morphine HCl (MORPHINE HCL), from (b) (6)) to (b) (6) at 3 mg single, intravenous for analgesic therapy; midazolam (DORMICUM [MIDAZOLAM]), from (b) (6)) to (b) (6) at 1 mg single (1 mg, single, a single administration; in total), intravenous for analgesic therapy; tapentadol hydrochloride (PALEXIA), from (b) (6)) to (b) (6) at 150 mg daily (150 mg, daily 50mg-0-0-100mg), oral for analgesic therapy. The patient's relevant medical history included: "Ex-drug abuser" (unspecified if ongoing), notes: Previous drug addiction in sostitution; "Spinal fracture", start date: (b)(6)* (unspecified if ongoing), notes: elective Th2-Th6 stabilization surgery, Th4 corpectomy, Th7 kyphoplasty and Th4 biopsy for atraumatic Th4 and Th7 fractures of unclear origin.; "Spinal stabilisation", start date: (b)(6)***, stop date:(b)(6)****, notes: elective Th2-Th6 stabilization surgery, Th4 corpectomy, Th7 kyphoplasty and Th4 biopsy for atraumatic Th4 and Th7 fractures of unclear origin. Concomitant medication(s) included: DAFALGAN oral taken for pain management, start date:(b)(6)**. The patient was taking Dafalgan 4 g/day and Palexia 150

Case ID: 23961490

mg/day (50mg-0-0-100mg) for pain management. However, due to failure to control the pain, on (b)(6)*** Ketalar 2 mg, Morphine HCl 3 mg and Dormicum 1 mg were administered, with subsequent observation of respiratory arrest following a probable accumulation of therapy. A laryngeal mask is therefore placed and ventilation is performed. The following information was reported: RESPIRATORY ARREST (hospitalization, medically significant) with onset(b)(6)******outcome "recovered" ((b)(6)***); TOXICITY TO VARIOUS AGENTS (hospitalization) with onset (b)(6)***, outcome "recovered" ((b)(6)***). The patient is transferred to another emergency hospital. Upon arrival he appears hemodynamically stable, lucid, conscious and oriented. Chest CT angiography excludes massive thromboembolism. He is admitted to Intensive Medicine for therapeutic care. The patient arrives in intensive care alert, cooperative, lucid, without focal deficits. There were no further episodes of desaturation or alteration of the GCS during hospitalization. Due to failure to control the pain, it was decided to suspend Palexia in favor of Patient-Controlled Analgesia with morphine and Transtec 52.5 mcg/h patch with partial benefit. Ketalgin therapy is also continued. Given the clinical stability of the patient, a transfer to a non-intensive department for continuation of treatment on (b)(6)*** is considered possible. The action taken for methadone hydrochloride was dosage not changed; for tapentadol hydrochloride was dosage permanently withdrawn on (b)(6)***. Relatedness of drug to reaction WHO Assessment Possible. Reporter Comment: patient hospitalized for respiratory arrest on opioid treatment (methadone, ketamine, morphine) No follow-up attempts are possible.

Relevant Medical History:

Disease/Surgical Procedure	Start Date	End Date	Continuing?
Ex-drug abuser			
Spinal fracture	(b) (6)		
Spinal stabilisation	(b) (6)	(b) (6)	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
CHEST CT	excludes massive thromboembolism				Y

Concomitant Products:

#	Product Name:	Dose/Frequency	Route	Dosage Text	Start Date	End Date	Indication(s)	Interval 1st Dose to Event
1	DAFALGAN	1 G Gram(S) / QID	Oral	1 g, 4x/day	May-2024		Pain management	

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

Case ID: 23961490

Reporter Source:

Study report?: No

Sender organization: PFIZER

503B Compounding Outsourcing Facility?:

Literature Text:

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

Case ID: 23980673

Case Information:

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

FDA Rcvd Date: 17-Jun-2024 **Mfr Rcvd Date:** 04-Jun-2024 **Mfr Control #:** NP-ENDO USA, INC.-2024-002518 **Combination Product Report:** No **Application #:** 016812

Patient Information:

Age: 29 YR **Sex:** Female **Weight:**

Suspect Products:

#	Product Name:	Compounded Drug ?	Dose/Frequency	Route	Dosage Text	Start Date	End Date	Indication(s)
1	KETALAR		/	Unknown	UNK Unknown, Unknown (for the past 8 years)			10074854

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

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			/			

Event Information:

Preferred Term (MedDRA Version: v.27.0) **ReC**

Sphincter of Oddi dysfunction

Drug abuse

Event/Problem Narrative:

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

Case ID: 23980673

A foreign literature report was received from Nepal, Citation: Sharma NR, Basnet A, Lamichhane S, Tiwari K, Varghese J, Gautam S et al. Sphincter of Oddi dysfunction induced by ketamine: A case report. Clinical Case Reports. 2024; 12(6) 1-4, concerning a 29-year-old female, who experienced sphincter of Oddi dysfunction (SOD) while using ketamine for recreational use (drug abuse). Medical history and concomitant medications were not reported. On an unknown date, the patient who was using recreational ketamine for the past 8 years (unknown dose, route and frequency), presented to the emergency department with right upper quadrant abdominal pain associated with nausea and non-bilious, non- bloody vomiting. At the presentation, her vitals were stable, and her physical examination was unremarkable except for the tenderness in the right upper quadrant, without guarding or rebound tenderness. Lab studies revealed an alkaline phosphatase of 116 U/L. Chest x-ray did not show any cardiopulmonary pathology. Electrocardiogram showed a normal sinus rhythm. Ultrasound of the abdomen revealed a prominent common bile duct (CBD) without gallbladder pathology. Computed tomography (CT) of the abdomen and pelvis showed dilatation of the CBD measuring up to 9 mm. The patient was admitted to the hospital for the workup of common bile duct dilation and pain management. During hospitalization, her pain was managed adequately with analgesics; however, her liver enzymes continued to increase. An inpatient gastroenterology consultation was done, and a shared decision was made to perform an endoscopic retrograde cholangiopancreatography (ERCP), given her symptoms of right upper quadrant pain, ketamine abuse, the elevation of liver enzymes, and dilatation of the CBD without obstructive pathology. ERCP revealed the dilatation of CBD and Type 2 SOD. Sphincterotomy was performed and post-sphincterotomy fluoroscopy was done which suggested reduced CBD dilatation. Sphincterotomy resulted in subsequent symptom resolution and eventual discharge with outpatient gastroenterology follow-up. The patient was happy with the treatment provided. At the time of this report, the action taken with ketamine was unknown. The outcome of the event of sphincter of Oddi dysfunction was recovered and the outcome of the event of drug abuse was unknown. A copy of the literature article is attached.

Relevant Medical History:

Disease/Surgical Procedure	Start Date	End Date	Continuing?
Recreational drug use			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	18 (on the day of hospitalization) U/L		7	56	N
ALANINE AMINOTRANSFERASE	520 (day 4) U/L		7	56	N
ALANINE AMINOTRANSFERASE	86 (one week) U/L		7	56	N
ASPARTATE AMINOTRANSFERASE	16 (on the day of hospitalization) U/L		10	40	N
ASPARTATE AMINOTRANSFERASE	489 (day 4) U/L		10	40	N

Case ID: 23980673

ASPARTATE AMINOTRANSFERASE	71 (one week) U/L	10	40	N
BILIRUBIN DIRECT	0 (on the day of hospitalization) mg/dL	0	0.3	N
BILIRUBIN DIRECT	0 (day 4) mg/dL	0	0.3	N
BILIRUBIN DIRECT	0 (one week) mg/dL	0	0.3	N
ALKALINE PHOSPHATASE	116 (on the day of hospitalization) U/L	40	129	N
ALKALINE PHOSPHATASE	241 (day 4) U/L	40	129	N
ALKALINE PHOSPHATASE	99 (one week) U/L	40	129	N
BILIRUBIN TOTAL	0.2 (on the day of hospitalization) mg/dL	0	1.2	N
BILIRUBIN TOTAL	0.2 (day 4) mg/dL	0	1.2	N
BILIRUBIN TOTAL	0.4 (one week) mg/dL	0	1.2	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:** ENDO **503B Compounding Outsourcing Facility?:**

Literature Text: Sharma NR, Basnet A, Lamichhane S, Tiwari K, Varghese J, Gautam S et al.. Sphincter of Oddi dysfunction induced by ketamine: A case report. Clinical Case Reports. 2024;12(6):1-4

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DOI: 10.1002/ccr3.9016

CASE REPORT

Clinical Case Reports WILEY

Sphincter of oddi dysfunction induced by ketamine: A case report

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Key Clinical Message

Chronic ketamine use can lead to sphincter of oddi dysfunction (SOD), causing various hepatobiliary complications. Recognizing substance abuse history is vital for early detection. Timely intervention can prevent irreversible liver and pancreas damage.

Abstract

Ketamine is commonly abused as a recreational drug worldwide due to its ability to induce euphoria-like effects. Ketamine abuse is associated with many hepatobiliary side effects ranging from cholestasis to biliary sepsis and death. Here we present a case of a young 29-year female with upper abdominal pain due to SOD resulting from chronic use of ketamine. SOD can result in obstruction or dysfunction of the bile and pancreatic ducts. Ketamine induces SOD by activation of the muscarinic receptors in the sphincter of oddi. Detail history of substance abuse is crucial for early identification of ketamine-induced SOD. Early identification and treatment of this rare condition can prevent permanent injury to the liver and pancreas.

KEYWORDS

biliary diseases, drug abuse, low-dose ketamine, sphincter of oddi dysfunction

1 | INTRODUCTION

Ketamine is used as a recreational drug (street ketamine) due to its ability to induce euphoria and a trance-like state. Street ketamine can be inhaled, swallowed, or injected. It is abused in many parts of the world.[1] Although the recreational dosage is 15%–20% lower than the amount used for anesthesia, the extended and widespread recreational use of this substance has led to an increase in both side effects and fatalities.[2] In the United States, more than 2.3 million teens and adults used ketamine in their lifetime.[2]

Although the effects of ketamine on the urinary bladder have been widely reported, its effects on the bile duct and its management have not been extensively studied.[3] We report a rare case of the sphincter of oddi dysfunction (SOD) in a young female who presented to the hospital with abdominal pain.

2 | CASE HISTORY/EXAMINATION

A 29-year-old female with a history of recreational ketamine use for the past 8 years presented to the emergency department with right upper quadrant abdominal pain associated with nausea and non-bilious and non-bloody vomiting.

At the presentation, her vitals were stable. Physical examination was unremarkable except for the tenderness in the right upper quadrant, without guarding or rebound tenderness.

3 | METHODS (DIFFERENTIAL DIAGNOSIS, INVESTIGATION, AND TREATMENT)

Lab studies revealed an Alkaline Phosphatase (ALP) of 116 U/L. Chest X-ray did not show any cardiopulmonary pathology. Electrocardiogram showed a normal sinus rhythm. Ultrasound of the abdomen revealed a prominent common bile duct (CBD) without gallbladder pathology. computed tomography (CT) of the abdomen and pelvis showed dilatation of the CBD measuring up to 9 mm.

She was admitted to the hospital for the workup of CBD dilation and pain management. During hospitalization, her pain was managed adequately with analgesics; however, her liver enzymes continued to increase (Table 1).

An inpatient gastroenterology consultation was done, and a shared decision was made to perform an Endoscopic retrograde cholangiopancreatography (ERCP), given her symptoms of right upper quadrant pain, ketamine abuse, the elevation of liver enzymes, and dilatation of the CBD without obstructive pathology. ERCP revealed the dilatation of CBD and Type 2 SOD (Figure 1). Sphincterotomy was performed (Figure 2) and post-sphincterotomy fluoroscopy was done which suggested reduced CBD dilatation.

4 | OUTCOME AND FOLLOW-UP

Sphincterotomy resulted in subsequent symptom resolution and eventual discharge with outpatient gastroenterology follow-up. The patient was happy with the treatment provided.

5 | DISCUSSION

SOD is a condition characterized by abnormal muscular valve function regulating the flow of bile and pancreatic juice into the duodenum. SOD can result in obstruction or dysfunction of the bile and pancreatic ducts, leading to symptoms including abdominal pain, nausea, vomiting, and diarrhea. The prevalence of SOD is estimated to be 1.5% in the general population and up to 29% in patients with chronic abdominal pain.[4]

Ketamine is a dissociative anesthetic drug used for pain management and sedation. Ketamine has a short half-life, undergoes extensive first-pass metabolism in the liver, and is primarily excreted through urine and bile.[5] Although some studies have shown that ketamine can induce the contraction of the sphincter, leading to obstruction of the bile and pancreatic ducts, more studies are still required to confirm this.[6,7] The mechanism by which ketamine induces SOD is not fully understood, but it is thought to involve the activation of the muscarinic receptors in the sphincter of oddi. It has been shown to enhance the release of acetylcholine, a neurotransmitter that activates the muscarinic receptors in the sphincter. This increases the tone and contraction of the sphincter, which can obstruct the bile and pancreatic ducts.[6,8] This can result in elevated liver enzymes, jaundice, and pancreatitis.

The diagnosis of SOD due to ketamine abuse is based on the patient's history of ketamine use, symptoms of biliary or pancreatic dysfunction, and imaging studies such as magnetic resonance cholangiopancreatography (MRCP) or endoscopic retrograde cholangiopancreatography (ERCP). MRCP can detect any structural abnormalities in the bile and pancreatic ducts, while ERCP can measure

TABLE 1 Progression of liver enzymes.

Liver function test	On the day of hospitalization	Day 1	Day 2	Day 3	Day 4	One Week	Normal range
Total Bilirubin (mg/dL)	0.2	0.3	0.2	0.3	0.2	0.4	0–1.2
Direct bilirubin (mg/dL)	0	0	0	0	0	0	0–0.3
AST (Aspartate aminotransferase, U/L)	16	148	168	91	489	71	10–40
ALP (Alkaline phosphatase, U/L)	116	139	165	173	241	99	40–129
ALT (Alanine aminotransferase, U/L)	18	113	151	520	520	86	7–56

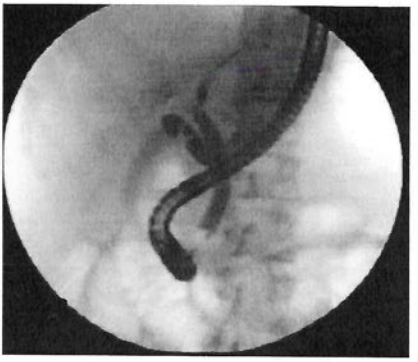

FIGURE 1 ERCP showing obstructive cholangiogram.

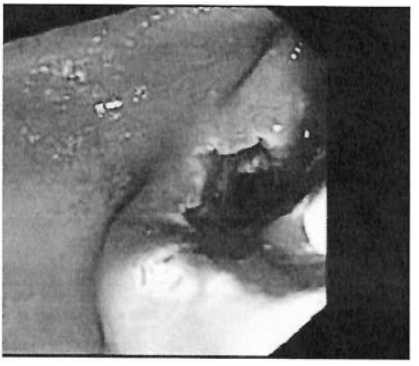

FIGURE 2 During sphincterotomy.

the sphincter's pressure and diagnose SOD.[8,9] The treatment of SOD due to ketamine abuse includes cessation of ketamine use and using medications to relax the sphincter, such as nitrates, calcium channel blockers, and anticholinergics. Endoscopic sphincterotomy, a procedure that involves cutting the sphincter, can also relieve the obstruction of the bile and pancreatic ducts.[9]

In conclusion, SOD due to ketamine abuse is a serious medical condition that can lead to biliary and pancreatic dysfunction. It is essential to identify the condition early to prevent complications such as pancreatitis and hepatic damage. Treatment involves cessation of ketamine use and the use of medications or endoscopic sphincterotomy to relieve the obstruction of the bile and pancreatic ducts.

6 | CONCLUSION

Ketamine is commonly abused among teens and adults worldwide. Ketamine-induced sphincter dysfunction can be life-threatening if an early diagnosis is not made. Physicians should be aware of this rare finding in patients with acute abdominal pain. Early diagnosis and management can prevent further hepatic and pancreatic injury.

AUTHOR CONTRIBUTIONS

Nava Raj Sharma: Conceptualization; methodology; writing – original draft; writing – review and editing. **Arjun Basnet:** Conceptualization; methodology; writing – original draft. **Saral Lamichhane:** Conceptualization; methodology; writing – original draft; writing – review and editing. **Kripa Tiwari:** Conceptualization; methodology; writing – original draft. **Jeffy Varghese:** Conceptualization; methodology; writing – original draft. **Sudarshan Gautam:** Conceptualization; methodology; writing – original draft. **Madalasa Pokhrel:** Conceptualization; methodology; writing – original draft.

FUNDING INFORMATION

None.

CONFLICT OF INTEREST STATEMENT

None.

DATA AVAILABILITY STATEMENT

All data regarding this case has been reported in the manuscript. Please contact the corresponding author if you are interested in any further information.

CONSENT

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of written consent is available for review by the Editor-in-Chief of this journal on request.

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

Case ID: 23989873

Case Information:

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

FDA Rcvd Date: 19-Jun-2024 **Mfr Rcvd Date:** 16-Jun-2024 **Mfr Control #:** GB-PFIZER INC-202400194168 **Combination Product Report:** No Information **Application #:** 074549

Patient Information:

Age: **Sex:** Female **Weight:** 104 KG

Suspect Products:

#	Product Name:	Compounded Drug ?	Dose/Frequency	Route	Dosage Text	Start Date	End Date	Indication(s)
1	Ketalar		/		70mg			

#	Product Name:	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler	OTC
1	Ketalar		Unknown	NA	325016			PFIZER	

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			/			

Event Information:

Preferred Term (MedDRA Version: v.27.0) **ReC**

Hypersensitivity

Event/Problem Narrative:

This is a spontaneous report received from an Other HCP from the United Kingdom's Medicines and Healthcare products Regulatory Agency (UK-MHRA). Regulatory number: GB-MHRA-MED-202406161534093730-RLDKZ (MHRA). A female patient received ketamine HCl (KETALAR), (Lot number: 325016) at 70mg.

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

Case ID: 23989873

The patient's relevant medical history and concomitant medications were not reported. The following information was reported: HYPERSENSITIVITY (medically significant), outcome "recovering", described as "Severe allergic reaction". The action taken for ketamine HCl was unknown. No follow-up attempts are possible.

Relevant Medical History:

ASKU

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:** PFIZER **503B Compounding Outsourcing Facility?:**

Literature Text:

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

Case ID: 23999511

Case Information:

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

FDA Rcvd Date: 21-Jun-2024 **Mfr Rcvd Date:** 18-Jun-2024 **Mfr Control #:** IL-PFIZER INC-PV202400080749 **Combination Product Report:** No Information **Application #:** 074549

Patient Information:

Age: 3 YR **Sex:** Female **Weight:**

Suspect Products:

#	Product Name:	Compounded Drug ?	Dose/Frequency	Route	Dosage Text	Start Date	End Date	Indication(s)
1	Ketalar		/		UNK	13-Mar-2024		

#	Product Name:	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler	OTC
1	Ketalar	2 Hour	Unknown	NA				PFIZER	

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			/			

Event Information:

Preferred Term (MedDRA Version: v.27.0) **ReC**

Dissociation

Event/Problem Narrative:

This is a spontaneous report received from a Pharmacist from Regulatory Authority. Regulatory number: 108546 (Israeli Health Authority internal reference number), Portal_41805 (Israeli Health Authority). A 3-year-old female patient received ketamine HCl (KETALAR), since (b)(6)***. The patient's relevant medical

Case ID: 23999511

history included: "Hydronephrosis without effect on renal function" (unspecified if ongoing); "undergo the procedure" (unspecified if ongoing), notes: under slight sedation. The patient's concomitant medications were not reported. The following information was reported: DISSOCIATION (medically significant), 2 hrs after the suspect product(s) administration, outcome "recovered", described as "Detachment (decisional sedation)". Clinical course: About two hours after recipient of the medication and after that the patient was walking by herself, the patient returned to a situation of Detachment (decisional sedation) for about 20 minutes and then it took more than 3 hours to return to herself. The seriousness of event was reported as serious. The action taken for ketamine HCl was unknown.

Relevant Medical History:

Disease/Surgical Procedure	Start Date	End Date	Continuing?
Hydronephrosis			
Medical procedure			

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:** PFIZER **503B Compounding Outsourcing Facility?:**

Literature Text:

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

Case ID: 24007576

Case Information:

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

FDA Rcvd Date: 25-Jun-2024 **Mfr Rcvd Date:** 11-Jun-2024 **Mfr Control #:** US-ENDO USA, INC.-2024-002609 **Combination Product Report:** No **Application #:** 016812

Patient Information:

Age: 80 YR **Sex:** Female **Weight:**

Suspect Products:

#	Product Name:	Compounded Drug ?	Dose/Frequency	Route	Dosage Text	Start Date	End Date	Indication(s)
1	KETALAR		100 Mg Milligram(S) /	Unknown	100 milligram, Unknown (ECT 3-day 9)			10054435
2	KETALAR		100 Mg Milligram(S) /	Unknown	100 milligram, Unknown (ECT 13-maintenance)			10088521

#	Product Name:	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler	OTC
1	KETALAR		Yes	NA				PAR	
2	KETALAR		Yes	NA				PAR	

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			/			

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

Case ID: 24007576

Event Information:

Preferred Term (MedDRA Version: v.27.0)	**ReC**
Serotonin syndrome	
Pneumonia aspiration	

Event/Problem Narrative:

A domestic literature report was received from United States, Citation: Deka A, Joseph E, Sharma N, Berhanu T, Kaplan J. Recurrent Serotonin Syndrome After Ketamine-assisted Electroconvulsive Therapy: A Case Report and Review of the Literature. Journal of Psychiatric Practice. 2024 May; 30 (3): 234-241, concerning a female in her 70's, who experienced serotonin syndrome and pneumonia aspiration while using ketamine as an anesthetic agent in electroconvulsive therapy (ECT) and for treatment-resistant depression (TRD). Medical history included hypothyroidism, hypertension, hyperlipidemia, unspecified anxiety, major neurocognitive disorder and major depressive disorder. Before admission, the patient had 6 weeks of worsening depressed mood, anhedonia, low energy, hypersomnia, poor appetite, psychomotor retardation, excessive guilt, and difficulty concentrating despite adherence to a psychotropic regimen of duloxetine and alprazolam (concomitant medications). She had undergone 4 sessions of ECT with symptomatic improvement. However, her depression worsened after discontinuation of ECT despite augmentation with mirtazapine and cariprazine (concomitant medications). She was subsequently admitted to inpatient psychiatry. ECT was considered as the patient had benefited from it in the past. After admission, her psychotropic drugs were modified. The patient underwent another cycle of ECT. She tolerated the first 2 treatments. Concomitant medications also included lorazepam, risperidone, simvastatin, losartan, levothyroxine, methohexital and succinylcholine. On an unknown date (for the third ECT treatment/hospital day 9), the anesthetic agent was changed from methohexital to ketamine at a dose of 100 mg (unknown route and frequency) because of suboptimal seizures in the first 2 treatments with methohexital. Post-ECT physical examination was significant for tremors, temperature of 103.3 °F, systolic blood pressure of 190 mmHg, altered mental status, diffuse hyperreflexia, and increased lower extremity muscle tone. The patient was diagnosed with serotonin syndrome (SS). Laboratory evaluation showed complete blood count (CBC) and comprehensive metabolic panel were within normal limits. Her creatine kinase (CK) was elevated, and a venous blood gas revealed lactic acid 4.3 mmol/L, pH 7.32, and bicarbonate 21.7 mmol/L. Computerized tomography (CT) of the brain was unrevealing. Urinalysis and cultures were normal. Her chest x-ray showed patchy infiltration, which led to suspicion of aspiration pneumonia that was treated with amoxicillin-clavulanate. Her orientation and physical examination improved. Psychotropics were stopped, except for benzodiazepines, due to concern for SS and she recovered with conservative measures, including intravenous (IV) fluids. After she was stabilized, ECT was resumed utilizing methohexital and succinylcholine. After her eighth ECT treatment, she began displaying symptoms of delirium, including paranoid delusions. She psychotropic drugs were modified, and benzodiazepines were held. When symptoms improved, she re-started lorazepam as needed for severe anxiety. Her severe anxiety and depression were also treated with clonazepam 0.5mg twice a day. In total, she received 15 ECT treatments while hospitalized. Ultimately, the patient's depression decreased, and she was discharged on mirtazapine, risperidone, and lorazepam with a plan for weekly outpatient maintenance ECT. After 5 weeks, ECT was changed to every other week. She had a relapse of depression, weekly ECT was re-started, and duloxetine was re-initiated and gradually increased. This was the last change to her medication regimen and took place 8 days before her 13th maintenance ECT. For her 13th ECT maintenance treatment, she came into the hospital in her usual state of health without any prodromal or acute signs and symptoms of SS. Ketamine was again used in place of methohexital due to concern about suboptimal seizures and for potential additive antidepressant effect in TRD. Post-ECT, she developed altered mental status, elevated temperature to 102.5 °F, rigidity in all limbs, upper extremity tremors, and diffuse hyperreflexia. Further laboratory evaluation included a normal comprehensive metabolic panel, urinalysis and chest x-ray. A CBC was significant for an elevated white blood cell count and her CK was elevated. CT of the brain was again unrevealing. Routine electroencephalography showed moderate generalized slowing consistent with unspecified encephalopathy. She was once again diagnosed with SS. All previous psychotropic agents were discontinued, and intravenous lorazepam and fluids were initiated. She was medically stabilized over the course of 5 days and then transferred to inpatient psychiatry. She underwent 12 further ECT sessions under methohexital and succinylcholine uneventfully. The etiology of the recurrent episodes of SS was attributed to the combination of ketamine and ECT. At the time of this report, the action taken with ketamine was drug withdrawn. The outcome of the events of serotonin syndrome and pneumonia aspiration was recovered. A copy of the literature article is attached.

Case ID: 24007576

Relevant Medical History:

Disease/Surgical Procedure	Start Date	End Date	Continuing?
Major depressive disorder			Yes
Hypothyroidism			Yes
Hypertension			Yes
Hyperlipidemia			Yes
Anxiety			Yes
Major neurocognitive disorder			Yes
Electroconvulsive therapy			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
BICARBONATE	21.7 (after first ECT treatment with ketamine) Mmol/L				N
CREATINE KINASE	1317 (after first ECT treatment with ketamine) U/L				N
CREATINE KINASE	390 (after second ECT treatment with ketamine) U/L				N
LACTIC ACID	4.3 (after first ECT treatment with ketamine) Mmol/L				N
VENOUS BLOOD PH	Venous blood gas with pH: 7.32 (after first ECT unknown				Y

Case ID: 24007576

TSH	Within normal limits (at emergency department) unknown	N
CULTURE	Cultures demonstrated no growth (after first ECT unknown	Y
COMPLETE BLOOD COUNT	Within normal limits (after first ECT treatment unknown	Y
COMPLETE BLOOD COUNT	Significant for WBC of 12.76×10^3/µL (after second unknown	Y
COMPREHENSIVE METABOLIC PANEL	Within normal limits (after first ECT treatment unknown	Y
COMPREHENSIVE METABOLIC PANEL	Normal (after second ECT treatment with ketamine) unknown	N
FREE T4	Within normal limits (at emergency department) unknown	N
URINALYSIS	Normal (after first ECT treatment with ketamine) unknown	N
URINALYSIS	Within normal limits (after second ECT treatment unknown	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)
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1	DULOXETINE	60 Mg Milligram(S) /	Unknown	60 milligram, daily (before admission)	10081270
2	DULOXETINE	30 Mg Milligram(S) /	Unknown	30 milligram, Unknown	
3	DULOXETINE	60 Mg Milligram(S) /	Unknown	60 milligram, daily (re-started)	
4	DULOXETINE	90 Mg Milligram(S) /	Unknown	90 milligram, daily (gradually increased from 60 to 90 mg/day)	
5	ALPRAZOLAM	0.25 Mg Milligram(S) / TID	Unknown	0.25 milligram, tid (before admission)	10081270
6	ALPRAZOLAM	0.5 Mg Milligram(S) /	Unknown	was increased to 0.5 milligram, tid prn (days 2 and 3)	
7	LORAZEPAM	1 Mg Milligram(S) / TID	Unknown	1 milligram, tid	10002855
8	LORAZEPAM	0.5 Mg Milligram(S) /	Unknown	0.5 milligram, prn (once as day as needed)	10081270
9	LORAZEPAM	0.5 Mg Milligram(S) / BID	Unknown	0.5 milligram, bid	
10	MIRTAZAPINE	15 Mg Milligram(S) /	Unknown	15 milligram, Unknown	10081270
11	MIRTAZAPINE	30 Mg Milligram(S) /	Unknown	Titrated to 30 milligram nightly	
12	CARIPRAZINE	/	Unknown	UNK Unknown, Unknown	10081270
13	RISPERIDONE	0.5 Mg Milligram(S) /	Unknown	0.5 milligram, Unknown (morning)	10081270
14	RISPERIDONE	1 Mg Milligram(S) /	Unknown	1 milligram, OD (nightly)	
15	SIMVASTATIN	40 Mg Milligram(S) /	Unknown	40 milligram, OD (at bedtime)	10070592
16	LOSARTAN	40 Mg Milligram(S) /	Unknown	40 milligram, daily	10070592

FDA - Adverse Event Reporting System (FAERS)
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Case ID: 24007576

17	LEVOTHYROXINE	75 Ug Microgram(S) /	Unknown	75 microgram, daily		10070592
18	METHOHEXITAL	/	Unknown	UNK Unknown, Unknown (ECT 1-day 4)		10054435
19	METHOHEXITAL	/	Unknown	UNK Unknown, Unknown (ECT 2-day 6)		
20	METHOHEXITAL	/		UNK Unknown, Unknown (received 15 more bilateral ECT sessions with methohexital back on psychiatric		
21	SUCCINYLCHOLINE [SUXAMETHONIUM]	/	Unknown	UNK Unknown, Unknown (ECT 1-day 4)		10054435
22	SUCCINYLCHOLINE [SUXAMETHONIUM]	/	Unknown	UNK Unknown, Unknown (ECT 2-day 6)		
23	SUCCINYLCHOLINE [SUXAMETHONIUM]	120 Mg Milligram(S) /	Unknown	120 milligram, Unknown (ECT 3-day 9)		
24	SUCCINYLCHOLINE [SUXAMETHONIUM]	/		UNK Unknown, Unknown (received 15 more bialteral ECT sessions with unknown amount of succinylcholine		

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

Case ID: 24007576

25	SUCCINYLCHOLINE [SUXAMETHONIUM]	80	Mg Milligram(S) /	Unknown	80 milligram, Unknown (ECT 13-maintenance)	

Reporter Source:

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

Literature Text: Deka A, Joseph E, Sharma N, Berhanu T, Kaplan J.. Recurrent Serotonin Syndrome After Ketamine-assisted Electroconvulsive Therapy: A Case Report and Review of the Literature. Journal of Psychiatric Practice. 2024;30 (3):234-241

Recurrent Serotonin Syndrome After Ketamine-assisted Electroconvulsive Therapy: A Case Report and Review of the Literature

Aniruddha Deka, MD, Emmanuel Joseph, MD, Neha Sharma, MD, Tirsit Berhanu, MD, and Jonathan Kaplan, MD

Abstract: Serotonin (5-HT) syndrome (SS) consists of changes in mental status as well as autonomic and neuromuscular changes. Though not well understood, serotonergic pathways have been implicated in the mechanism of action of electroconvulsive therapy (ECT). Ketamine has been used as an induction agent in ECT and as therapy for treatment-resistant depression. Utilizing a case report and literature review, we explored the underlying serotonergic mechanisms of ECT and ketamine by which a syndrome of serotonin toxicity may be precipitated. We describe the case of a 72-year-old woman who developed recurrent SS on 2 occasions in similar circumstances involving the administration of ketamine for ECT. In our literature review, we found 5 cases in which SS was associated with ECT and 1 case linking ketamine to SS. There is emerging evidence that the mechanism of ECT involves 5-HT1A and 5-HT2A receptors, the same receptors that are involved in SS. ECT can transiently increase the permeability of the blood-brain barrier, leading to increased levels of antidepressants in the brain. ECT can, therefore, enhance 5-HT transmission and the likelihood of SS in the presence of serotonergic agents. The effect of ketamine on 5-HT transmission is mediated by the glutamate α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor. Ketamine increases α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid activity in the medial prefrontal cortex, which leads to downstream 5-HT release through glutamate. Through this mechanism, ketamine can increase 5-HT transmission, leading to SS. To our knowledge, this is the only case report of recurrent SS with concurrent use of ECT and ketamine. As ketamine is frequently used in ECT and many patients undergoing ECT are on serotonergic medications, it is important to recognize ketamine as a potential risk factor for SS. There is no evidence for added efficacy when combining ECT and ketamine. Thus, one should proceed with caution when combining these treatments. The burgeoning use of ketamine in ambulatory settings makes it necessary to elucidate the risks, which we discuss further. More research is needed into the mechanisms of ketamine and ECT, specifically how the combination of these treatments influence 5-HT levels.

Key Words: serotonin syndrome, electroconvulsive therapy, ketamine, case report, literature review

(*J Psychiatr Pract* 2024;30:234–241)

From the Department of Psychiatry and Behavioral Sciences, Rush University Medical Center, Chicago, IL.

Informed consent was obtained from the patient to publish this case. The IRB determined that this work did not constitute Human Subjects Research and was, therefore, exempt from the IRB approval process.

The authors declare no conflicts of interest.

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DOI: 10.1097/PRA.0000000000000787

Serotonin syndrome (SS) is a cluster of autonomic and neurologic symptoms that occurs in the setting of exposure to medications known to raise serotonin (5-HT) levels in the central and peripheral nervous systems. Hunter's criteria are used to diagnose SS (Table 1).[1,2] Typical autonomic symptoms of SS include fever, tachycardia, and diarrhea. Possible neurological symptoms include tremors, clonus, myoclonus, hyperreflexia, and increased muscle tone. Mental status changes include restlessness, anxiety, confusion, and agitation. In severe cases, patients will present with delirium, profound autonomic instability, and life-threatening hyperthermia that can progress to coma and death without prompt medical intervention.[3] Before the publication of Hunter's criteria, Sternbach's criteria were used to diagnose SS, but they fell out of favor due to an overemphasis on mental status changes, which reduced sensitivity and specificity.[2,4]

The diagnosis of SS requires a history of exposure to serotonergic agents in addition to the symptoms described above. Many substances are known to have serotonergic properties, including over-the-counter and prescribed medications, as well as herbal supplements. Psychiatric medications combined with 1 or more of these other agents may lead to SS. The risk for SS is increased by abrupt and significant increases in the dose of a medication or the addition of multiple serotonergic agents all at once. Various classes of psychotropics have been associated with SS. The combination of monoamine oxidase inhibitors and selective serotonin reuptake inhibitors (SSRIs) is the most studied cause of psychotropic-induced SS. However, cases have also been seen with SSRI overdoses, with monotherapy with tricyclic antidepressants or selective serotonin norepinephrine reuptake inhibitors, and with tricyclic antidepressants or serotonin norepinephrine reuptake inhibitor overdoses.[3,5] Herbal agents such as St. John's wort, turmeric, ginseng, and nutmeg have also been associated with SS.[6] Opioid pain medications, illicit medications, and anesthetics—most notably fentanyl—have also been implicated. Ketamine, discussed below, has been less commonly implicated but possesses a serotonergic potential that is amplified under certain conditions. (Table 2 presents a more comprehensive list of serotonergic agents.)

Treatment of SS involves the prompt discontinuation of all serotonergic agents, in addition to the provision of supportive care. Supportive care typically includes intravenous fluids, benzodiazepines for agitation, and hyperthermia management with cooling procedures. Cyproheptadine is considered in moderate to severe cases. Dantrolene and antipsychotics are avoided due to potential serotonergic effects.[3,5,6]

Electroconvulsive therapy (ECT) has long been utilized as an effective therapy for treatment-resistant depression (TRD). The treatment utilizes bilateral or unilateral

TABLE 1. Hunter's Criteria for Diagnosing Serotonin Toxicity

In the presence of a serotonergic agent:
1. IF (spontaneous clonus = yes) THEN serotonin toxicity = YES
2. ELSE IF (induced clonus = yes) AND [(agitation = yes) OR (diaphoresis = yes)] THEN serotonin toxicity = YES
3. ELSE IF (ocular clonus = yes) AND [agitation = yes) OR (diaphoresis = yes)] THEN serotonin toxicity = YES
4. ELSE IF (tremor = yes) AND (hyperreflexia = yes) THEN serotonin toxicity = YES
5. ELSE IF (hypertonic = yes) AND (temperature > 38 degree C) AND [(ocular clonus = yes) OR (inducible clonus = yes)] THEN serotonin toxicity = YES
6. ELSE serotonin toxicity = NO

Adapted with permission from Dunkley et al 2003.[2]

electrodes that deliver electrical currents through the brain, inducing a seizure. The exact mechanism of action of ECT in TRD is not well understood, but serotonergic and dopaminergic pathways have been implicated. In animal studies, ECT leads to an upregulation of postsynaptic serotonin (5-HT1A and 5-HT2A) receptors in the prefrontal cortex and the hippocampus. In humans, it is been shown that ECT decreases 5-HT1A and 5-HT2A receptor binding in the brain, similar to what is seen in response to antidepressants.[7] Other data suggest that ECT increases the permeability of the blood-brain barrier and allows for a transiently increased uptake of antidepressant medications into the central nervous system.[8] The most notable side effect of ECT is memory dysfunction, which is more likely in bilateral than unilateral ECT and potentially mediated through effects on the hippocampus.[9]

Ketamine is an N-methyl-D-aspartate (NMDA) receptor antagonist with anesthetic effects that can be used as an induction agent for ECT (Table 3 lists anesthetic induction agents that are commonly used in ECT). Ketamine has also shown efficacy in the treatment of TRD and acute suicidality.[13–15] The FDA approved esketamine, an enantiomer of ketamine administered intranasally, in combination with an oral antidepressant for the treatment of TRD. The mechanism of action of ketamine and esketamine is not completely understood. Ketamine acts on a wide range of NMDA and non-NMDA receptors, each being implicated in the antidepressant effect.[16,17] Potential side effects of ketamine include headache, blurred vision, transient increases in heart rate and blood pressure, urological complications (cystitis, bladder dysfunction), hepatotoxicity, cognitive symptoms (altered mental status, memory impairment), seizure, dissociation, anxiety, psychosis, and delirium. Ketamine also has the potential for abuse and the development of a substance use disorder.[18,19]

Although the mechanisms of action of ECT and ketamine in the treatment of depression are not fully understood, some of the benefits are attributable to their serotonergic effects. However, neither has been shown to precipitate SS on its own. Here, we describe a case of repeat SS in a patient exposed to ketamine as part of the ECT protocol. To our knowledge, this is the first reported case of SS secondary to the use of ECT plus ketamine.

CASE DESCRIPTION

The patient was a 78-year-old woman with a history of hypothyroidism, hypertension, hyperlipidemia, unspecified anxiety, major neurocognitive disorder, and major depressive disorder. She presented with worsening depression while adherent to duloxetine 60 mg/day and alprazolam 0.25 mg 3 times daily. Before this admission, she had undergone 4 sessions of ECT with symptomatic improvement. However, her depression worsened after discontinuation of ECT despite augmentation with mirtazapine and cariprazine. She was subsequently admitted to inpatient psychiatry. Table 4 presents a summary timeline of events.

After admission, duloxetine was discontinued, mirtazapine was titrated to 30 mg nightly, and lorazepam was substituted for alprazolam. The patient underwent another cycle of ECT. She tolerated the first 2 treatments. For the third treatment, the anesthetic agent was changed from methohexital to ketamine because of suboptimal seizures in the first 2 treatments, as ketamine has been shown to produce longer seizures compared with methohexital.[12] Post-ECT physical examination was significant for tremors, temperature of 103.3°F, systolic blood pressure of 190 mm Hg, altered mental status, diffuse hyperreflexia, and increased lower extremity muscle tone. The patient was diagnosed with serotonin syndrome. Laboratory evaluation showed complete blood count and comprehensive metabolic panel within normal limits, creatine kinase 1317 U/L, venous lactic acid 4.3 mmol/L, venous blood gas with pH 7.32, and bicarbonate 21.7 mmol/L. Computerized tomography (CT) of the brain was unrevealing. Urinalysis was normal, and cultures demonstrated no growth. Her chest x-ray showed patchy infiltration, which led to suspicion of aspiration pneumonia that was treated with amoxicillin-clavulanate. Psychotropics were stopped, except for benzodiazepines, due to concern for SS and she recovered with conservative measures, including intravenous (IV) fluids.

After the patient was stabilized, ECT was resumed utilizing methohexital and succinylcholine. After her 8th ECT treatment, she began displaying symptoms of delirium, including paranoid delusions. Risperidone 0.5 mg nightly was added and titrated up to 1.5 mg and benzodiazepines were held. When symptoms improved, she was restarted on lorazepam 0.5 mg once a day as needed for severe anxiety. In total, she received 15 ECT treatments. Ultimately, the patient's depression decreased, and she was discharged on mirtazapine 30 mg nightly, risperidone 1.5 mg daily, and lorazepam 0.5 mg twice a day with a plan for weekly outpatient maintenance ECT. After 5 weeks, ECT was changed to every other week. She had a relapse of depression, weekly ECT was restarted, and duloxetine was reinitiated and gradually increased to 90 mg/day. This was the last change to her medication regimen and took place 8 days before her 13th maintenance ECT.

For her 13th ECT maintenance treatment, she came into the hospital in her usual state of health without any prodromal or acute signs and symptoms of SS. Ketamine was again used in place of methohexital due to concern about suboptimal seizures and for potential additive antidepressant effect in TRD. Post-ECT, she developed altered mental status, elevated temperature to 102.5°F, rigidity in all limbs, upper extremity tremors, and diffuse hyperreflexia. Further laboratory evaluation included a normal comprehensive metabolic panel and a complete blood count significant for WBC of $12.76 \times 10^3/\mu L$; urinalysis was within normal limits, chest x-ray was normal, and creatine kinase was 390 U/L. CT of the brain was again unrevealing. Routine electroencephalography showed moderate generalized slowing consistent with unspecified

TABLE 2. Serotonergic Agents and the Mechanisms by Which They Increase Serotonin

Mechanism	Associated Drugs
Inhibit serotonin uptake	Amphetamines/weight loss drugs: phentermine Antidepressants: bupropion, nefazodone, and trazodone Anti-emetics: granisetron, ondansetron Antihistamines: chlorpheniramine Certain opiates: levomethorphan, levorphanol, meperidine, methadone, pentazocine, pethidine, tapentadol, tramadol Drugs of abuse: cocaine, MDMA ("Ecstasy") Herbal supplements: St. John's wort (*Hypericum perforatum*) Over-the-counter cold remedies: dextromethorphan SNRIs: desvenlafaxine, duloxetine, venlafaxine SSRIs: citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline TCAs: amitriptyline, amoxapine, clomipramine, desipramine, doxepin, imipramine, maprotiline, nortriptyline, protriptyline, and trimipramine
Inhibit serotonin metabolism	Anxiolytics: buspirone Herbal supplements: St. John's wort (*Hypericum perforatum*) MAOIs: furazolidone, isocarboxazid, linezolid, methylene blue, phenelzine, selegiline, Syrian rue, and tranylcypromine Triptans: almotriptan, eletriptan, frovatriptan, naratriptan, rizatriptan, sumatriptan, and zolmitriptan
Increase serotonin synthesis	Amphetamines/weight loss drugs: phentermine Dietary supplements: L-tryptophan Drugs of abuse: cocaine
Increase serotonin release	Antidepressants: mirtazapine Amphetamines/weight loss drugs: phentermine Certain opiates: meperidine, oxycodone, tramadol Drugs of abuse: MDMA ("Ecstasy") Over-the-counter cold remedies: dextromethorphan Parkinson's disease treatment/amino acid: L-dopa
Activate serotonin receptors	Anxiolytics: buspirone Antidepressants: mirtazapine, trazodone Antimigraine: dihydroergotamine, triptans Certain opiates: fentanyl, meperidine Drugs of abuse: LSD Mood stabilizers: lithium Prokinetic agents: metoclopramide
Inhibit CYP450 microsomal oxidases	CYP2D6 inhibitors: fluoxetine, sertraline CYP2D6 substrates: dextromethorphan, oxycodone, phentermine, risperidone, and tramadol CYP3A4 inhibitors: ciprofloxacin, ritonavir CYP3A4 substrates: methadone, oxycodone, venlafaxine CYP2C19 inhibitors: fluconazole CYP2C19 substrates: citalopram

CYP indicates cytochrome P 450 enzyme; LSD indicates lysergic acid diethylamide; MAOI, monoamine oxidase inhibitor; MDMA, methylenedioxymethamphetamine; SNRI, serotonin-norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant

encephalopathy. She was once again diagnosed with SS. All previous psychotropic agents were discontinued, and intravenous lorazepam and fluids were initiated. She was medically stabilized over the course of 5 days and then transferred to inpatient psychiatry. She underwent 12 further ECT sessions under methohexital and succinylcholine uneventfully. The etiology of the recurrent episodes of SS was attributed to the combination of ketamine and ECT.

The differential diagnoses included malignant hyperthermia, neuroleptic malignant syndrome, and malignant catatonia. Malignant hyperthermia was excluded because she had repeated exposure to succinylcholine without similar symptoms. Neuroleptic malignant syndrome was unlikely as she had tolerated low-dose risperidone without any symptoms, there was no change in the dose, and she had no new exposure to dopamine antagonists. Allergic reaction to ketamine was ruled out as she had received several intravenous ketamine treatments for TRD in the remote past without any adverse effects.

DISCUSSION

The case presented here describes 2 episodes of sudden onset SS in the same patient after exposure to ketamine during ECT. While the patient was taking serotonergic medications, no changes were made in the dose or frequency of the medications, and no additional serotonergic agents were added to the treatment regimen. Therefore, we concluded that the patient developed SS from the combination of ECT and ketamine. To our knowledge, this is the first case report of SS induced by ketamine plus ECT. The onset of SS tends to be acute, usually within 6 to 8 hours after exposure to serotonergic agents. In our patient, the symptoms presented immediately after exposure to ketamine and ECT but without any recent changes in her serotonergic medications (last change >7 d previously). There have been case reports of "delayed serotonin syndrome," but even in these cases, the onset of symptoms occurred within 72 hours (in one of the cases,

TABLE 3. Anesthetic Induction Agents Commonly Used in Electroconvulsive Therapy (ECT)

Induction agent	Characteristics	Effect on seizure
Methohexital	Short-acting barbiturate	Minimal anticonvulsant effect[10]
Propofol	Most commonly used agent Works through GABA-A agonism Faster recovery	Shortest seizure duration due to significant anticonvulsant effect[10] Often used when there is history of prolonged seizures or post-ictal agitation
Etomidate	Positive allosteric modulator on the GABA-A receptor Fewer cardiovascular risks compared with other agents. Agent of choice in hemodynamically unstable patients. Risk of adrenal suppression	Longer duration of seizures[10]
Ketamine	NMDA antagonist Has intrinsic antidepressant properties Cardiovascular side effects and emergence phenomenon can occur	Increases seizure duration with reduced electrical dose requirements[10,11] Longer seizures compared with methohexital; particular in those who had short seizure duration with methohexital previously[12]

GABA-A indicates γ-aminobutyric acid type A; NMDA, N-methyl-D-aspartate.

cyproheptadine, a 5-HT antagonist, had been co-ingested which was thought to be the reason for the delayed presentation).[20,21] Before the exposure to ketamine and ECT, our patient was in her usual state of health and had no prodromal or mild symptoms of SS, such as nausea, vomiting, elevated temperature, or mental status changes. There had not been any recent changes in dosing or introduction of any serotonergic agent. In addition, despite having been on several serotonergic agents for many months, she did not develop SS until she received the combination of ketamine and ECT. She had received ECT using other induction agents on numerous other occasions without signs or symptoms of SS, ruling out ECT as the primary explanation for her episodes of SS. This suggests that the combination of ECT and ketamine was the inciting factor in this presentation.

We conducted a literature review by searching databases, including PubMed and Scopus, to identify case reports of SS being precipitated by ECT, ketamine, or both (Table 5). We found 5 case reports of ECT precipitating SS in patients with pre-existing risk factors.[22–26] We found only 1 case report of ketamine being linked to the onset of SS.[27] We did not find any case reports in which concomitant use of ketamine and ECT was linked to SS, nor did we find any cases of recurrent SS occurring under these conditions. Our literature review highlighted possible risk factors for developing SS with ECT, which included sex (all 5 case reports were about female patients), the presence of multiple serotonergic agents (in 3 of the cases, more than 1 serotonergic agent was involved), and possibly older age. Of the 5 case reports concerning ECT, 3 involved bilateral ECT, 1 involved unilateral ECT, and, in the fifth case, it was unclear whether the ECT was bilateral or unilateral. In the case described here, both instances of SS occurred in the setting of bilateral ECT, but this is of unclear significance.

While the primary mechanism of action for the antidepressant effect of ketamine is thought to be through its action on the NMDA receptor and glutamatergic neurotransmission, this is far from settled. Other possible mechanisms include the action of ketamine metabolites, downstream effects of glutamate α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors, and anti-inflammatory actions.

Studies have also investigated the effects of ketamine on nonglutamatergic neurotransmitters, especially the monoaminergic system and 5-HT.[16,28] In 2013, Gigliucci et al[29] investigated whether 5-HT transmission is involved in the antidepressant action of ketamine. They demonstrated that ketamine's antidepressant activity diminished when a tryptophan hydroxylase inhibitor, which is an essential enzyme in serotonin synthesis, was used. In 2019, Lopez et al[30] proposed a pathway for ketamine's antidepressant action that included downstream effects of increased glutamate in the medial prefrontal cortex, leading to stimulation of the prefrontal projection to the dorsal raphe nucleus and locus coeruleus. This would then stimulate the release of 5-HT and norepinephrine. Furthermore, Yamamoto et al[31] demonstrated that ketamine binding to the serotonin transporter (SERT), measured by positron emission tomography (PET) scan, transiently increased 5-HT levels in the extracellular fluid of the prefrontal cortex in monkeys, which was measured using microdialysis techniques. A similar PET study in humans demonstrated a positive association between ketamine plasma levels and SERT binding.[32]

In addition to the 5-HT1A receptor, the 5-HT1B receptor is a target for antidepressant action. Patients with major depressive disorder have been found to have lower 5-HT1B receptor binding, and 5-HT1B agonists have shown antidepressant-like effects.[33] In 2014, Yamanaka et al,[34] using PET studies, found that ketamine increased 5-HT1B receptor binding and reduced SERT binding in the nucleus accumbens and ventral pallidum. They also found that when the primates were pretreated with an α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid antagonist known to block the antidepressant effect of ketamine, the increase in 5-HT1B receptor binding did not occur with ketamine, while the ketamine-induced decrease in SERT binding was maintained. This indicated that the antidepressant effect of ketamine is critically linked to 5-HT1B receptor binding.[34]

In 2020, Tiger et al[33] performed a randomized controlled PET study of ketamine's effect on 5-HT1B receptor binding in patients with TRD. They could not replicate Yamanaka's findings and did not find an increased 5-HT1B receptor binding with ketamine compared with placebo. However, on further analysis, they found that there was a significant increase in binding in the hippocampus.[33]

While ECT has been a mainstay in the treatment of TRD, the mechanism by which it confers its antidepressant

TABLE 4. Timeline of Events

Before admission	Six weeks of worsening depressed mood, anhedonia, low energy, hypersomnia, poor appetite, psychomotor retardation, excessive guilt, and difficulty concentrating despite adherence to a psychotropic regimen that included duloxetine 60 mg/d and alprazolam 0.25 mg t.i.d. ECT considered as the patient had benefited from it in the past.
Emergency department	Presented for admission for ECT. CBC, CMP unrevealing; TSH and free T4 within normal limits.
Admission day 1	Home medications continued: duloxetine 30 mg, mirtazapine 15 mg, alprazolam 0.25 mg t.i.d., simvastatin 40 mg at bedtime, losartan 40 mg/d, and levothyroxine 75 mcg/d. Brain imaging with no intracranial abnormality, age-appropriate cerebral volume loss, and chronic microvascular ischemic changes.
Days 2 and 3	Alprazolam was increased to 0.5 mg t.i.d. prn, then changed to lorazepam 1 mg t.i.d. (last dose before 9 pm on pre-ECT days).
Day 4	ECT #1 (left anterior, right temporal) under methohexital and succinylcholine. An 8 s seizure followed by a well-modified 21 s seizure. Duloxetine discontinued; mirtazapine increased to 30 mg nightly.
Day 6	ECT #2 (left anterior, right temporal) under methohexital and succinylcholine. Achieved 14 s well-modified seizure.
Day 9	ECT #3 (bilateral) under ketamine 100 mg and succinylcholine 120 mg. A 19 s well-modified seizure. Immediately post-ECT, febrile, tremulous, hyper-reflexive, and confused. Systolic blood pressure in the 190s. SS diagnosed. Transferred to the general medical floor for intravenous hydration and stabilization.
Medical admission (6 d)	Duloxetine and mirtazapine were held. Patient was treated for aspiration pneumonia. Orientation and physical examination improved. Severe anxiety and depression continued and were treated with clonazepam 0.5 mg b.i.d.
Back on psychiatric floor	Received 15 more bilateral ECT sessions, all under methohexital and succinylcholine. Medications were adjusted to mirtazapine 30 mg nightly, lorazepam 0.5 mg b.i.d., and risperidone 0.5 mg in the morning and 1 mg nightly.
Post-discharge	Weekly maintenance bilateral ECT while discharge medications were continued. Duloxetine restarted and gradually increased to 90 mg/d.
Week 15 post-discharge	Duloxetine increased from 60 to 90 mg/d 8 d before the next ECT.
Week 16 post-discharge and post-outpatient ECT #13	Presented for bilateral ECT in the usual state of health. Immediately post-ECT developed hyperthermia (102.5°F), rigidity, tremors, hyperreflexia, and altered mentation. Succinylcholine 80 mg and ketamine 100 mg were the induction agents instead of methohexital. SS was diagnosed.
Subsequent hospitalization	Hospitalized for 5 d. All psychotropics except lorazepam were held, and the patient improved with supportive care before she was transferred to Psychiatry. After transfer, she underwent 12 further ECT sessions under methohexital and succinylcholine uneventfully.
Discharge and outpatient follow-up	Improved on the Psychiatry floor and was discharged to outpatient follow-up. Mood symptoms were subsequently stabilized on a regimen of clozapine 12.5 mg in the morning and 25 mg nightly, lithium 150 mg b.i.d., lorazepam 2 mg/day in 3 divided doses (0.5 mg in the morning, 1 mg in the afternoon and 0.5 mg at night), and buspirone 10 mg b.i.d. Has not required further ECT.

CBC indicates complete blood count; CMP, comprehensive metabolic panel; ECT, electroconvulsive therapy; SS, serotonin syndrome; T4, thyroxine; TSH, thyroid stimulating hormone.

effect is not well understood. Various mechanisms have been hypothesized, which include the involvement of neurotransmitters, neuroendocrinological mechanisms, brain-derived and other neurotrophic factors, neurogenesis, and neuroplasticity. Downstream effects of neurotransmitters, especially 5-HT, have been thought to play a role in the ultimate antidepressant effect of ECT.[35] Several animal and human studies have demonstrated that electrical seizures

TABLE 5. Literature Review Concerning SS in Association with ECT or Ketamine

Case report	Possible inciting cause	Description
Okamoto et al 2012[22]	Paroxetine+ECT	SS following bilateral ECT #1 with propofol in a 67-year-old female
Klysner et al 2014[23]	Fluoxetine+ECT	A 31-year-old female who developed SS after 9 bilateral ECT sessions
Cheng et al 2015[24]	Bupropion, trazodone, and quetiapine+ECT	SS after bilateral ECT #1 with propofol in a 70-year-old female
Deuschle et al 2017[25]	Mirtazapine, venlafaxine, quetiapine, and lithium+ECT	A 45-year-old female with SS following unilateral ECT #5
Herrington et al 2018[26]	Lamotrigine, mirtazapine, venlafaxine+ECT	SS after ECT #1 (unclear if unilateral or bilateral) with methohexital in 56-year-old female
Witkin et al 2020[27]	Fluoxetine+ketamine	A 40-year-old female who developed SS after day 7 of IV ketamine

ECT indicates electroconvulsive therapy; SS, serotonin syndrome.

TABLE 6. Studies Demonstrating That Induced-seizures Can Increase the Permeability of the BBB

Study	Subject type	Agent used to induce seizure	Substrate used to study permeability	Proposed mechanism for permeability
Angel et al, 1966[36]	Rats	Electroshock, chlorpromazine, imipramine, amitriptyline, nortriptyline	Cocaine	Underlying mechanism not specified
Lorenzo et al, 1975[37]	Cats	Metrazol (pentylenetetrazol)	Horseradish peroxidase	Prolonged seizure allows passage through capillary inter-endothelial tight junctions
Bolwig et al, 1977[38]	Rats	Electroshock	Radiotracer labeled Na, Cl, C-urea, C-thiourea, Evan's blue	Increased capillary surface area by stretching and/or capillary intermittency.
Bolwig et al, 1977[39]	Humans	Electroshock	Radiotracer labeled Na, Cl, C-urea, C-thiourea	Increase in cerebral blood flow during seizures leads to stretching of the endothelial cells and area for passive diffusion and/or opening up of new capillaries
Hedley-Whyte et al, 1977[40]	Cats	Metrazol (pentylenetetrazol)	Horseradish peroxidase	Seizure leads to an increase in permeability through an increase in endothelial vesicles, allowing vesicular transit across endothelium (transendothelial channels)
Zimmermann et al, 2012[8]	Humans	Electroconvulsive stimulation	Amyloid β peptides	Increased permeability through seizure itself or increased blood pressure Also, seizure itself can increase concentration of peptides and increase diffusion despite intact BBB.
Ito et al, 2017[41]	Rats	Electroconvulsive stimulation	Sodium fluorescein	Enhanced permeability of BBB due to astrocyte endfeet changes

BBB indicates blood-brain barrier.

can cause transient increases in the permeability of the blood-brain barrier, which allows some molecules to cross the blood-brain barrier more easily. The mechanism of increased permeability is unclear, with hypotheses suggesting a role of pinocytosis, exocytosis, changes in astrocyte morphology, and an increase in cerebral blood flow (Table 6).[8,36–41]

In humans, there are 2 silos of 5-HT: 1 in the central nervous system (CNS) and 1 in the peripheral nervous system.[42] Peripheral 5-HT generally does not cross the blood-brain barrier.[43] Given the increased permeability of the blood-brain barrier after ECT, it is possible, although not yet proven, that peripheral 5-HT and antidepressants enter the CNS. It is also unknown what effect ECT has on drug transporters such as p-glycoprotein and how this affects drug transmission into the CNS. If transient changes in permeability increase the transmission of antidepressant drugs or 5-HT into the CNS, this will increase the risk of SS.

In addition, electrophysiological studies have demonstrated that 5-HT1A receptor sensitization in postsynaptic neurons may be an important mechanism by which ECT exerts its antidepressant effect.[9] It is interesting to note that hyperstimulation of 5-HT1A and 5-HT2A receptors is thought to play an important role in the genesis of SS.

While there have not been any studies examining the effects on 5-HT transmission when both ECT and ketamine are used together, considering the findings discussed above, it is reasonable to postulate that a combination of ECT, ketamine, and serotonergic medications may synergistically increase the risk of SS.

CONCLUSIONS

Ketamine was synthesized in 1960 and was approved by the United States Food and Drug Administration (FDA) for general anesthesia and procedural sedation in 1970. It was lauded for its relatively safe profile compared with other anesthetics.[44,45] In the early 2000s, researchers began studying ketamine as a potential treatment for depression. In 2019, esketamine, an enantiomer of ketamine, was approved by the FDA for the treatment of TRD.[46]

Ketamine also emerged with medical providers as a therapeutic option for the treatment of various diseases, including acute suicidality, chronic pain, and PTSD, with studies of its effect on various other illnesses underway.[47,48] This has contributed to the establishment of hundreds of ketamine infusion centers across the country, serving thousands of patients annually. Although there are generally

accepted protocols with evolving evidence for use, standardized guidelines for intravenous ketamine infusions are lacking.[49]

While ECT clinics and ketamine clinics typically function independently and separately from each other, providers and patients still need to be aware of potential interactions between these 2 therapies, including the risk of SS. This is especially important for patients with TRD as they make up a significant portion of patients who receive either or both types of treatments and are often exposed to multiple serotonergic agents. Patients may also receive ketamine for pain management or for procedural anesthesia. Some patients may also use ketamine recreationally without their physicians' knowledge. In addition, there is no evidence of synergism or an augmentation effect on depression or neuropsychological outcomes when ketamine is paired with ECT.[50,51] While individually, both ECT and ketamine are effective treatments for depression, it would be prudent for clinicians to maintain a high index of suspicion for SS in patients whose therapy includes both treatments and even more so for those who are also on serotonergic agents.

Therefore, a patient who receives ketamine and takes serotonergic medications may need to be warned about the risk of SS when receiving ECT. Similar considerations arise when ketamine is used for procedural anesthesia, pain management, or recreationally by patients outside the hospital. Further directions of inquiry include identifying factors such as age, other demographic factors, doses of medications, etc, which might help in the stratification of this risk. More research is needed concerning the mechanisms of ketamine and ECT, specifically how they interact and how they may influence serotonin when used in combination.

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