Serotonin Syndrome Associated with Metaxalone Overdose

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Abstract

Introduction Serotonin syndrome is a potentially life-threatening entity associated with pro-serotonergic medications in therapeutic use, in overdose, or when co-administered with other drugs. A broad range of drugs and drug combinations have been associated with serotonin syndrome. Metaxalone overdose associated with serotonin syndrome has not been previously reported.

Case Report (Case 1) A 23-year-old female overdosed on tramadol and metaxalone. She developed dysautonomia, diaphoresis, lower extremity rigidity and spontaneous clonus, flaccid upper extremities, and hyperthermia 5 h after ingestion. Her course was complicated by status epilepticus. (**Case 2**) A 56-year-old female overdosed on metaxalone and was found unresponsive. She developed dysautonomia, lower extremity rigidity and spontaneous clonus, flaccid upper extremities, rhabdomyolysis, acute renal failure, and hyperthermia. Non-depolarizing neuromuscular blockade and cooling blankets were required to control hyperthermia in both cases. Serum metaxalone levels were markedly elevated in both cases.

Conclusion These are the first reported cases of metaxalone overdose associated with serotonin syndrome, which may be related to monoamine oxidase inhibition.

Keywords Serotonin syndrome · Metaxalone · Monoamine oxidase inhibitor · Muscle relaxant · Oxazolidinone

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Introduction

Serotonin syndrome (SS) is defined by the triad of altered mental status, autonomic instability, and neuromuscular abnormalities. However, not all of these findings are consistently present in all patients with this disorder, complicating the diagnosis. Hyperthermia and hypertonicity occur in life-threatening cases with clonus, hyperreflexia, and rigidity that is typically greater in the lower extremities than the upper extremities. Many medications have been associated with developing SS [1].

Metaxalone (Skelaxin®) is a FDA-approved adjuvant therapy to rest, physical therapy, and other measures for relief of discomfort associated with acute, painful, musculoskeletal conditions. It is commonly prescribed as a muscle relaxant, although it has no direct muscle relaxant effects. The recommended dose is 800 mg 3–4 times a day for patients aged >12 years [2]. The exact mechanism of action has yet to be identified. Adverse effects reported are drowsiness, dizziness, headache, nervousness, nausea, vomiting, and hypersensitivity reaction [3]. Metaxalone overdose has not been previously associated with SS. We report the first two cases of SS associated with metaxalone overdose and a probable mechanism of action leading to its pro-serotonergic properties.

Case 1

A healthy 23-year-old female presented to the emergency department 2 h after ingesting tramadol (1.5 g), metaxalone (12 g), and naproxen (unknown quantity/dose) in a suicidal gesture. These medications were prescribed 2 weeks prior for back pain. She denied use of any herbal supplements or other over the counter medications. Vital signs on arrival included a blood pressure (BP) of 135/79 mmHg, heart rate (HR) of 137 beats/min, respiratory rate (RR) of 18 breaths/min, oxygen

saturation of 98 % on room air, and afebrile. Physical exam was unremarkable except for somnolence. All lab values were in the normal reference range. Salicylate and acetaminophen were undetectable. She became obtunded 4 h after ingestion with a Glasgow Coma Scale (GCS) of 9, miotic pupils, and respiratory depression. Naloxone (0.4 mg) was administered a total of three times over the next hour with increased alertness and respiratory rate. No seizures developed. After the three doses of naloxone, her lower extremities became rigid with sustained spontaneous clonus, flaccid upper extremities, mydriasis, and the patient became unresponsive to stimuli. Diazepam was administered with resolution of rigidity but hypoxemia developed. The patient was intubated with etomidate and rocuronium, and placed on a midazolam infusion (4 mg/h). She was transferred to the intensive care unit of a tertiary care hospital under the medical toxicology service.

On presentation to the ICU, 10 h after ingestion, vitals assign were BP=158/92 mmHg, HR=163 beats/min, oxygen saturation=100 % with FiO_2 of 60 %, RR=22 breaths/min, and temperature of 38.7 °C (T_{max} 39.8 °C). Lab values at that time included white blood cell count (WBC) 18.9 K/mm³, glucose 87 mg/dL, and creatinine phosphokinase 136 IU/L. All other lab values were in the normal reference range. Arterial blood gas (ABG) analysis revealed a pH of 7.213, pCO_2 of 58.2 mmHg, pO_2 of 251 mmHg, bicarbonate of 22.6 mmol/L, and base deficit of 5.5 mmol/L. Physical exam was remarkable for diaphoresis, rigid lower extremities with sustained spontaneous and inducible clonus, flaccid upper extremities with normal reflexes, mydriatic pupils (8 mm), and unresponsive to all stimuli. Remainder of the physical exam was benign. Serotonin syndrome was diagnosed based on physical exam, hyperthermia, and autonomic dysfunction. During physical examination, recurrent fine, bilateral upper extremity jerking movements lasting up to 20 s with rhythmic biting of the endotracheal tube was observed. Seizures were suspected and two doses of lorazepam were given without resolution. Next, a phenobarbital (20 mg/kg) infusion over 20 min was given for suspected convulsive status epilepticus. Rhythmic movements persisted and a second phenobarbital infusion was administered with subsequent termination. No report was available to determine if seizures had occurred prior to or during transport to our center. An electroencephalogram was then obtained to exclude non-convulsive status epilepticus. A prolactin level sent during the rhythmic movements was elevated at 58.5 ng/mL (3.3–26.7). There was no electroencephalographic evidence of seizures and no further convulsive activity was witnessed. A comprehensive urine drug screen analysis by gas chromatography–mass spectrometry (GC/MS) revealed tramadol, metaxalone, and naproxen. Cyproheptadine was administered, with the first dose given 20 h after ingestion. The patient had recurrent and sustained hyperthermia with a T_{max} of 39.8 °C occurring following seizure termination. A cooling blanket and multiple doses of

vecuronium (first dose 11 h after ingestion) were needed to prevent recrudescence of hyperthermia.

On day 2 of hospitalization, rigidity resolved but sustained clonus and hyperreflexia continued in the lower extremities. Vecuronium and cooling blanket were discontinued, as hyperthermia and tachycardia resolved. Creatinine phosphokinase peaked at 2,806 IU/L. By day 3, the patient's clonus and hyperreflexia resolved, and she was now responding to external stimuli. A repeat prolactin level was 13.7 ng/mL. Blood and urine cultures along with a chest x-ray obtained on admission were unremarkable. The patient was extubated on day 4. She was discharged on day 6 neurologically intact. Tramadol and metaxalone levels drawn 13-h post ingestion were 6,300 ng/mL (therapeutic range 230–380 ng/mL) and 34 µg/mL (no reference ranges available; mean peak plasma concentration 0.87 µg/mL at 3.3 ± 1.2 h following 400-mg dose [4]), respectively.

Case 2

A 56-year-old female with a history of poly-substance abuse was found obtunded. A bottle of metaxalone filled the day prior was found next to her and was missing 40–50 800-mg tablets. Other prescribed medications were oxycodone and clonazepam. Vitals on arrival to the emergency department included a BP of 151/77 mmHg, HR of 136 beats/min, RR of 40 breaths/min, oxygen saturation of 99 % on 2 L/min by nasal cannula, and afebrile. She was intubated for airway protection based on a GCS of 8 using etomidate and succinylcholine. Abnormal labs on arrival included WBC=21.4 K/mm³, glucose=120 mg/dL, blood urea nitrogen=31 mg/dL, creatinine=2.16 mg/dL, potassium=5.1 mmol/L, anion gap=23, AST=307 IU/L, ALT=79 IU/L, and creatinine phosphokinase=14,297 IU/L. An ABG analysis with FiO_2 of 50 % revealed a pH of 7.248, pCO_2 of 50 mmHg, pO_2 of 119 mmHg, bicarbonate of 21.1 mmol/L, and base deficit of 5.8 mmol/L. Acetaminophen and salicylate were undetectable. Urine drug screen was negative, including testing for oxycodone, opiates, and methadone.

The patient was noticed to be diaphoretic with a temperature of 38.3 °C 1 h after intubation (T_{max} 39.3 °C 2 h after intubation). Physical exam findings included rigid lower extremities with sustained clonus, flaccid upper extremities with normal reflexes, and mydriasis. The remainder of the physical exam was benign. Serotonin syndrome was diagnosed. Cyproheptadine was not administered. The patient required non-depolarizing neuromuscular blockade and use of a cooling blanket for hyperthermia. Rigidity resolved 18 h after intubation with complete resolution of abnormal physical exam findings an additional 14 h later. Creatinine phosphokinase peaked at >20,000 IU/L and normalized prior to discharge. Acute kidney insufficiency resolved after intravenous

hydration. The patient was successfully extubated on day 3 and medically cleared for transfer to a behavioral health facility on day 4. She claimed only to have ingested metaxalone. A serum metaxalone level drawn on the day of admission was 61 $\mu\text{g/mL}$ (no reference ranges available; mean peak plasma concentration $0.87 \mu\text{g/mL}$ at 3.3 ± 1.2 h following 400-mg dose [4]).

Discussion

Serotonin syndrome is a potentially life-threatening adverse drug reaction that results from therapeutic drug use, intentional self-poisoning, or inadvertent interactions between drugs [1]. Diagnosis of SS is based on physical exam findings and known exposure to pro-serotonergic medications. The cases presented fulfill the Hunter criteria for diagnosis of SS [5], and also represent severe SS. The most remarkable physical finding in these cases was extreme rigidity of the lower extremities with sustained spontaneous clonus and flaccid upper extremities. This finding has been reported in SS, and is a helpful physical exam finding for the clinician in diagnosing SS, if present. Inducible, ocular, or spontaneous clonus is a critical element in the diagnosis of serotonin syndrome [1, 5]. A substantial number of drugs and drug combinations have been associated with SS.

Metaxalone is a commonly prescribed “muscle relaxant” without direct muscle relaxing properties and an unknown mechanism of action [3]. Data on metaxalone adverse effects are rare. Death has been reported in overdose but these deaths primarily involved co-ingestants [2]. Forrester reported a series of 142 cases of metaxalone adverse effects. Patients ingesting >2,400 mg (maximal daily dose) were more likely to have pronounced and prolonged symptoms, with three cases developing life-threatening symptoms. The most common adverse effect was lethargy, with other reported findings including: tachycardia, hypertension, muscle rigidity, seizure, mydriasis, diaphoresis, hyperthermia, and coma [2]. Limitations of this study were the absence of reported metaxalone levels, the possibility of co-ingestions, and data limited to poison center charts. However, many of the reported clinical manifestations of metaxalone overdose by Forrester are also seen in SS and in the two cases presented here with confirmed supratherapeutic metaxalone levels. Igneri et al. [6] recently reported a 52-year-old female on citalopram who developed SS after taking a second therapeutic dose of 800-mg metaxalone. Metaxalone levels were not reported in that case. The lack of existing literature associating metaxalone with SS may be related to its unknown mechanism of action, limited side effect profile, under-recognition of SS by healthcare providers, and the limited number of reported overdoses.

Metaxalone, which is 5-(3,5-dimethylphenoxy)methyl-2-oxazolidinone, was first synthesized by Lunsford et al. [7]

Oxazolidinone analogs were developed as potential antidepressants and antimicrobial agents. Toloxatone, which is 3-(3-methylphenyl)-5-hydroxymethyl-2-oxazolidinone, is a reversible monoamine oxidase inhibitor (MAOI) structurally similar to metaxalone [Fig. 1]. Azoyan et al. reported 122 cases of toloxatone poisoning with severe cases manifesting muscular rigidity and hyperthermia when combined with tricyclic antidepressants, consistent with SS [8]. Linezolid was the first oxazolidinone approved for treatment of gram-positive pathogens and is a reversible MAOI. Co-ingestion of linezolid and pro-serotonergic medications has been associated with the development of SS [9]. Monoamine oxidase inhibitors alone in overdose have produced SS, but are typically associated with SS in combination with other pro-serotonergic medications [10]. We hypothesize, based on its similar structure to known reversible MAO inhibitors, that metaxalone at supratherapeutic concentrations may act as a reversible MAOI like other oxazolidinone analogs. Therefore, metaxalone may be associated with SS alone in overdose (case 2) or in combination with other pro-serotonergic medications (case 1). Monoamine oxidase polymorphism may also be a factor in those developing SS at therapeutic doses versus in overdose or in combination with other pro-serotonergic medications.

Tramadol is an agonist at μ -opioid receptors and has been implicated in precipitating SS by its ability to stimulate pre-synaptic release and reuptake inhibition of serotonin [11]. Patients with mydriasis following tramadol overdose are more

Fig. 1 Oxazolidinone compounds containing 2-oxazolidinone (box) in the structure. **a** Metaxalone, **b** toloxatone, and **c** linezolid

prone to seizures, and as SS may cause mydriasis; seizures resulting from tramadol overdose may be related to excessive serotonin [11]. The tramadol overdose in case 1 surely contributed to the development of SS, in addition to metaxalone based on the proposed mechanism delineated above. The tramadol overdose in case 1 may have been the primary cause of the witnessed status epilepticus but seizures have also been reported with SS [1, 11]. Both cases demonstrated similar clinical findings with elevated plasma metaxalone levels and a proposed mechanism of action that could lead to increased synaptic serotonin and SS following metaxalone administration. A limitation in case 2 is the absence of GC/MS testing to exclude presence of other pro-serotonergic medications. However, the significantly higher metaxalone level strongly suggests a large ingestion. An empty bottle of metaxalone found at the scene and the patient's denial of other co-ingestions lend further support to the case. We were unable to determine if metaxalone has other pro-serotonergic properties, such as increasing release or inhibiting reuptake of serotonin, in addition to possible monoamine oxidase inhibition. Further research is required to confirm our hypothesis.

Conclusion

Serotonin syndrome is a potentially life-threatening entity resulting from excessive serotonin in the synapse and culminating in lower extremity rigidity, dysautonomia, and hyperthermia in severe cases. These are the first reported cases of metaxalone overdose associated with SS with a plausible mechanism described for its pro-serotonergic properties. Clinicians should be aware of the potential risk of developing SS when metaxalone is co-administered with pro-serotonergic medications therapeutically or in overdose.

Conflict of Interest The authors have no conflicts of interest to disclose.

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