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Case Report Open Access

Multi-drug Overdose Induced Seizure Associated with Mirtazapine

Nadia Ferguson[1]*, Wilma Correa-Lopez[2] and Brenda Gitman[3]

[1]Clinical Pharmacy Manager for Critical Care, Weiler Hospital of Albert Einstein College of Medicine, 1825 Eastchester Road, Bronx, NY 10461, USA
[2]Weiler Hospital of Albert Einstein College of Medicine
[3]Pharmacy Practice Resident

Introduction

Drug-induced seizures are a well documented adverse effect of medications such as tricyclic antidepressants, haloperidol, risperidone, clozapine, and lithium [1]. The risk of drug – induced seizures is markedly increased in those patients with a past medical history of epilepsy, possibly due to lowering the seizure threshold. Little is known regarding drug-induced seizures in patients with no known past medical history of epilepsy [1]. The first reports of drug-induced seizures were in the 1950's shortly after the introduction of tricyclic antidepressants; primarily with imipramine and amitriptyline. These medications were found to cause EEG changes in both epileptic and non-epileptic patients.

Mirtazapine belongs to a pharmacologic class known as tetracyclic antidepressants (Figure 1). It is structurally similar to the tricyclic antidepressant class (Figure 2). Mirtazapine functions as central presynaptic alpha$_2$ antagonist, increasing the release of norepinephrine and serotonin. It is also a potent antagonist of 5-HT$_2$ and 5-HT$_3$ serotonin receptors and H1 histamine receptors. Mirtazapine was approved by the Food and Drug Administration in June of 1996 for the treatment of depression. The recommended starting dose is 15 mg/day, administered in a single dose, preferably in the evening prior to sleep. The maximum daily dose is 45 mg/day. It is highly bound to protein (85%).The administration half life is 20 – 40 hours, which is extended in patients with renal or hepatic impairment. Mirtazapine is extensively metabolized hepatically via CYP1A2, CYP2C9, CYP2D6, CYP3A4, demethylation (forming demethylmirtazapine- the active metabolite), and hydroxylation (forming inactive metabolites). Approximately 75% of the drug is excreted in the urine and about 15% in the feces as metabolites [2,3] In clinical trials, the most common side effects associated with Mirtazapine are somnolence, increase in appetite, weight gain, asthenia, increased sweating, drowsiness, sedation, dry mouth, constipation, nausea. There is one case report of seizure by Zia Ul Hag M, et al. [4] in a patient with a history of seizures during previous treatment with clomipramine.

Sertraline (Figure 3) is a selective serotonin reuptake inhibitor. Specifically, sertraline inhibits the neuronal presynaptic serotonin (5-HT) reuptake to increase mood and function as an antidepressant. Sertraline, in addition to being FDA approved for major depressive disorder, is also approved for the treatment of obsessive-compulsive disorder, panic disorder, posttraumatic stress disorder, premenstrual dysphoric disorder, and social phobia [5]. The dosing of sertraline is dependent on the disease state being treated; the dosage range is from 25 – 200mg/day. The therapeutic onset of action of sertraline occurs in about one week but takes approximately 8 – 12 weeks to reach a full response. The peak concentration is achieved within 4 – 8 hours and absorption is increased with concomitant ingestion of food. It is 98% protein bound and is primarily metabolized via N-demethylation (forming desmethylsertraline- weakly active metabolite), then hydrolyzed, oxidized, and reduced [5]. Half of the inactive metabolites of sertraline are eliminated in urine and half in the feces. Most common adverse events associated with this medication include nausea, vomiting, constipation, diarrhea, headache, insomnia, tremors, and reduced libido. More serious adverse events include exacerbation of depression, suicidal thoughts, Serotonin syndrome, Stevens-Johnson syndrome, hyponatremia, and seizure at 0.2%. Pre-marketing trials

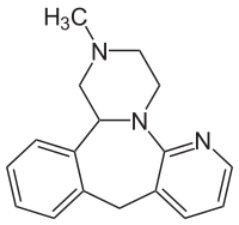

Figure 1: Chemical structure of mirtazapine.

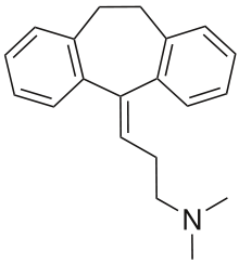

Figure 2: Chemical structure of amitriptyline, a tricyclic antidepressant.

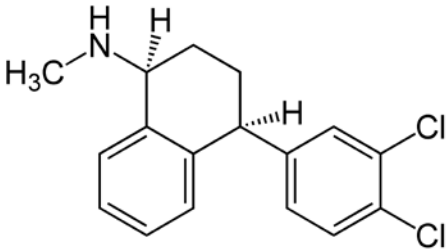

Figure 3: Chemical structure of sertraline.

***Corresponding author:** Nadia Ferguson, Clinical Pharmacy Manager for Critical Care, Weiler Hospital of Albert Einstein College of Medicine, 1825 Eastchester Road, Bronx, NY 10461, USA, E-mail: nafergus@montefiore.org

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excluded patients with a past medical history of seizure disorder. No seizures were observed among approximately 3000 patients treated in for major depressive disorder, but seizures were reported in 4 out of approximately 1800 patients treated for obsessive compulsive disorder. Of note 3 of the 4 patients were adolescents, 2 of whom had seizure disorders and 1 had a family history of seizure.

Gabapentin (Figure 4) is FDA approved for adjunct treatment of partial seizures and post herpetic neuralgia. The structure of the drug is related to that of the gamma-aminobutyric acid (GABA) receptor (Figure 5), although the drug does not exert any of its effect on the receptor. The antiepileptic or analgesic mechanism of action is unknown [6]. Gabapentin prevents pain-related behavior in response to a normally innocuous stimulus as well as an exaggerated response to painful stimuli. It also prevents seizures in mice and rats in both the maximal electroshock and pentylenetetrazole seizure models. The dosing of gabapentin is best when titrated to efficacy, starting dose for FDA approved indications are 300mg and then titrated upwards to a maximum daily dose of 1800mg. Gabapentin bioavailability is not dose proportional; bioavailability of gabapentin is approximately 60%, 47%, and 34% following 900, 1200, and 2400mg/day given in 3 divided doses, respectively [6]. Less than 3% of gabapentin circulates bound to plasma protein and is renally excreted as an unchanged drug. The most common adverse events seen are asthenia, headache, somnolence, dizziness, infection, abdominal pain, diarrhea, constipation, nausea, vomiting, and dry mouth. In controlled clinical trials, which including epileptic patients greater than 12 years of age, seizure was reported in 0.6% of patients treated with gabapentin (n=543) compared with 0.5% of those treated with placebo (n=378) who received gabapentin or placebo plus their current antiepileptic drug therapy [5].

This present paper reports and comments upon a case of overdose with mirtazapine, sertraline, and gabapentin with a non-fatal outcome. To the best of our knowledge no paper discusses the outcome of this combination of medication in overdose.

Case Summary

A 53-year-old Caucasian female with Past Medical History of dyslipidemia, chronic low back pain, diverticulosis, allergic rhinitis, panic disorder, post-traumatic stress disorder, and depression associated with multiple suicide attempts was found at home obtunded, laying down next to empty bottles of sertraline, mirtazapine, and gabapentin. She was brought in by EMS to the ER where in addition to her depressed mental status, she also presented with complaints of abdominal pain, nausea, and vomiting. She was admitted to the hospital for altered mental status secondary to a deliberate multiple drug overdose.

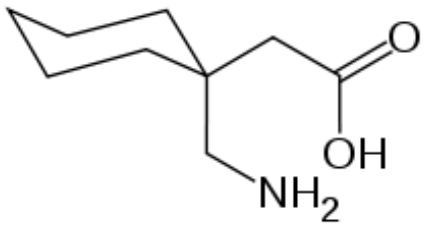

Figure 4: Chemical structure of gabapentin.

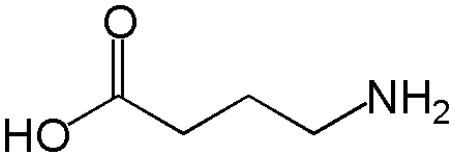

Figure 5: Chemical structure of GABA.

Based on her pharmacy refill history, it was estimated that the patient consumed approximately 3 G of sertraline, 16 G of gabapentin, and 1.2 G of mirtazapine. She admitted to ingesting approximately 100 tablets. On initial examination, the patient was obtunded, but oriented to person, place, and time. Her pupils were 4mm and briskly reactive to light bilaterally, without evidence of nystagmus. She was able to follow simple commands and move all extremities spontaneously with symmetry and adequate strength. Her physical exam was otherwise unremarkable. The patient was hemodynamically stable on admission: blood pressure 101/56 mmHg, heart rate 74 beats/min, respiratory rate 16 breaths/min, pulse oximetry 100% on room air. She was initially able to protect her airway. Significant abnormalities in her laboratory were as follows: serum potassium, 3.1mEq/L; amylase, 206 U/L; lipase, 533 U/L. Serum acetaminophen, aspirin, and ethanol levels were negative. The osmolar gap was not increased. ECG was significant for sinus rhythm at71 beats/min and a prolonged QTc at 486 msec. Urine toxicology was negative for benzodiazepines, amphetamines, barbituates, phencyclidine, cocaine, opiates and cannabinoids. In the ED the patient was administered 2 liters of Normal Saline 0.9% and monitored for any changes in her ability to protect her airway. After 10 hours from the time of presumptive ingestion, the patient was noted to have a generalized tonic-clonic seizure. She was given lorazepam 2mg IVP leading to cessation of the seizure activity. Upon re-evaluation, the patient was subsequently intubated for airway protection using succinylcholine 100 mg IV. She was started on continuous infusion of midazolam 2mg/hr and transferred to the intensive care unit. No subsequent seizure activity was observed. She was weaned off the midazolam and extubated on day 2. Her hospital course was complicated by development of pneumonia and Acute Respiratory Distress Syndrome requiring re-intubation on day 4. She was successfully extubated on day 11 and transferred to the general ward.

Discussion

In our review of the literature and according to data from a thorough MEDLINE search, we have identified few previous reports of drug-induced seizures with overdose of sertraline, mirtazapine, and gabapentin.

In an article published in the *Journal of Clinical Toxicology* in 2007, a retrospective review was performed of 117 charts from patients admitted to the Toxicology Unit of the Royal Infirmary of Edinburgh after taking an overdose of mirtazipine [7]. Data collected included, date and time of overdose, amount ingested, type and amount of co-ingested drugs, time elapsed from ingestion to admission, age and gender. Clinical data included, Glasgow Coma Scale, vitals, basic metabolic panel, creatinine kinase, liver enzymes, and an ECG. The median stated amount of mirtazipine ingestion was 450mg. The researchers also noted that 15% of the patients had co-ingested other antidepressants. The major complication seen in this study with mirtazipine was drowsiness and reduced consciousness in 28% of patients. One patient, who had co-ingested large amounts of other sedative drugs, required ventilator support secondary to respiratory depression; during which it was found that mirtazipine was not the culprit. Authors concluded that mirtazapine is comparatively non-

toxic in overdose [7]. This is consistent with other published case reports mirtazapine overdose, suggesting non-toxic adverse events [8]. Adverse events included drowsiness, miosis, and sinus tachycardia.

On the contrary, there was a case report of mirtazapine overdose resulting in rhabdomyolysis, which was self-limiting [9]. Kuliwaba et al. reported a non-lethal overdose of mirtazipine resulting in rhabdomyolysis. A 40 year old patient had ingested 1.8G of mirtazipine and 2L of wine. Symptomatically the patient presented with dizziness, nausea, tremor, blurred vision, and headache. Comparing the patients previous liver function tests (LFTs) to the results on this admission, the marked increase in LFTs was indicatively related to the overdose of mirtazipine and alcohol, ultimately resulting in acute hepatitis.

The threshold for seizure with sertraline is low, as it is thought of as an antidepressant that does not cause generalized seizures [10]. A case report by Phutane et al describes a case of partial seizures with secondary generalized seizures with clozapine and sertraline [11]. A 19 year old male with paranoid schizophrenia had been initiated on a regimen of clozapine 300mg, which remitted his psychotic symptoms. Sertraline 50mg, titrated to 100mg in four days, was initiated due to an increase in suicidality. A week after the sertraline dose was increased to 100mg; the patient noticed small facial twitching which turned to a generalized tonic – clonic seizure within minutes. The patient was treated with phenytoin for the seizure, and clozapine and sertraline were discontinued. The authors concluded that since about 10% of patients on clozapine develop seizures, the elevation of clozapine concentrations by the addition of sertraline caused the adverse event.

In 1998, Meier and Lam report the first case report of sertraline 4000 mg overdose with co-ingestion of naproxen 7700 mg, in a 14 year old female [12]. The patient was brought to the ED approximately 3 hours post ingestion and was given activated charcoal as well as prochlorperazine 4mg IV for the subjective complaint of nausea. After 4 ½ hours in the ED the patient experience a generalized tonic clonic seizure and was transferred to the Intensive Care Unit (ICU). While in the ICU, approximately 5 ½ hours post ingestion the patient experienced a second seizure; anticonvulsants were not administered. Afterwards the patient was clinically stable and discharged. The authors concluded that the drug-induced seizure was secondary to CNS depression from the combination of medications.

Brendel and Yang report a non-lethal, 8G overdose of sertraline with no co-ingestion [13]. The patient, a 51 year old female, was admitted the ED and experienced acute mental status changes after 3 days. The patient experienced agitation, hallucinations, mydriasis, hypertension with a blood pressure of 150/115 mmHG, and hyperthermia with a body temperature of 101.4°F. No seizure activity was noted in this patient. The authors concluded that this patient had suffered from serotonin syndrome. The patient survived this event without adverse outcomes.

There is a lack of literature available of serious toxicity with gabapentin, although there have been several case reports published of non-fatal overdoses, and one fatal outcome [14,15,16].

Verma A et al. present a case of massive gabapentin overdose in a 30 year-old woman without serious side effects. [17] The patient had a past medical history of systemic lupus erythematosis, had suffered from a middle cerebral artery stroke, and renal failure. She began having generalized tonic-clonic seizures for which she was prescribed valproic acid 1250mg/day and gabapentin 600mg three times daily. After experiencing tremulousness and difficultly with cognitive abilities, serum levels of anticonvulsant medications were obtained. The valproic acid serum concentration was 71mcg/ml and gabapentin concentration was 85mcg/ml. The gabapentin was then decreased then discontinued, but the patient still had persistent tremors. The valproic acid was also discontinued and the patient was initiated on phenytoin, to which the tremors had abated [17].

Owen Middletown discusses a case of a 62 year-old woman who was found unresponsive in her hotel room after an intentional ingestion of what was thought to be 4.5G of gabapentin [18]. The patient did not survive this event. Upon autopsy, it was found that the patient had also co-ingested simvastatin, clonazepam, and fluoxetine, though not in toxic doses. The authors concluded that the gabapentin "likely hastened the cardio-respiratory compromise from the overdose."

Fischer JH et al. report a case of a 16 year old girl with no past medical history, admitted to the emergency department after ingesting 48.9G of her father's gabapentin [19]. The patient was lethargic but had no other symptoms. Approximately 40 hours post-ingestion the patient was discharged following intensive in-patient drug rehabilitation.

The gabapentin package insert states that a "lethal dose" has not be identified in mice and rats, signs of acute toxicity that were noted in animals included ataxia, shortness of breath, sedation, and hypo-activity. Gabapentin can be removed by hemodialysis, although this has not been preformed in the reported cases of overdose [6].

Conclusion

There is always great difficulty in determining the offending agent in cases with multi-drug ingested overdoses. Mirtazapine safety at therapeutic doses and supratherapeutic doses seems to be well documented [20]. Mechanism of action, however may indicate potential for adverse events, due to the antagonism of the histaminergic or muscarinic receptors, although the exact mechanism of action for seizure induction of Mirtazapine and other heterocyclic antidepressants remain unclear [21]. As such, the possibility of seizure seems plausible even though seizure with monotherapy overdoses has not been reported. Other tetracyclic antidepressants assessed by Poison Control data, have demonstrated a seizure incidence of 12-24%. In addition to the fact that tricyclic antidepressants are the most common class of medications causing iatrogenic seizures [22]. On the contrary, seizure with sertraline monotherapy and gabapentin monotherapy has not been reported. This report describes a case of a multi-drug overdose with the high suspicion for a mirtazapine induced seizure. The exact cause however, of this isolated seizure remains unclear and may truly be multi-factorial.

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