Co-ingestion of tricyclic antidepressants with selective norepinephrine reuptake inhibitors

Overdose in the emergency department

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Case description

An 18-year-old female student presents to the emergency department (ED) with a decreased level of consciousness. She was last seen awake the night before, and her parents could not rouse her from sleep that morning. She has a known history of depression, which is treated with an oral 100-mg dose of desvenlafaxine daily and an oral 100-mg dose of amitriptyline once daily at bedtime. There is no history of recent travel, trauma, or illness. Her parents do not believe she drinks alcohol or uses illicit drugs. Empty bottles of desvenlafaxine and amitriptyline were found in the patient's room (each bottle held approximately 60 tablets).

The patient's examination findings reveal a temperature of 36°C, heart rate of 160 beats/min, respiratory rate of 12 breaths/min, blood pressure of 105/70 mm Hg, and oxygen saturation of 100% on room air. There is no evidence of any head or facial trauma. Her pupils are symmetrical, reactive to light, and dilated. Her neck is found to be supple. Her skin is dry and she is not responsive to painful stimuli. She has a Glasgow Coma Scale score of 3. An examination of the extremities reveals no deformities or track marks. Her cardiorespiratory assessment includes normal first and second heart sounds, no murmurs, and good air entry bilaterally. Laboratory investigations reveal a glucose level of 5.0 mmol/L, and findings from a chest x-ray and computed tomographic scan of the head are normal. Her electrocardiogram (ECG) shows a widened QRS complex with a QTc of 650 milliseconds.

Tricyclic antidepressant (TCA) overdose was first reported in 1959, 2 years after TCAs' clinical usefulness became known.[1] Many patients who overdose on TCA agents have concurrent substance use disorders, most commonly opioid dependence.[2] The Drug Abuse Warning Network in the United States reports rates of ED admissions due to "nonmedical" use of prescription medications.[2] While opioids and benzodiazepines account for most of these visits, tertiary amine tricyclics, such as amitriptyline

EDITOR'S KEY POINTS

- Having a clinical approach to patients with unknown toxic ingestion is imperative. Family physicians must be able to identify and manage patients who overdose on multiple antidepressant agents, especially as these pharmacologic agents are commonly prescribed.
- Identification of patients with tricyclic antidepressant overdose is based on high clinical suspicion and electrocardiogram findings of QRS widening. Early management should involve sodium bicarbonate.
- There is a risk of QT prolongation and torsades de pointes for patients who overdose on tricyclic antidepressants and have concomitantly ingested selective norepinephrine reuptake inhibitors. It is important to note that in regard to desvenlafaxine, there are currently insufficient data to present precise conclusions about a link between a QT prolongation risk and the medication.

POINTS DE REPÈRE DU RÉDACTEUR

- Il est impératif d'adopter une approche clinique avec les patients qui présentent une ingestion toxique d'origine inconnue. Les médecins de famille doivent être capables d'identifier et de prendre en charge les patients qui ont pris une surdose d'agents antidépresseurs multiples, surtout que ces agents pharmacologiques sont couramment prescrits.
- L'identification des patients qui ont pris une surdose d'antidépresseurs tricycliques se fonde sur une forte suspicion clinique et un élargissement du complexe QRS dans les résultats de l'électrocardiogramme. La prise en charge initiale devrait comporter du bicarbonate de sodium.
- Il y a un risque d'allongement de l'intervalle QT et de torsades de pointes dans les cas de surdoses d'antidépresseurs tricycliques et d'ingestion concomitante d'inhibiteurs sélectifs du recaptage de la norépinéphrine. Il importe de souligner, à propos de la desvenlafaxine, que les données sont insuffisantes pour conclure avec précision qu'il y a un lien entre un risque d'allongement de l'intervalle QT et le médicament.

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and imipramine, account for 0.8% of visits. This suggests that the rate of suicide attempts using tertiary tricyclic agents is small but not inconsequential.[2] The rare but fatal consequences of TCAs have been well described in the literature. However, the co-ingestion of a TCA with a selective norepinephrine reuptake inhibitor (SNRI) makes this case unique. The interaction of these agents, as well as their individual complications, will be discussed. It is imperative that family physicians be able to identify and manage such patients who overdose on multiple antidepressant agents.

Tricyclic antidepressant overdose can affect both the neurologic and cardiovascular systems, resulting in seizures, cardiac conduction abnormalities, and refractory hypotension (**Table 1**).[1] The toxic effects of TCAs include anticholinergic effects, direct α-adrenergic blockade, and inhibition of norepinephrine reuptake at nerve terminals.[1] In addition, the medications can slow the depolarization of the cardiac action potential by inhibiting the sodium current, thereby delaying depolarization through the myocardium. This results in the prolongation of the QRS complex and can predispose patients to cardiac arrhythmias.[1]

Initial assessment

For patients with suspected overdose, it is imperative to perform a rapid evaluation of the airway, breathing, and circulation. If the patient is not protecting his or her airway, owing to a decreased level of consciousness, rapid sequence intubation should be initiated. If a patient is intubated and there has been a recent ingestion, charcoal might also be considered. The patient should receive oxygen administration, 2 large-bore intravenous lines, cardiac monitoring, and a point-of-care glucose assessment. For any patient with an altered level of consciousness, naloxone should be administered regardless of whether there is definite history to suggest narcotic ingestion. A history can be taken from the patient, if possible, witnesses, or family members. Details about the possible source of ingestion, past medical history, and co-ingestion of alcohol or illicit drugs should be elicited. As prescription history is key for diagnosis, consider examining pill bottles, using a provincewide prescription database, if available, or contacting pharmacies used by the patient to retrieve this information. If necessary, collateral information from family members, paramedics, and mobile phones can be used if indicated by the case.

A targeted physical examination should assess the patient's vital signs, and a brief neurologic assessment should include pupillary response and a gross motor and sensory examination. Classic symptoms of anticholinergic syndrome include mydriasis, delirium, dry skin, fever, and flushing; these symptoms can be remembered with the mnemonic *hot as a hare, red as a beet, dry as a bone, blind as a bat, and mad as a hatter.*

Table 1. Complications of TCA overdose

CATEGORIES	SIGNS AND SYMPTOMS
Neurologic	Convulsion, rigidity, delirium, ophthalmoplegia, and drowsiness
Cardiovascular	Sinus tachycardia, prolonged QT interval, vasodilation, hypotension, cardiogenic shock, and possible ventricular fibrillation or tachycardia
Anticholinergic	Pyrexia, dry mouth, visual changes (dilated pupils and blurred vision), and urinary retention

TCA—tricyclic antidepressant.
Data from Kerr et al.[1]

Cardiorespiratory assessment and evaluation of the skin for temperature, moisture, and track marks can be done. A basic toxicologic bloodwork panel should be sent including complete blood count, electrolyte and creatinine levels, serum osmolality, venous blood gas, and serum acetylsalicylic acid, acetaminophen, and ethanol levels to rule out co-ingestion. An ECG should be ordered to assess for arrhythmias and intraventricular conduction delay with QRS widening.

Management

The Guidelines in Emergency Medicine Network from the United Kingdom outline management of patients who overdose on TCAs and present with the following conditions.[3]

Central nervous system depression. Owing to the serious risk of sedation and rapid deterioration, there should be a low threshold for performing rapid sequence intubation.[3] If the ingestion is known to have occurred within the hour, activated charcoal can be considered in an alert patient.[1,3]

Ventricular dysrhythmias. Upon the patient's presentation to the ED, an ECG should be ordered to assess for QRS widening. Sodium bicarbonate can be used to bring pH levels between 7.45 and 7.55 to treat arrhythmias, hypotension, and ECG changes, even in the absence of an initial acidosis.[3-5] It is posited that sodium bicarbonate can help increase plasma pH levels, increasing plasma protein binding of TCA and thereby reducing the free drug levels. It can also reduce binding of TCA to the myocardial sodium channel receptors because of decreased amounts of nonionized TCA. For dysrhythmias causing hemodynamic instability in TCA overdose, magnesium sulfate can be considered.[3] In refractory cases, lipid emulsion therapy is an emerging treatment option owing to the lipophilic properties of TCAs. A 20% concentration of lipid emulsion is given as a bolus dose of 1.5 mL/kg, followed by an infusion at a rate of 0.5 mL/kg per minute.[5]

Cardioversion and defibrillation are unlikely to be successful. Note that drugs commonly used for dysrhythmias such as procainamide and amiodarone, as well as β-blockers, are contraindicated.[1]

Hypotension. Hypotension is a common complication due to the effect of α-receptor blockade. Intravenous crystalloid fluid and vasopressors (phenylephrine or norepinephrine) are the treatment of choice.

Seizures. Tricyclic antidepressants have the potential to lower the seizure threshold. If a patient presents with seizures, he or she can be treated initially with benzodiazepines. Phenytoin should be avoided owing to possible interaction with TCAs.[3] It is the ability of TCAs to inhibit the cytochrome P450 system that results in decreased phenytoin hydroxylation and subsequent accumulation of the medication.[6]

Monitoring

In regard to monitoring patients with TCA overdose, most complications tend to occur in the first 6 hours after ingestion. As a result, patients should be monitored for a minimum of 6 hours if the initial ECG results are found to be normal. If not, cardiac monitoring should be done until the ECG returns to the patient's pre-overdose baseline and can continue for up to 12 to 24 hours in an intensive care unit setting. Tricyclic antidepressants are highly protein bound and have a large volume of distribution; therefore, removal of these compounds from the blood with hemodialysis is unlikely to be of any considerable benefit.[7] Physicians should contact poison control for local recommendations.

What about desvenlafaxine? There is a risk of QT prolongation and torsades de pointes for patients who overdose on TCAs and who have concomitantly ingested selective serotonin reuptake inhibitors (SSRIs) or SNRIs. It is important to note that in regard to desvenlafaxine, there are currently insufficient data to present precise conclusions about a link between a QT prolongation risk and the medication.[8]

Other potential complications

Serotonin syndrome: Serotonin syndrome presents with a clinical triad of mental status changes, autonomic hyperactivity, and neuromuscular abnormalities.[9] It is important to note that myoclonus is the most common finding in serotonin syndrome and is rare in other conditions that can mimic this condition. The risk of serotonin syndrome is potentiated further by the addition of a second antidepressant agent. Therefore, clinicians need to be more vigilant in cases of concomitant ingestion of TCAs and SSRIs or SNRIs.

Family physicians need to be aware of the symptoms associated with serotonin syndrome to recognize and ensure rapid management. Symptoms include mydriasis, diaphoresis, agitation, tachycardia, autonomic instability (possible hypertensive), hyperreflexia (greater in lower extremities), and clonus (greater in lower extremities).[9] Most patients with serotonin syndrome return to baseline in 24 hours with supportive care, removal of the precipitating drug, and treatment with benzodiazepines.[9] If hyperthermia is present, with a temperature of more than 41.1°C, it is imperative for family physicians to recognize this and obtain assistance for managing such patients through contact with poison control and an intensivist.

Seizure: Risk of seizure increases following overdose with antidepressants. There is a dose-dependent

relationship between antidepressant drugs and seizures. Therefore, a co-ingestion of a TCA and an SNRI is of serious concern. In addition, the antidepressant medications interfere with anticonvulsant levels (as described above).

Case resolution

The patient was given naloxone initially upon arrival to the ED in the setting of an unknown overdose. There was no response to this. A decision was made to intubate with ketamine and rocuronium, as she was not protecting her airway. A bicarbonate drip was initiated using 150 mmoL (3 amps) in 1 L of normal saline at 100 to 300 mL/hr. Poison control confirmed bicarbonate as the mainstay of therapy, along with supportive management and monitoring of the ECG waves. Her QTc returned to normal, her QRS complex narrowed, and she was extubated within 24 hours. Results of her urine toxicology were positive for TCA. No other co-ingestions (such as benzodiazepines or opioids) were detected. She was admitted to the psychiatry unit for severe depression and attempted suicide.

Conclusion

This case demonstrates a management plan that follows treating both a TCA and SNRI overdose. The challenge in such cases is recognizing the combined drug classes—TCA and SNRI—in the absence of corroborating information in the unconscious patient. It is imperative that physicians have a clinical approach to patients with unknown toxic ingestion. Family physicians need to be aware of cases such as the one presented here because SSRIs, SNRIs, and TCAs are commonly prescribed pharmacologic agents. This case is also of value to family physicians who practise in EDs, as it presents an organized approach to managing patients who overdose on multiple antidepressant agents.

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Competing interests
None declared

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