"Don't worry, that's the 'safe' drug"

DALHOUSIE UNIVERSITY
Inspiring Minds

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Roman's case

Roman, 30, is brought into the ED after a friend, who found him very drowsy and difficult to arouse, called an ambulance. Roman admits to the paramedics that after breaking up with his girlfriend, he had taken a handful of his venlafaxine tablets about an hour earlier. He denies any other ingestion.

Examination

On examination, Roman is mildly drowsy, but aware. The following is noted:

- Pulse: 120 bpm
- BP: 105/70 mmHg
- Respiratory rate: 18 breaths per minute
- Temperature: 37 C
- ECG: shows a narrow complex tachycardia

A colleague remarks to you that venlafaxine "is one of the new antidepressants, so he'll be fine."

Questions

1. What is our approach to this patient?
2. In overdose, is venlafaxine indeed a "safe" drug?
3. How should we specifically manage this overdose?

Read on to find out the answers to these questions.

Questions & Answers

1. *What is our approach to this patient?*

Until the picture is clearer, any patient whom you suspect has acutely taken an overdose (OD) of medication should be considered potentially very unstable. Intravenous access and cardiac monitoring should be instituted immediately. An assessment of the patient's ability to protect the airway is essential and can be done by observing how they manage their secretions; listen for noisy breath sounds and look for swallowing movements. If they are not protecting their airway or maintaining adequate respiratory effort, you should consider obtaining a definitive airway.

In a deeply drowsy or comatose patient, empiric naloxone may reverse the effects of an opioid overdose; however, the use of flumazenil (a benzodiazepine antagonist) is contraindicated in OD management as it may lead to intractable seizures or arrhythmias since the "protective effect" of the benzodiazepine in a mixed OD is reversed, allowing the full effect of the co-ingestant to "run wild."

In spite of Roman's denial of ingesting other medications, your inquiries of the patient and any other sources (*e.g.*, friends, family, paramedics, drug store, *etc.*) include a high suspicion for any co-ingestants. Salicylates and acetaminophen are very common in bathroom cupboards across the world and their co-ingestion is frequently not mentioned. Blood levels of these drugs should be drawn in almost all OD situations.

2. *In OD, is venlafaxine indeed a "safe" drug?*

Salicylates and acetaminophen are very common in bathroom cupboards across the world and their co-ingestion is frequently not mentioned. Blood levels of these drugs should be drawn in almost all OD situations.

Venlafaxine is chemically unrelated to any of the conventional antidepressant drugs (*i.e.*, tricyclic antidepressants [TCAs], selective serotonin reuptake inhibitors [SSRIs] or monoamine oxidase inhibitors). In fact, it is structurally and pharmacologically related to the analgesic tramadol.

Antidepressants act primarily by increasing the availability of noradrenaline and serotonin at the post-synaptic receptor. TCAs, which are one of the the most feared OD drugs, act by inhibiting pre-synaptic reuptake of noradrenaline and/or serotonin, but also have actions on receptors of:

- Dopamine
- Histamine
- Muscarinic
- α-adrenergics

In combination with the noradrenergic and serotoninergic actions, these account for a wide range of potential toxicities. Most importantly in OD, myocardial sodium channel blockade can cause profound cardiovascular instability shown by QRS widening on ECG.

SSRIs are believed to avoid much of these toxicities by specifically blocking serotonin reuptake. Unfortunately, this safety profile comes at the price of slightly diminished clinical effectiveness.

Venlafaxine has been termed a serotonin/noradrenaline reuptake inhibitor (SNRI) in that it inhibits neuronal serotonin and noradrenaline (and to a much lesser degree, dopamine). This is believed to give the drug a slightly better clinical effect than SSRIs. Because it does not inhibit monoamine oxidase, block muscarinic receptors, or have any appreciable affinity for α-adrenergic or histaminergic binding sites, it also avoids much of the toxicity encountered with the older agents. Having said this, the wider spectrum of effect does still appear to significantly increase its toxicity in OD. Recent data and experience suggests that venlafaxine is more toxic than the SSRIs and is as much, or more toxic than some TCAs. Furthermore, ODs measured in tablets will cause a false sense of security when compared to TCAs, as a daily dose of TCA is often four to six tablets compared to one to two tablets for venlafaxine.

Significant venlafaxine OD has a unique toxicological profile that seems to be a hybrid of TCA and SSRI toxidromes. Although there is minimal sedation or anticholinergic effect in most ODs, seizures occur with a frequency 10 times that of

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SSRIs and four times that of TCAs.[1]

Tachycardia, hypotension and QRS prolongation occur at a similar rate to TCAs. Serotonin toxicity is 35 times more common in venlafaxine OD than in TCA OD and 20 times more common than in a SSRI OD.[1]

In a recent review of deaths due to antidepressant OD in the United Kingdom,[2] venlafaxine (at 13.2 deaths/million prescriptions) was found to be responsible for more deaths than commonly seen TCA ODs, such as clomipramine (12.5), nortriptyline (5.5) or trazodone (4.0). This compares with 0.9 for fluoxetine and 0.7 for paroxetine OD, reinforcing the relative safety of SSRI OD.

3. *How should we specifically manage this OD?*

Recognition of the danger facing the patient and vigilance for early signs of cardiovascular or neurological disaster is critical. One of the most important things to do, if faced with a drug OD that you are not familiar with managing, is to contact the nearest poison centre, preferably before any complications ensue. Although the use of activated charcoal is less emphasized than in the past, it can be used in patients who present within one to two hours post-ingestion and can protect their airways. (Charcoal aspiration is a disaster!).

Complications can be most effectively managed in an ICU setting: consider early referral in large ODs. Seizures should be managed with benzodiazepines. If the seizures are refractory to benzodiazepines, consider propofol, thiopental and/or paralysis with ventilatory support. Cardiovascular complications should be anticipated and QRS widening (> 100 ms) or ventricular tachycardia should be treated with sodium bicarbonate boluses. Remember that certain antiarrhythmic drugs may exacerbate the cardiac effects of antidepressants (call the poison centre). Treat hypotension with fluids and if necessary, norepinephrine. Dx

Although there is minimal sedation or anticholinergic effect in most venalafaxine ODs, seizures occur with a frequency 10 times that of SSRIs and four times that of TCAs.

References
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