Case Studies from the Medical Examiner

Amitriptyline and Venlafaxine Intoxication Contributes to Patient Death
Winter 2020

Case Studies from the Medical Examiner are a deliverable of the collaborative work of the Adult Inquest Review Committee. The College of Pharmacists of Manitoba, the College of Physicians and Surgeons of Manitoba, and the Chief Medical Examiner's Office work togeter to learn from deaths related to prescription drugs, focusing on opioids and other drugs of misuse. All dates, patient initials, names of pharmacies, and prescribers have been changed and de-identified to protect the identity of the patient and their family.

Introduction

PL was a 59-year-old female found lying unresponsive in bed by her spouse on October 17, 2019. She was taken hospital, but all attempts at resuscitation were unsuccessful. Her spouse mentioned that PL appeared "spaced out" a few hours before going to bed. PL's medical history included drug misuse, hypertension, and depression. The immediate cause of death was determined to be hypertensive cardiovascular disease. Amitriptyline and venlafaxine intoxication were found to be contributing causes of death. The manner of death was deemed accidental.

Discussion

Amitriptyline and venlafaxine intoxication were contributing causes of PL's accidental death. Antidepressants play an important role in managing major depressive disorders; however, it is important to recognize the potential risk associated with these agents when used at higher doses.

"Patients on multiple sedating agents are at higher risk of experiencing an accidental opioid-related overdose."

"Amitriptyline and venlafaxine are often among the most common antidepressants responsible for accidental and intentional overdoses.

Compared to other antidepressant classes, tricyclic antidepressants (TCAs) have the highest risk for mortality in overdose.[1,2] Venlafaxine has also been associated with a higher risk of cardiotoxic effects at high doses compared to selective serotonin reuptake inhibitors (SSRIs).[3,4] The risk of death in overdose has been estimated to be approximately 5 times higher for venlafaxine, and almost 28 times higher for TCAs, compared to SSRIs.[1] Amitriptyline and venlafaxine are often among the most common antidepressants responsible for accidental and intentional overdoses.[5]

Moreover, PL's amitriptyline use was combined with other sedating medications, such as oxycodone, clonazepam, and gabapentin. Research has shown that patients on multiple sedating agents are at higher risk of experiencing an accidental opioid-related overdose.[6,7]

Toxicology Results

Drug	Level in blood (ng/mL)	Therapeutic Range (ng/mL)
Amitriptyline Nortriptyline (active metabolite) Total	348 152 500*^	75 - 200
Codeine Morphine	97 45	10 - 100 10 - 80
Clonazepam 7-aminoclonazepam (active metabolite)	0 58	20 - 70 20 - 140
Cyclobenzaprine	2	3 - 3
Oxycodone Oxymorphone	110* 16	10 - 100 1 - 30#
Venlafaxine O-desmethylvenlafaxine (active metabolite)	1100* 5400*	62 - 138 118 - 252
Drug	**Level in urine (µg/mL)**	**Therapeutic Range (µg/mL)**
Gabapentin	39*	2 - 20

* Above therapeutic range
^ Tricyclic antidepressants undergo post-mortem redistribution and levels may be slightly elevated in the toxicology report.
#Therapeutic blood concentrations of oxymorphone are not established, but existing data suggests reference ranges similar to hydromorphone (i.e. 1-30 ng/mL).

Three Month DPIN History Preceding Patient's Death

Generic Name	Date Dispensed	Strength	Quantity	Days Supply	Prescriber	Pharmacy
Acetaminophen/ Oxycodone	Oct. 16, 9, 2 Sep. 27, 20 Sep. 13 Sep. 9, 4, 12 Aug. 25,18, 3, July 27	325 mg/ 5 mg	60 60 18 60 60 60	7 7 3 7 7 7	Dr. Vee	XYZ Pharmacy
Amitriptyline	Oct. 15 Sep. 29, 16, 4 Aug. 25, 13 July 28	50 mg	56 42 42 42	14 14 14 14	Dr. Vee	XYZ Pharmacy
Clonazepam	Oct. 16, 2 Sep. 27, 20,13, 4, 1 Aug. 25, 18, 10, 3, July 27	1 mg	14 14 14 14	7 7 7 7	Dr. Vee	XYZ Pharmacy
Gabapentin	Oct.16, 9, 2 Sep. 27, 13 Sep. 9 Sep. 4, 1 Aug. 25, 18, 10, 3 July 27	300 mg	84 84 36 84 84 84	84 84 36 84 84 84	Dr. Vee	XYZ Pharmacy
Venlafaxine	Oct. 15 Sep. 29, 16, 2 Aug. 25, 13 July 28	37.5 + 150 mg	14 14 14 14	14 14 14 14	Dr. Vee	XYZ Pharmacy

Recommendations

Note that PL was receiving two different antidepressants. While the indication is not known in this case, amitriptyline is often used off-label[8] for a number of conditions, including fibromyalgia, neuropathic pain, migraine prophylaxis, and abdominal pain associated with irritable bowel syndrome with a usual maximum dose ranging from 50 mg to 150 mg per day depending on indication (usual maximum dose for depression is 300 mg/day).[9] Combining antidepressants might also be considered for patients who had partial response to monotherapy for major depressive disorder.[10,11] In these cases, it is generally advised to use drugs that do not pose greater safety risks than monotherapy and to use agents with complementary mechanisms of action (e.g., SSRI with norepinephrine-dopamine reuptake inhibitor).

If a TCA were to be added to a serotoninnorepinephrine reuptake inhibitor (SNRI) or SSRI, low TCA doses (25-75 mg daily) and monitoring of TCA blood levels are recommended.[12] PL's amitriptyline dose was increased from 150mg/day to 200mg/day two days prior to her death. Low-dose overdoses with TCAs have been reported, and pharmacists should be aware that even "typical" doses of TCAs may pose a risk to the patient, particularly if combined with other medications that may interfere with their metabolism.

Even "typical" doses of TCAs may pose a risk to the patient, particularly if combined with other medications that may interfere with their metabolism.

It is a pharmacist's primary responsibility to ensure patient safety when dispensing a prescription medication.

All members are reminded of their professional obligation to ensure that each prescription is reviewed thoroughly, and potential issues addressed, even if it means there may be a difficult patient encounter. Measures must be taken to address issues with appropriateness of drug therapy, drug interactions, therapeutic duplication, and inappropriate or unsafe dosing. Pharmacists do not have the obligation to dispense medications that they believe may cause patient harm. In such cases, the patient must be referred appropriately according to the Referring a Patient Practice Direction.

References

[1] Hawton K, Bergen H, Simkin S, et al. Toxicity of antidepressants: rates of suicide relative to prescribing and non-fatal overdose. Br J Psychiatry 2010;196(5):354-8.

[2] Nelson JC, Spyker DA. Morbidity and mortality associated with medications used in the treatment of depression: an analysis of cases reported to U.S. Poison Control Centers, 2000-2014.. Am J Psychiatry. doi: 10.1176/appi. ajp.2016.16050523.

[3] Howell C, Wilson AD, Waring WS. Cardiovascular toxicity due to venlafaxine poisoning in adults: a review of 235 consecutive cases. Br J Clin Pharmacol 2007;64(2):192-7.

[4] Leong C, Alessi-Severini S, Enns MW, et al. Cerebrovascular, cardiovascular, and mortality events in new users of selective serotonin reuptake inhibitors and serotonin norepinephrine reuptake inhibitors: A propensity score-matched population-based study. J Clin Psychopharmacol 2017;37(3):332-340.

[5] Sinyor M, Howlett A, Cheung A, Schaffer A. Substance used in completed suicide by overdose in Toronto: an observational study of coroner's data. Can J Psychiatry 2012;57(3):184-191.

[6] Smolina K, Crabtree A, Chong M, Zhao B, Park M, Mill C, et al. Patterns and history of prescription drug use among opioid-related drug overdose cases in British Columbia, Canada, 2015-2016. Drug and Alcohol Dependence2019;194:151-158.

[7]Gjelsvik B, Heyerdahl F, Hawton K. Prescribed medication availability and deliberate self-poisoning: a longitudinal study. J Clin Psychiatry 2012;73(4):e548-554.

[8] Wong J, Motulsky A, Abrahamowicz M, Eguale T, Buckeridge DL, Tamblyn R. Off-label indications for antidepressants in primary care: descriptive study of prescriptions from an indication based electronic prescribing system. BMJ 2017'Feb21;356:j603.

[9] RxTx. Tricyclic Antidepressants. Available: https://www-e-therapeutics-ca.uml.idm.oclc.org/search. Accessed December 1, 2020.

[10] Fava M. Augmentation and combination strategies in treatment-resistant depression. J Clin Psychiatry 2001;62 (Suppl18):4-11.

[11] Kennedy SH, Lam RW, McIntyre RS, et al. Canadian Network for Mood and Anxiety Treatments (CANMAT) 2016 clinical guidelines for the management of adults with major depressive disorder: Section 3. Pharmacological treatments. Can J Psychiatry 2016;61:540-60.

[12] Papakostas GI, Mischoulon D, Shyu I, et al. S-adenosyl methionine (SAMe) augmentation of serotonin reuptake inhibitors for antidepressant nonresponders with major depressive disorder: a double-blind, randomized clinical trial. Am J Psychiatry 2010;167:942-8.