Case Studies from the Medical Examiner

Multi-Drug Overdose Involving Carfentanil and Methadone Leads to Patient Death

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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

KF was a 40-year-old woman who was found deceased at home in December 2018. She had a past medical history of opioid addiction and was on a methadone maintenance treatment program. There was no suicide note found and no indication of trauma. An autopsy was performed, and cause of death was determined to be multi-drug overdose involving carfentanil and methadone. This case was identified by the College as an important learning opportunity for pharmacists to review dispensing practices.

Discussion

There are multiple factors that are important to consider.

Although benzodiazepines did not contribute to the patient's death, it is still important to note that KF was prescribed near or higher than recommended doses of benzodiazepines. The Ashton Manual[1] is an excellent benzodiazepine reference and includes a chart for determining approximate oral dosages of benzodiazepines in diazepam equivalents. The Compendium of Pharmaceuticals and Specialties (CPS)[2] and the Canadian Guideline for Safe and Effective Use of Opioids for Chronic Non-Cancer Pain Opioid Manager[3] are also excellent resources that can be used to determine approximate diazepam equivalents. Prescribing more than 30-40 mg of diazepam or equivalent per day is generally not recommended. At 2 mg of alprazolam per day (20 to 40 mg diazepam equivalents) in addition to 30 mg of temazepam per day (10 to 15 mg diazepam equivalents), the patient may have received greater than the recommended cumulative dose of benzodiazepines.

Long-term use of benzodiazepines is not supported by evidence and prescribing more than one at a time is not recommended. There is no evidence that combination benzodiazepines improves efficacy, but combination treatment may increase risk of harm. This practice may be an attempt to treat anxiety and insomnia individually without consideration of their common causes. Patients should have a long-term plan for managing anxiety and insomnia in place, including a strategy for discontinuing the benzodiazepine once the effects of long-term treatment (e.g., SSRI/SNRI, psychotherapy) begin to take effect. Buspirone could also be considered an alternative to a benzodiazepine for anxiety.

Prescribing benzodiazepines concurrently with methadone can result in excessive sedation and lead to increased risk of respiratory depression.

Prescribing benzodiazepines concurrently with methadone can result in excessive sedation and lead to increased risk of respiratory depression. If it is necessary to prescribe them together, daily dispensing or dispensing along with methadone is recommended. For more information about appropriate prescribing practices in opioid

Toxicology Results

Drug	Level in blood (ng/mL)	Therapeutic Range (ng/mL)
Methadone	650*	100-400
EDDP (inactive methadone metabolite)	88	N/A
Carfentanil	1.11 (The lowest carfentanil is 0.05 ng/mL)	N/A

*Please note that a level of 650 ng/ml methadone in a long-term, stable opioid replacement therapy (ORT) patient cannot necessarily be interpreted as a toxic level. This level may be appropriate and it cannot be assumed that the methadone was overused.

Recent DPIN History Preceding Patient's Death

KF's DPIN showed that she was dispensed the following drugs (and had been for the preceding six months):

Generic Name	Date Dispensed	Strength	Quantity	Days Supply	Prescriber	Pharmacy
Methadone	Dec 20, 2018	10 mg/ml	16*	5*	Dr. Psy	TT Pharmacy
Alprazolam	Dec 13, 2018	1 mg	56	28	Dr. Psy	Bullseye Pharmacy
Temazepam	Dec 13, 2018	30 mg	28	28	Dr. Psy	Bullseye Pharmacy

*Daily dose 3.2 mL (32 mg). Patient received a total of two witnessed doses and five carry doses weekly.

replacement therapy, refer to the Opioid Agonist Therapy (OAT) Guidelines for Manitoba Pharmacists.

Consider providing naloxone kits to patients at risk of opioid overdose (e.g., >90 mg morphine equivalent, ORT patients, multiple prescribers, frequent early refills, frequent emergency visits requesting opioid, history of opioid use disorder, concomitant CNS depressants, during tapering plan). Note that greater than normal doses of naloxone may be required to reverse an overdose for more potent opioids, like fentanyl and carfentanil.

The patient's benzodiazepines did not appear on the toxicology report. The patient may have been diverting the medication or was not taking them. The patient was supplementing with street drugs (carfentanil) which in combination with the patient's methadone, resulted in a fatal overdose. Patients showing signs of instability should not be given carries.

It would have been advisable for the pharmacist dispensing the patient's medications to have a conversation with the prescriber about the combination, dosages, and quantities dispensed of the medications prescribed. These conversations should always be documented appropriately.

It is a pharmacist's primary responsibility to ensure patient safety when dispensing prescription medication. All members are reminded of their professional obligation to ensure that each prescription is reviewed thoroughly. Proper measures must be taken to address issues with appropriateness of drug therapy, drug interactions, therapeutic duplication as well as correct dosage.

Additional Reading

1. The Ashton Manual https://www.benzo.org.uk/manual/bzcha01.htm#24

2. Canadian Pharmacists Association. Compendium of Pharmaceuticals and Specialties (CPS) Available: https://www.pharmacists.ca/products-services/compendium-of-pharmaceuticals-and-specialties/

3. Michael G. DeGroote National Pain Centre. McMaster University. Canadian Guideline for Safe and Effective Use of Opioids for Chronic Non-Cancer Pain Practice Toolkit. Available: http://nationalpaincentre.mcmaster.ca/documents/practicetoolkit.pdf

4. The Center for Effective Practice (CEP) Practice Tool: Benzodiazepine Use.

5. Katzman et al., Canadian Clinical Practice Guidelines for the Management of Anxiety, Post-traumatic Stress and Obsessive-Compulsive Disorders. BMC Psychiatry 2014;14(Suppl 1):S1.

6. CADTH. High dose and watchful dosing of benzodiazepines: A review of the safety and guidelines. November 21, 2012. Available: https://www.cadth.ca/high-dose-and-watchful-dosing-benzodiazepines-review-safety-and-guidelines.

7. Choosing Wisely. Pharmacists. Recommendation 6: Don't prescribe or dispense benzodiazepines without building a discontinuation strategy into the patient's treatment plan (except for patients who have a valid indication for long-term use. Available: https://choosingwiselycanada.org/pharmacist/.

8. Choosing Wisely. Drowsy without feeling lousy. A toolkit for reducing inappropriate use of benzodiazepines and sedativehypnotics among older adults in primary care. Version 10. July 2017.

9. CADTH. Discontinuation Strategies for Patients with Long-term Benzodiazepine Use: A review of clinical evidence and guidelines. July 29, 2015. Available: https://www.cadth.ca/sites/default/files/rc0682-bzd_discontinuation_strategies_final_0.pdf.

10. CCSA. Effective Interventions to Manage Symptoms of Benzodiazepine Withdrawal in Seniors. November 2014. Available: http://www.ccsa.ca/Resource%20Library/CCSA-Benzodiazepine-Withdrawal-Seniors-Rapid-Review-2014-en.pdf.

11. Opioid Agonist Therapy Guidelines for Manitoba Pharmacists. December 2020.

12. Canadian Centre on Substance Use and Addiction (CCSA). Resources related to the opioid crisis.

13. School of Pharmacy. University of Waterloo. Naloxone and Opioid Crisis Resources.