Case Studies from the Medical Examiner

Accidental Mixed Drug Toxicity Contributes to Patient Death
Spring 2019

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-identifi d to protect the identity of the patient and their family.

Introduction

BR is a 35 year old male found unresponsive in the morning in his friend's home. He was taken to hospital where he was pronounced dead. He had been reportedly partying the night before. He had a history of drug misuse that had spiraled out of control. He had just started an opioid replacement therapy treatment program over a week earlier.

Discussion

The toxicology report (see chart, right page) shows that cocaine (and its metabolites), methadone (and its metabolite), alprazolam, hydromorphone (presumptive), and cannabinoids (presumptive) were present in BR's case.

After an autopsy is performed, BR's death is ruled accidental mixed drug toxicity.

BR had begun methadone that was witnessed daily by the pharmacist. Overdose from methadone in patients on opioid replacement therapy (ORT) is most likely to occur in the fi st 2 weeks of starting the medication. Starting dose of methadone is 10-30 mg/day. The lower end of the dosing range should be used for patients at higher risk of toxicity (eg. elderly, concomitant use of sedating medications or methadone metabolism inhibitors). The dose of methadone can be increased by 5 to 10mg every three to four days as required. Although BR's prescribed methadone dose fell within these guidelines, the induction schedule may have been aggressive for this patient, especially when BR was on a concomitant benzodiazepine.

Many patients will continue to use their drug of choice during the fi st couple weeks as methadone will not yet be at a maintenance dose and withdrawal and cravings may occur. Use of benzodiazepines with methadone can be dangerous. BR had a high level of alprazolam on his toxicology report. This alprazolam was not prescribed to BR. In most methadone-related deaths, concurrent use of sedatives such as benzodiazepines and alcohol are found to have contributed to the cause of death.

Recommendations

If a patient is already on ORT and is prescribed a benzodiazepine, both the prescriber of the benzodiazepine and ORT prescriber should be contacted to decide if the prescription for the benzodiazepine is appropriate. Many ORT prescribers will require that their patients see them for any of these types of medications.

Benzodiazepines are CNS depressants and have a high potential for addiction; therefore, they should be prescribed and dispensed with caution for patients on ORT. For any patient being started on ORT, benzodiazepines should ideally be dispensed daily, along with daily-observed methadone/buprenorphine dosing. As treatment progresses and carry (take-home) doses are awarded, benzodiazepines can be dispensed according to the same schedule as the methadone/buprenorphine.

For the majority of patients, long-term use of benzodiazepines is not recommended. Wherever possible, alternate medications or behavioural therapy should be considered before prescribing benzodiazepines or other CNS depressants. Additional caution should be taken in patients at risk of respiratory compromise (e.g., asthma, COPD) who are receiving methadone and other

Toxicology Results

Drug	Level in blood (ng/mL)	Therapeutic Range (ng/mL)
Cocaine	180	N/A
Benzoylecgonine (inactive cocaine metabolite)	342	N/A
Methylecgonine (inactive cocaine metabolite)	Unknown	N/A
Methadone	810	100-400
EDDP (inactive methadone metabolite)	400	N/A

Recent DPIN History Preceding Patient's Death

Generic Name	Date Dispensed	Strength	Quantity	Days Supply	Prescriber	Pharmacy
Methadone	Aug. 14, 2017 Aug. 13, 2017 Aug. 12, 2017 Aug. 11, 2017 Aug. 10, 2017 Aug. 9, 2017 Aug. 8, 2017 Aug. 7, 2017 Aug. 6, 2017	10mg/mL	4.0 3.0 3.0 3.0 2.0 2.0 2.0 2.0 2.0	1 1 1 1 1 1 1 1 1	Dr. Dave	365 Pharmacy
Acetaminophen/ codeine	July 26, 2017	15 mg	30	30	Dr. Dee	XYZ Pharmacy
Lorazepam	July 26, 2017	1 mg	30	30	Dr. Dee	XYZ Pharmacy
Salbutamol	July 26, 2017	100 mcg	200	25	Dr. Dee	XYZ Pharmacy

CNS depressants. BR had received a refill or salbutamol, lorazepam, and acetaminophen with codeine approximately three weeks earlier, and could have benefi ed from counseling on his risks for experiencing methadone toxicity.

Pharmacists should consider providing naloxone kits to patients at risk of opioid overdose (e.g., >90 mg morphine equivalent, ORT patients, respiratory illness (e.g., COPD, asthma, sleep apnea), multiple prescribers, frequent early refills frequent emergency visits requesting opioids, 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.

Patients must be counselled on the risks of interactions and adverse effects of using certain prescription and illicit drugs when they are started on methadone or other opioid replacement therapies.

Additional Reading

Opioid Replacement Therapy Guidelines for Manitoba Pharmacists

College of Physicians and Surgeons of Manitoba: Manitoba Methadone & Buprenorphine Maintenance – Recommended Practice

Prescribe to Prevent. Instruction for healthcare professionals: prescribing naloxone.

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

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