Potent sedatives in opioids in BC: Implications for resuscitation, and benzodiazepine and etizolam withdrawal

Mortality due to drug overdose has risen to unprecedented levels in British Columbia. In 2020, 1724 people died of drug overdose compared to 984 people in 2019.[1]

There has been a significant increase in the proportion of opioid samples containing strong sedatives. These sedatives include benzodiazepines, etizolam, and xylazine. In January 2021, benzodiazepines were found in 20% of opioid samples checked by the BC Centre on Substance Use and 50% of samples from the Vancouver Island Drug Checking Project. Particularly concerning is that benzodiazepines were detected in 50% of illicit drug toxicity deaths in BC in December 2020 and January 2021.[2]

Benzodiazepines and etizolam enhance the action of the inhibitory neurotransmitter, gamma aminobutyric acid. Patients with benzodiazepine overdoses may have profound CNS depression. Symptom onset occurs in 0.5 to 2 hours. Symptom duration can vary depending on the agent and dose; generally, patients with etizolam overdoses will be sedated for many hours. Also of note is that urine toxicology will not detect all benzodiazepines. Point-of-care screens in BC will detect etizolam but their reported sensitivity is 50% to 70%. It is, therefore, important to treat patients clinically if benzodiazepine toxicity is suspected.

Dependence to and withdrawal from benzodiazepines or etizolam may occur after exposures of only a few weeks.[3] Increasing exposure to benzodiazepines puts many people who use drugs at risk for withdrawal symptoms (e.g., agitation, sleeplessness, autonomic instability), which may be difficult to clinically differentiate from opioid withdrawal or stimulant toxicity. Withdrawal from benzodiazepines and etizolam has been increasingly reported across BC over the past 6 months.

The effects of both benzodiazepines and etizolam can be reversed with flumazenil. However, flumazenil should not be used in the treatment of suspected benzodiazepine or etizolam overdose because it is associated with ventricular dysrhythmias and seizures. Flumazenil can also precipitate benzodiazepine or etizolam withdrawal. If seizures occur after the use of flumazenil, they can be very difficult to treat.[4] Xylazine is a partial alpha-2-adreneric agonist pharmacologically related to clonidine. Toxic effects include hypotension, bradycardia, and respiratory depression.

Benzodiazepine adulteration makes the resuscitation of patients with illicit drug overdose complex. The mainstay of overdose treatment is monitoring and supportive care. As respiratory depression is the major cause of opioid overdose mortality and morbidity, patients' respiratory status should be monitored. Simply measuring a patient's respiratory rate may be an unreliable estimate of respiratory function; therefore, monitoring oxygen saturation and end tidal carbon dioxide should be instituted if available. Hypoventilation should be treated with respiratory support. Hypoglycemia may occur in opioid overdose, so clinicians should check serum glucose.[5]

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Naloxone is a competitive opioid antagonist that is effective in reversing opioid overdose. In cases where opioid overdose is suspected, lay and health care responders should give naloxone to patients with hypoventilation or who are unable to protect their airway. Where

Additional resources from the BCCDC

- Summary sheet for health professionals. Benzodiazepines found in opioids in BC. https://towardtheheart.com/resource/benzos-in-opioids-in-bc/open.
- Fact sheet: Etizolam in BC's illicit drug market. https://towardtheheart.com/resource/etizolam-in-bc-illicit-market/open
- Position statement: Observed consumption services. www.bccdc.ca/resource-gallery/Documents/Statistics%20and%20Research/Statistics%20and%20Reports/Overdose/Final_OCSStatement_June2019.pdf

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benzodiazepines are adulterants in an illicit opioid overdose, patient sedation may be enhanced and patients' response to naloxone may be incomplete. However, responders should still administer naloxone, as it will reverse opioid-related toxicity. Naloxone should be titrated to effect, and opioid withdrawal precipitated by naloxone should be avoided. At the BC Drug and Poison Centre, we recommend the following naloxone regimen if there is clinical suspicion of opioid overdose: 0.04 to 0.1 mg initially, followed by subsequent doses (q2–3 min): 0.4 mg, 0.4 mg, 2.0 mg, 4.0 mg, then 10 mg.[6] If ongoing sedation persists due to prolonged effects of concurrent benzodiazepines, patients should be monitored until they are safely ventilating and their level of consciousness returns.

Please contact the BC Drug and Poison Information Centre in all suspected cases. We are pleased to work with you in the management of these complex cases. ■

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to collectively improve coordination of care for priority populations locally and provincially. A maternity network was the first to be created in 2017 to improve interprofessional collaboration and delivery of maternity care in BC. The network has since grown to involve 25 communities/divisions, and is transitioning to a community of practice. Other Spread Networks cover adult mental health and substance use, chronic pain, coordination of care for older adults, and palliative care. Read more at https://sharedcarebc.ca/our-work/spread-networks.

Learn more at www.CollaborateOnHealthBC.ca. ■

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1. Institute for Healthcare Improvement. The IHI Triple Aim. Accessed 15 March 2021. www.ihi.org/Engage/Initiatives/TripleAim/Pages/default.aspx.