

BC CORONERS SERVICE – PREVENTABLE DEATH BULLETIN

May 13, 2014

Ministry of Justice
BC Coroners Service

Management of Methadone Overdose

Background:

A 37 year old man died at home approximately 10 hours after discharge from a rural emergency department following a 90 minute stay for the treatment of a methadone overdose.

On review of the case it became clear the facility did not have a protocol for the management of suspected methadone overdoses, including an adequate period of observation.

In follow up the Health Authority has committed to review the case and institute clinical guidelines for the management of overdoses.

This is important as methadone use for opiate substitution and chronic pain management is in place throughout the province, including in many small communities where such events may be uncommon.

Recommendation:

- All emergency departments are advised to follow the BC Drug and Poison Information Centre (DPIC) protocol for the treatment of a methadone overdose (attached below) and keep the patient at least 10 hours after treatment for observation – even if the patient is asymptomatic.
- **Call the DPIC when a patient with poison and overdose presents at the ED (24 hours: 604-682-5050 or 1-800-567-8911).**

Overview of the BC Coroner's Preventable Death Bulletin reviewing the death of a patient following treatment in an Emergency Department for a Methadone Overdose

Summary:

- The Report from the Coroner was released on June 30, 2014;
- The patient was brought to emergency with a reported Methadone overdose;
- Patient was treated with Naloxone (also known as Narcan); he was alert and oriented within 90 minutes and discharged home;
- The patient died at a private residence 10 hours later;
- Post Mortem toxicology revealed a mixed toxicity (Methadone, Diazepam, Codeine, and Cocaine).

Recommendation:

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METHADONE

Synonyms

Metadol[®], Methadose[®]

Description

Long-acting synthetic opioid used mainly for the treatment of heroin dependency (as substitution maintenance therapy) and for management of chronic pain. Available as oral solution, tablets, and powder.

Toxicity

Opioid intoxication generally includes CNS depression, respiratory depression, and miosis. Bradycardia and mild hypotension are also common. Severe toxicity may result in respiratory arrest, shock, dysrhythmias, and acute lung injury. Onset of symptoms may be delayed and duration prolonged.

Children, nontolerant adults, the elderly, and patients switching from other opioids to methadone or having rapid dose escalation are at greater risk for severe toxicity. Prolonged QTc interval may be seen especially with dose increases, chronic therapy with > 120 mg/d, or concurrent use of agents that inhibit methadone clearance or also prolong QTc interval.

Mechanism of Toxicity

Mu receptor agonist like other opioid analgesics. **See** OPIOIDS.

Also blocks reuptake of serotonin and norepinephrine. Methadone inhibits cardiac potassium channels and can prolong the QTc interval and result in torsades de pointes (dose dependent).

Toxic Dose

Varies with age, degree of opioid tolerance, and medical history. Children are more susceptible to toxic effects.

Adults: In opioid-naïve adults, 50 mg can be life threatening. Usual dose for methadone maintenance therapy ranges from 40-120 mg/day (> 120 mg/day is considered a high dose).

Children: Multiple reports of life threatening toxicity with ingestion of 5 mg; 10 mg has been lethal. In a series of 33 methadone-related deaths (median age 2 years) the median dose was 35 mg. **See** Case Reports.



Case Reports

A 4-year-old became unresponsive with pinpoint pupils after 2 doses of amoxicillin suspension that was inadvertently reconstituted with methadone solution (total methadone dose 24 mg). Patient did not respond to naloxone (1.6 mg, single dose) but recovered with supportive care. Methadone was detected in blood and urine.

A 3-year-old ingested an unknown amount of methadone and was comatose by 8 hours post ingestion. Pupils were constricted and unreactive, and patient had frequent apnea with respiratory acidosis. He became rousable (GCS 15) with reactive pupils after a naloxone bolus; naloxone infusion was required for 6 hours after admission. Initial blood glucose was 21 mmol/L without ketonuria; hyperglycemia resolved and child fully recovered.

A 3-year-old ingested an unknown amount of methadone and within approximately 8 hours post ingestion was comatose with no response to painful stimuli. He had bilateral miotic pupils unreactive to light and frequent apnea. BP was 100 mmHg, HR 160 beats/min and ABGs were pH 7.27, pCO₂ 60 mmHg, HCO₃ 28 mmol/L. IV naloxone bolus was given and child became rousable with GCS 15, BP 101 mmHg, HR 140 beats/min, RR 20/min and pupils reacted to light. Initial blood glucose was 21 mmol/L (378 mg/dL) with no ketonuria. Naloxone infusion was required for 6 hours post admission. Hyperglycemia normalized and child fully recovered.

A 44-year-old ingested 240 mg of his own methadone and 2 mg flunitrazepam. His methadone maintenance dose was 70 mg/day. Approximately 2.7 hours later he was comatose with pinpoint pupils, respiratory rate of 10/minute, and oxygen saturation of 75%. Patient responded to IV naloxone bolus and required naloxone infusion for 31 hours. Patient recovered fully.

Pharmacokinetics

Well absorbed orally. Onset of symptoms generally within 3-4 hours post ingestion. Duration may be several days. Widely distributed; volume of distribution increases with chronic dosing.

Metabolized in liver primarily by CYP3A4 and other enzymes to inactive metabolites which are eliminated in urine.

Elimination half-life is variable; ranges from 12-55 hours. Half-life may be prolonged in the elderly and in patients on chronic therapy or concurrent medications that inhibit metabolism.

Clinical Effects

General: Symptoms generally include CNS depression, miosis, and respiratory depression. Death from respiratory arrest. Onset of symptoms generally within 3-4 hours post ingestion; may be delayed up to 9 hours. Onset of symptoms in children may be more rapid. Duration may be several days.

HEENT: Miosis (common); mydriasis may be seen. Acute bilateral hearing loss has been reported with severe overdose (reversible in many cases). Tremor of tongue and floor of mouth have been reported in children.



CVS: Hypotension, bradycardia. Circulatory collapse and cardiac arrest in severe overdose. Prolonged QTc interval may be seen especially with dose increases, chronic therapy > 120 mg/day, or concurrent use of agents that inhibit methadone clearance or also prolong QTc interval. Torsades de pointes has been reported.

Respiratory: Respiratory depression, apnea. Acute lung injury; onset may be delayed.

Neurologic: Analgesia, euphoria, confusion; drowsiness may progress to coma. Seizures, hallucinations (uncommon). Toxic leukoencephalopathy has been reported in children. Serotonin syndrome has been reported (usually caused by interaction with other serotonergic drugs).

GI: Nausea, vomiting (common). Constipation with chronic use.

GU: Urinary retention reported. Rhabdomyolysis leading to acute renal failure reported in patients with prolonged coma.

Fluids/Lytes/Acid-Base: Nonketotic hyperglycemia has been reported in children following acute overdose.

Skin: Flushed; itching due to histamine release.

Musculoskeletal: Myoclonus has been reported with high-dose parenteral methadone, as well as with serotonin syndrome involving methadone.

Other: Fever has been reported in children with severe toxicity. Aluminum toxicity has been reported in a patient who was boiling his oral methadone in aluminum cookware prior to IV injection, **see ALUMINUM**.

Withdrawal: Sign and symptoms (restlessness, shivering, sweating, dysphoria, insomnia, abdominal cramping, diarrhea, fever, sinus tachycardia, hypertension) may begin within 1-2 days; peak 4-6 days, and last up to several weeks. Symptoms are rarely life threatening.

Lab: Routine urine screens for opioids will not detect methadone. Specific urine tests may confirm recent use. False-positive results may be caused by diphenhydramine, doxylamine, citalopram or verapamil - consult technical specifications for assay.

Treatment

1. ***Asymptomatic*** patients with suspected overdose and children ingesting any amount should be **monitored for at least 10 hours**.
2. ***Symptomatic*** patients should be monitored until all symptoms resolve; observe for **resedation for at least 6 hours after last dose of naloxone, see below**.
3. Do not induce vomiting. Consider activated charcoal for recent ingestions.
4. Protect airway and assist ventilation as needed.



5. Naloxone should be administered to patients with respiratory depression, **see** below. Prolonged therapy will likely be required.
6. Monitor vital signs, ECG, electrolytes, glucose, renal function, oxygenation. Perform chest x-ray and blood gases in patients with acute lung injury.
7. Maintain fluid and electrolyte balance.
8. Hypotension can generally be managed with IV fluids.
9. QTc prolongation should be closely monitored. Correct any underlying electrolyte abnormalities. Treat torsades de pointes as per ACLS protocol.
10. Seizures should be managed with benzodiazepines.
11. **Antidote:** Naloxone should be given for respiratory depression. Administer 0.05 - 0.4 mg IV initially; if no effect, repeat doses up to 10 mg. Large doses may be required to reverse effects of methadone. Observe for re sedation for at least 6 hours. Additional doses or an IV infusion will likely be required as elimination half-life of naloxone is shorter than that of methadone. **See also** NALOXONE antidote monograph.

Key Points

- ✓ *Asymptomatic* patients with suspected overdose should be monitored for at least 10 hours.
- ✓ *Asymptomatic* children ingesting any amount should be monitored for at least 10 hours. Multiple reports of life threatening toxicity following ingestion of 5 mg in a child; 10 mg has been lethal.
- ✓ Opioid intoxication includes CNS depression, respiratory depression, and miosis. Death from respiratory depression and cardiac arrest.
- ✓ QTc prolongation may be seen in those on chronic high dose or with concurrent medications.
- ✓ Onset of symptoms may be delayed up to 9 hours post ingestion; duration of toxicity may be several days.
- ✓ Treatment is symptomatic and supportive. Naloxone should be administered for respiratory depression; may require high initial doses and prolonged IV infusions.