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Utox Update

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UTAH POISON CONTROL CENTER

Methadone Toxicity

Introduction

Traditionally, methadone has been used for the treatment of opioid dependence. It is now being used with increased frequency as an analgesic due to its low cost, long half-life, rapid onset, and safety in chronic renal failure and stable liver failure. Methadone's use as an analgesic is controversial because of its variable kinetics, potential toxicities, and a recent increase in the number of fatalities associated with use in this setting.

Methadone displays wide inter-individual pharmacokinetic variability, making initial dose determination, analgesic dose converting, and dose adjusting difficult and potentially dangerous. In Utah, the number of deaths from unintentional or undetermined intent (i.e., excludes suicidal intent) due to methadone increased more than 14-fold, from 2.3 per year prior to 1999 to 32.7 per year from 1999 to 2003. Death due to other prescription opioids increased only five-fold during this same period.[1] Drug Enforcement Administration (DEA) records show that the amount of methadone distributed in Utah during this time period (excluding methadone clinics) increased only by a factor of 6.[1] A similar trend of increasing fatalities has been noted in other states.

In addition to the respiratory and CNS toxicity, another concern is the potential for methadone to cause cardiac conduction disturbances, specifically QT prolongation and Torsades de pointes. Another opioid analgesic, levacetylmethadol (LAAM), is closely related to methadone and was recently removed from the market due to its propensity to cause similar cardiac toxicity.

Pharmacology/Pharmacokinetics

Methadone has agonist activity at the mu, kappa, and delta opioid receptors like other opiate analgesics. However, it also has antagonistic effects at N-methyl-D-aspartate (NMDA) receptors, and blocks reuptake of serotonin and norepinephrine. Cross tolerance with other opioids is not complete, so care must be taken in converting to methadone therapy as respiratory depression may occur even in opioid-tolerant patients.

Gastrointestinal absorption is generally rapid and complete, but somewhat variable, and peaks 1 to 6 hours after ingestion. The elimination half-life of methadone averages 33 hours, with a range of 27-59 hours. Alkaline urine increases the elimination half-life. Drug accumulation is a potential problem, due to the disparity between elimination half-life and duration of analgesia (around 4-12 hours). Plasma concentrations can vary significantly between individuals who have received the same dose. The pharmacokinetic variability most likely results from the variation in the activities of the cytochrome P450 enzymes responsible for metabolism. Variability in CYP 3A4 activity is significant (up to 400-fold) and can be due to drug interactions or to genetic differences in enzyme expression.[2]

Tolerance to sedative effects generally occurs after several days, while tolerance to the analgesia develops after days to months. Particularly dangerous is the loss of tolerance to respiratory depression that can result after missing doses for just a day or two. This loss of tolerance has been noted as a factor in some fatalities.[3]

Clinical Toxicology

The Opioid Toxidrome

The classic presentation of opioid toxicity includes pinpoint pupils, CNS depression, respiratory depression, hypotension, bradycardia, and decreased bowel sounds. The clinical picture may be clouded by co-ingestants with different toxicological effects. Miosis can be an unreliable

sign, particularly in children, since a small subset of patients may present with mydriasis or normal-sized pupils.[4] Death results from cessation of respiration.[3]

Torsade de pointes

Methadone has been shown to block the rapid delayed potassium rectifier channel (IKr) in cardiac myocytes, thus interfering with the potassium current that is essential for repolarization and prolonging the QT interval. QT prolongation is dose-related and can take a week to resolve due to the long half-life of methadone.[5]

A number of reports of Torsade de pointes or prolonged QT associated with methadone have been published.[6-12] Other risk factors for arrhythmias were often present in these case reports and included electrolyte abnormalities, concomitant QT prolonging drugs such as cocaine, and drugs that inhibit the metabolism of methadone.

Toxic Dose

As little as 10mg has been fatal in children.[4] The minimum lethal dose in an opioid naïve adult may be as low as 30 to 50 mg.[4] Larger doses may be tolerated. An opiate-naïve 76 year-old woman unintentionally received 320 mg of methadone over 12 hours and was successfully treated with naloxone and supportive care after experiencing respiratory depression and pulmonary edema.[13]

Pregnancy/Lactation Issues

Methadone maintenance treatment can be safely continued in pregnant and lactating women. The biggest concern is the potential for the fetus to experience an opioid withdrawal syndrome after birth.

Treatment

Treatment of methadone toxicity is the same as for other opioids with the exception that the symptomatic patient should be observed for 48 to 72 hours due to the drug's long half-life. A dose of naloxone can be diagnostic and resolution of signs and symptoms should occur within 2-3 minutes. In the absence of life-threatening respiratory arrest, small doses may be preferred to restore spontaneous breathing while allowing the patient to remain comfortably sedated. The customary initial dose is 0.4 mg IV, but stable opioid-dependent patients can be started out with much smaller doses (0.05 mg) repeated every 2-3 minutes until desired response is achieved. If no response is seen after administration of 10-15 mg, the diagnosis of opioid overdose should be reevaluated. A continuous infusion of naloxone may be preferred to frequent periodic dosing. The infusion may be started at 0.4-0.8 mg/hr (or 2/3 of the initial dose required to wake the patient given each hour) in NS or D5W and titrated to effect. Care must be taken to avoid precipitating withdrawal symptoms in the opiate dependent patient.

Patients should be monitored for QT interval prolongation. Situations of increased risk include a prior history of QT prolongation or structural heart disease, electrolyte abnormalities, presence of other QT-prolonging drugs, or drugs that may inhibit the metabolism of methadone.[8,12] Most cases of methadone-related QT prolongation and Torsade de pointes resolve with correction of electrolyte abnormalities, reduction of methadone dose, discontinuation of concomitant QT prolonging drugs, and/or discontinuation of methadone. Restoration of a normal QT interval may take a week.[5] Restarting methadone after discontinuation has resulted in recurrence of the QT prolongation.[14]

Hemodialysis is not indicated due to methadone's large volume of distribution and high protein binding. Although acidic urine has been shown to increase the clearance of methadone, the risks associated with acidifying the urine outweigh any benefit.

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References

1. Increase in poisoning deaths caused by non-illicit drugs—Utah, 1991-2003. *MMWR Morb Mortal Wkly Rep.* Jan 21 2005;54(2):33-36.
2. Thummel KE, Wilkinson GR. In vitro and in vivo drug interactions involving human CYP3A. *Annu Rev Pharmacol Toxicol* 1998;38:389-430.
3. White JM, Irvine RJ. Mechanisms of fatal opioid overdose. *Addiction* 1999;94(7):961-972.
4. Wolff K. Characterization of methadone overdose: clinical considerations and the scientific evidence. *Ther Drug Monit* 2002;24(4):457-470.
5. Krantz MJ, Garcia JA, Mehler PS. Effects of buprenorphine on cardiac repolarization in a patient with methadone-related torsade de pointes. *Pharmacotherapy*. Apr 2005;25(4):611-614.
6. Cruciani RA, Sekine R, Homel P, et al. Measurement of QTc in patients receiving chronic methadone therapy. *J Pain Symptom Manage* 2005;29(4):385-391.
7. Martell BA, Arnsten JH, Ray B, Gourevitch MN. The impact of methadone induction on cardiac conduction in opiate users. *Ann Intern Med* 2003;139(2):154-155.
8. Sticherling C, Schaer BA, Ammann P, Maeder M, Osswald S. Methadone-induced Torsade de pointes tachycardias. *Swiss Med Wkly* 2005;135(19-20):282-285.
9. Krantz MJ, Lewkowiez L, Hays H, Woodroffe MA, Robertson AD, Mehler PS. Torsade de pointes associated with very-high-dose methadone. *Ann Intern Med* 2002;137(6):501-504.
10. Gil M, Sala M, Anguera I, et al. QT prolongation and Torsades de Pointes in patients infected with human immunodeficiency virus and treated with methadone. *Am J Cardiol* 2003;92(8):995-997.
11. Piguet V, Desmeules J, Ehret G, Stoller R, Dayer P. QT interval prolongation in patients on methadone with concomitant drugs. *J Clin Psychopharmacol* 2004;24(4):446-448.
12. Walker PW, Klein D, Kasza L. High dose methadone and ventricular arrhythmias: a report of three cases. *Pain* 2003;103(3):321-324.
13. Hantson P, Vanbinst R, Wallemacq P. Accidental methadone overdose in an opiate-naive elderly patient. *Intensive Care Med* 2003;29(11):2105.
14. Decerf JA, Gressens B, Brohet C, Liolios A, Hantson P. Can methadone prolong the QT interval? *Intensive Care Med* 2004;30(8):1690-1691.

Meet the UPCC Staff

Su Bryner-Brown started as a specialist in poison information at the poison center in October of 2004. She has been a RN since 1985. She has worked in a variety of places, including St. Marks Hospital ED and UUMC ED. She started the first Sexual Assault Resource Team in the State of Utah, in 1993. This team moves the sexual assault victims from the ED's to a private clinic setting for examinations and interventions. She is interested in networking and building a stronger relationship with ED nurses. She enjoys needlework, sewing and writing science fiction with her son.

Announcing New Web URL

www.utahpoisoncontrol.org

We are pleased to introduce a new poison center website URL. This new URL allows clear communication of the poison center website. It will be easier for the public and your patients to remember. Note- our existing URL: http://uuhsc.utah.edu/poison will continue to work.

Information for Your Patients

As the holiday season approaches, the Utah Poison Control Center would like to inform you about certain holiday hazards. The holidays are full of celebrations, decorations, visitors, and food, all of which may create potential hazards to children and adults. We believe that awareness is the key to prevention!

Toxic Decorations

- Mistletoe and holly berries may be poisonous if swallowed.
- Lamp oils are colorful and attractive to children, but they are extremely toxic.
- Tinsel/icicles are non-toxic, but may cause airway or bowel obstruction. Old tinsel may contain lead.
- Glass ornaments are easily broken and can be swallowed and may cause lacerations.
- Fireplace color crystals are metallic chemicals that can cause burns.
- Poinsettia has a bad reputation, but it is NOT highly poisonous. It may cause varying degrees of irritation to the mouth and stomach.
- Bubble lights are filled with alcohol or other solvent. They can cause eye or skin irritation or nausea. Beware of broken glass if a child bites into a bulb.

Cough and Cold Season

- There is no such thing as childproof, only child-resistant. Keep all medicines locked up.
- When visiting grandparents, remember that they may not use child-resistant caps.
- Read labels carefully. Many cough and cold preparations include ibuprofen and acetaminophen. Double dosing can occur with similar ingredients.

Miscellaneous

- Pay special attention to toys with button batteries. These are easily swallowed or inhaled. If it leaks, it can cause severe burns.
- Garage items such as antifreeze, windshield washer fluid, and ice melts can cause serious problems. Keep them out of reach of children.
- Remember that even a small amount of alcohol can cause serious problems for small children.

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*CSPI denotes Certified Specialist in Poison Information.

Employment Opportunities

The UPCC has one open Specialist in Poison Information-Pharmacist position available. You can find out more about this position on our website at *www.utahpoisoncontrol.org/employment.*

New Web Resource

The Utah Poison Control Center is pleased to announce a new plant identification web resource. It consists of a searchable database with photographic images of the most common poisonous plants in Utah. This is an easy to use reference for the public to identify potential toxic plants in the home or outdoors. The specialists in poison information at the UPCC can direct callers to the website for more accurate plant identification. The web address is www.utahpoisoncontrol.org. Try it. We would appreciate your feedback. Send comments to poison@hsc.utah.edu.

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