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TOXICOLOGY TODAY

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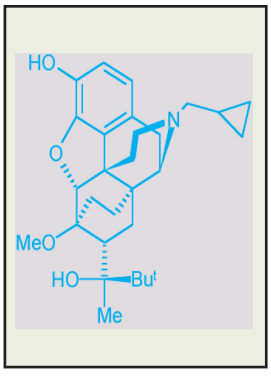
The University of Utah
Utah Poison Control Center

BUPRENORPHINE

by Elizabeth Stark, PharmD

Introduction

Buprenorphine is an opioid analgesic. It was approved by the United States Food and Drug Administration (FDA) in 1981 as a parenteral treatment for acute and chronic pain and as a supplement to anesthesia. In 2002, the FDA approved a sublingual form of buprenorphine for the treatment of opioid dependence, which is marketed alone (Subutex™) and in combination with naloxone (Suboxone™). (Table 1) The addition of naloxone, which has poor sublingual and oral absorption, decreases the abuse potential making it less desirable to abusers.



Buprenorphine photo courtesy of NAABT

Pharmacology

Buprenorphine is a derivative of thebaine, a morphine alkaloid. It is a partial agonist at the mu opioid receptor and a weak antagonist at the kappa opioid receptor. It has a higher affinity for the mu opioid receptor than antagonists (e.g., naloxone), therefore, making it difficult to displace by antagonists. Binding to the mu opioid receptor produces analgesia and also is responsible for respiratory depression, decreased gastrointestinal motility, and miosis. Binding to the kappa receptor produces some analgesia but also results in dysphoric effects including hallucinations. Opioids with mixed agonist/antagonist properties were developed with the hope they would have less respiratory depression and addiction potential than the pure agonists. They typically have similar analgesic and adverse effects.

As a partial agonist, the effects of buprenorphine plateau at higher doses. This may lead to less respiratory depression and a wider safety profile than full agonists such as morphine, heroin, and methadone. Low-dose buprenorphine has an analgesic potency 25-40 times that of similar does of morphine. With high-doses the maximal analgesic effect is limited because of a ceiling effect. Buprenorphine slowly dissociates from mu opioid receptors resulting in a long duration of action. Animal studies suggest that buprenorphine may have less physical dependence, and possibly fewer signs and symptoms of opioid withdrawal compared to full agonists.

Pharmacokinetics

The average bioavailability of buprenorphine by the oral route is only 10% but improves to 55% after sublingual administration. Peak plasma concentrations occur approximately 2 hours after administration. It is lipohilic and rapidly distributes to the brain. The half-life is approximately 42 hours for

(cont. on pg. 2)

IN THIS ISSUE

LAST HARD COPY ISSUE!

HURRY TO REGISTER FOR FUTURE ISSUES!

Utox Update/Toxicology Today is transitioning to an electronic format. This issue is the last issue to be printed and sent via US Postal Service. To continue to receive this newsletter, go to our website at **www.utahpoisoncontrol.org/newsletters** and register to receive the newsletter electronically via E-mail. Don't miss any exciting issues! If you have questions, need assistance registering or you don't have email, please feel free to call us at (801) 587-0600.

INFORMATION TO SHARE WITH YOUR PATIENTS

As the holiday season approaches, the Utah Poison Control Center wants to remind you about some of the hazards during the holidays. The holidays are full of celebrations, decorations, visitors, and food, all of which may create potential hazards to children and adults. Please take the opportunity to educate parents of young children about these potential hazards. 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. If swallowed, these oils can be easily aspirated.
- Tinsel/icicles are non-toxic, but may cause airway or bowel obstruction. Old tinsel may contain lead.
- Glass ornaments are easily broken and may cause lacerations if swallowed.
- Fireplace color crystals are metallic chemicals that are irritating and may cause burns if swallowed.
- Poinsettia, thought by some to be toxic, is a very safe plant. It may cause varying degrees of irritation to the mouth and stomach if a large amount is ingested.
- Bubble lights are filled with alcohol or other solvents. Beware of broken glass if a child bites into a bulb. Eye and skin irritation may result from contact with the chemical. Some contain methylene chloride which may be harmful if swallowed.

MEDICATIONS

- There is no such thing as a childproof lid. Medicine bottle lids are only child-resistant. Keep all medicines locked up.
- Be aware when you are hosting visitors, or visiting other homes, of potential hazards to small children including medications that may not be in child resistant containers.
- Read labels carefully. Many cough and cold preparations have similar ingredients and also include analgesics such as ibuprofen and acetaminophen. Using more than one product may result in unintended double dosing due to the same or similar ingredients in different products.

MISCELLANEOUS

- Pay special attention to toys with button batteries. They can be easily swallowed or inhaled and cause burns.
- In the garage, items such as antifreeze, windshield washer fluid, and ice melts pose a risk to children and pets. Keep them out of reach.
- Remember that even a small amount of alcohol can be toxic to small children. Empty all cups and glasses after guests leave.

(cont. from pg. 1)

Buprenorphine

buprenorphine and 57 hours for its active metabolite, norbuprenorphine. It is metabolized by the liver. While there are no stringent guidelines, the dose may need to be adjusted in patients with significant liver disease.

Drug interactions can occur with medications that induce or inhibit the cytochrome P-450 3A4 system. Drugs that induce 3A4 include erythromycin, ketoconazole, rifampin, carbamazepine, phenytoin, phenobarbital, and fluoxetine. Inhibitors include some of the HIV-1 protease inhibitors- ritonavir, indinavir, and saquinavir. Caution should be exercised when other sedative drugs are used in combination with buprenorphine.

Buprenorphine is currently considered Category C in pregnancy. Withdrawal symptoms may occur in newborns of opioid-dependent mothers on buprenorphine and may include tremor, agitation, myoclonus, and rarely apnea or bradycardia. In addition, formulations that contain naloxone have been associated with neonatal seizures, and should not be used. It passes into breast milk and breastfeeding is not advised.

Adverse Effects

The most common adverse events are headache, abdominal pain, nausea, vomiting, constipation, anxiety, insomnia, somnolence, depression, and sweating. Withdrawal symptoms are more mild than those seen with full agonists and may be delayed due to the slow dissociation of buprenorphine from the mu opioid receptor. Formulations of buprenorphine that contain naloxone are likely to produce intense withdrawal symptoms if they are misused parenterally by people dependent on full opioid agonists. Hypersensitivity to buprenorphine has been reported, although the incidence is unknown. Use caution when administering buprenorphine to the elderly, those with severe hepatic, renal, or respiratory depression; acute alcoholism or other CNS depressants, coma, and individuals heavily dependant on opioids.

Toxicity

Buprenorphine has a high safety margin. However, cases of overdose and death have been reported. Most cases involve crushed buprenorphine tablets administered intravenously, often with other drugs such as benzodiazepines or ethanol. Toxic effects of buprenorphine include mental status changes, small pupils, and respiratory depression. Although the ceiling effect on the mu opioid receptor should limit the respiratory depression, it has been reported with intravenous and sublingual forms. Patients with opioid dependence can develop a mild withdrawal syndrome with the use of buprenorphine. Most STAT toxicology screens do not detect buprenorphine.

Treatment

Naloxone can be used to reverse opioid effects, including respiratory depression, but standard doses of naloxone may not be sufficient. Naloxone doses of 5 to 10 mg may be needed to overcome the high affinity of buprenorphine for the mu opioid receptor. These high doses of naloxone are not likely to precipitate withdrawal symptoms in people who use buprenorphine alone, but may produce withdrawal in people who are using full agonists concomitantly. The effects of naloxone can be delayed for 30 to 60

(cont. on pg. 3)

ASPIRIN TOXICITY

by Casey Jowers, MD

Classic signs of acute salicylate toxicity include tinnitus, tachypnea, vertigo, nausea, and vomiting. Severe toxicity can present with altered mental status, hyperthermia, and non-cardiac pulmonary edema, in addition to the classic acid-base abnormalities of respiratory alkalosis and anion gap metabolic acidosis. Chronic toxicity often presents with insidious onset of vague complaints similar to the signs of acute ingestion, but much less dramatic. A high index of suspicion must be maintained as delayed diagnosis is common and has been associated with 25% mortality. In acute ingestion, plasma salicylate concentrations between 10 - 30 mg/dl are considered therapeutic and greater than 30 mg/dl are associated with toxicity. Make sure the units are correct (mg/dL, not mg/L) when interpreting the serum concentrations. Delayed GI absorption necessitates measuring salicylate concentrations every 2 to 4 hours until consecutive concentrations show a clear decrease from the peak measurement. Salicylate concentrations usually peak 6 hours post ingestion, however, peaks as late as 35 hours have been reported. Use of activated charcoal for early decontamination is beneficial in decreasing salicylate absorption. Repeated charcoal administration was of benefit in experimental volunteers. Alkalinization of the urine and plasma, utilizing intravenous sodium bicarbonate, to a blood pH 7.45 to 7.5 and a urine pH 7.5 to 8.0 facilitates the renal elimination through distal tubule ion trapping and prevents salicylate from entering the CNS. Hemodialysis should be considered in patients with renal failure, acute pulmonary edema, refractory acidosis or electrolyte imbalance, persistent CNS symptoms (i.e. coma, seizure) vital sign deterioration, acute salicylate concentration greater than 100 mg/dL, or liver failure with coagulopathy.

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Buprenorphine

minutes, and repeated doses may be necessary due to the long acting nature of buprenorphine. Nalmefene, another opioid antagonist, is not routinely recommended because its longer duration of action requires longer periods of observation for resedation. Signs and symptoms of toxicity can persist for longer than 12 hours owing to the long half-life of the parent drug and active metabolite. Patients with significant signs and symptoms of overdose should be admitted to the hospital for observation for 24 hours.

Conclusion

Buprenorphine is the only medication approved for office-based treatment of opioid dependence. Due to its ability to partially bind mu opioid receptors, respiratory depression is limited by a ceiling effect. In addition, when compared to full opioid agonists, buprenorphine has fewer withdrawal symptoms. Its unique pharmacology offers advantages over full opioid agonists used to treat opioid dependence, but also presents difficulties in treating acute poisonings. High doses of naloxone may be needed to reverse respiratory depression, and even then full reversal may not occur. Understanding buprenorphine's unique properties will become more important as its use to treat opioid dependence increases. Consult the Utah Poison Control Center for assistance in managing any poisoning emergency.

Table 1:
Available Formulations of Buprenorphine

Generic Name	Brand Name	Dosage Forms	Strength
Buprenorphine	Buprenex™	Injection	0.3 mg/ml
Buprenorphine	Subutex™	Sublingual	2 mg 8 mg
Buprenorphine/ Naloxone	Suboxone™	Sublingual	2mg/0.5mg 8mg/2mg

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MEET THE UPCC STAFF

MIKE DONNELLY

comes to the UPCC after 24 years at the University of Utah working as a Registered Nurse. His experiences there included medical/surgical nursing, SICU and trauma nursing, MICU, Certification in Critical Care Nursing, and nursing management. For the past 12 years, he was the manager of the Neuro Critical Care and 3 North Intermediate Care Units. A native of Salt Lake City, Mike grew up in the Brickyard area. He and his wife Marion have been married for 35 years, and have two grown daughters, Megan and Amy. Transitioning to the UPCC has been a great experience, despite the almost vertical learning curve. The opportunity to shift careers and do something this unique has been fascinating. Everyone at UPCC has made this experience less terrifying for someone who worked so long in a different patient care environment. Outside of work, Mike likes reading and collecting books, home improvement, great conversation, and traveling in the desert and mountains.

TOXINS IN THE NEWS

FDA ALERTS

- **Benzocaine spray** used in the mouth and throat can result in potentially dangerous levels of methemoglobin. Patients should be given the minimum amount required.
- There is an increased risk of overdose when venlafaxine is combined with alcohol or other medications. Fatal outcomes with **venlafaxine** may be higher than with SSRIs, but are lower than tricyclic antidepressants.
- Serotonin syndrome may occur when **triptans** (e.g sumatriptan) are used together with a **SSRI** (e.g. fluoxetine) or a **serotonin/norepinephrine reuptake inhibitors** (e.g. venlafaxine, duloxetine).
- Dietary supplements containing **ephedrine** alkaloids, regardless of the dosage, are considered adulterated and pose an unreasonable risk of illness or injury to users, especially those suffering from heart disease and high blood pressure.

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*CSPI denotes Certified Specialist in Poison Information.

THANK YOU

The Utah Poison Control Center expresses its sincere thanks to McNeil Consumer & Specialty Pharmaceuticals for their generous contribution that allows us to produce and distribute this newsletter.

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