

Special Interest Articles:

- High Dose Insulin-Euglycemia Therapy
- Naloxone Kits
- Aczone



Did you know?

In the October 2016 issue of *Pediatrics*, The American Academy of Pediatrics urged parents and health care providers to stop giving codeine to children. Codeine is converted to morphine in the liver and “ultra-rapid metabolizers” may experience severely slowed breathing rates or even die after standard doses of codeine.

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Calcium Channel Blocker Treatment with High Dose Insulin-Euglycemia Therapy in Overdose

Jessica Akin, Pharm. D. Candidate, 2017

Calcium channel blockers (CCBs) exert their therapeutic and toxic effects by the direct blockade of L-type calcium channels producing relaxation of the smooth muscle, with subsequent vasodilation and in the case of verapamil and diltiazem, inhibition of the sinoatrial (SA) and atrioventricular (AV) nodes. Calcium channel blockade provokes the heart to switch into carbohydrate metabolism as opposed to the free fatty acid oxidation that occurs in the myocardium in a non-stressed state. Calcium channel antagonism can also result in blockade of L-type Ca^{2+} channels located in the pancreas, inhibiting insulin secretion thus producing hyperglycemia. The most common and life-threatening finding in an acute CCB poisoning is hypotension, typically caused by a combination of bradycardia, decreased inotropy, and peripheral vasodilation. Patients can also present asymptomatic and subsequently worsen rapidly to severe cardiogenic shock.

High-dose insulin-euglycemia therapy, along with glucose supplementation, has emerged as an effective treatment for calcium channel-blocker poisoning. Initial treatment is primarily supportive care including saline fluid resuscitation, which is essential to correct vasodilation and low cardiac filling pressures. Conventional therapies such as atropine, calcium, and glucagon may fail to improve the hemodynamic status in severely poisoned patients. The increased myocardial oxygen demand that results from vasopressors and catecholamines may be harmful in the setting of hypotension and decreased coronary perfusion.

There are three main mechanisms of benefit for high-dose insulin-euglycemia therapy: increased inotropy, improved local microcirculation, and increased intracellular glucose and transport. The primary goal of this therapy is to restore hemodynamic stability. The major adverse effects associated with high-dose insulin therapy are hypoglycemia and hypokalemia. Glucose concentrations should be regularly monitored and it is likely that supplementation of glucose will be required throughout therapy and for up to 24 hours after discontinuation of high-dose insulin. There is a shift of potassium from the extracellular to intracellular space rather than a decrease in total body stores, which causes a change in serum potassium concentrations.

There are no official guidelines regarding the insulin dosing in CCB overdose, however one of the most common recommendations consists of a 1 unit/kg bolus dose followed by a continuous infusion at 0.5-1 unit/kg per hour which can be titrated to response. Insulin doses up to 10 units/kg per hour have been recommended. A healthcare professional may want to consult with their local Poison Center at 1-800-222-1222. A continuous dextrose infusion (0.5 g/kg/hour) is also a common recommendation for initiation. Blood glucose should be checked every twenty minutes during first hour, then can be checked hourly. The onset of high-dose insulin-euglycemia therapy is around 15-60 minutes, but can be delayed for several hours. High-dose insulin therapy should be continued until hemodynamic stability is achieved.

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Naloxone Kits Available in Retail Pharmacies for the General Population Jordan Loper, Pharm. D. Candidate, 2017

Naloxone is a pure opioid antagonist that competes with and displaces opioids at opioid receptor sites. It is used for the emergency treatment of known or suspected opioid overdose, manifested by respiratory or CNS depression. Recently, there has been a push to make naloxone kits available in retail pharmacies for the general population to purchase and have on hand in the event of an opioid overdose. In recent years, heroin and fentanyl overdoses have been on the rise throughout the country. In Jefferson County, there were 46 heroin deaths and 34 fentanyl deaths between January 1 and June 30, 2016. Walgreens Pharmacy plans to make naloxone available without a prescription in 35 states by the end of the year, including Alabama. CVS Pharmacy made naloxone available in 14 states. Some smaller chains and independent pharmacies also provide naloxone without a written prescription, based on their state's protocol.

Each state has the authority to pass laws about whether to sell naloxone without a written prescription from a physician. The sale of naloxone is available through either the state's collaborative practice agreement or through a standing order with a local physician. In Alabama specifically, recent laws have been passed that remove criminal and civil liability for physicians, dentists, pharmacists, and nurses who administer or dispense naloxone. Furthermore, a layperson is also immune to liability when they administer naloxone.

The standing order in Alabama states that naloxone can be sold without a prescription to patients who are at risk of an opioid overdose, friends and family members of someone with an

opioid addiction, and law enforcement or fire department personnel. It is especially important to counsel patients who are purchasing naloxone on the proper administration of naloxone, as well as the opioid toxidrome that would signal that someone has potentially overdosed. The opioid toxidrome consists of CNS depression, respiratory depression, miosis, bradycardia, hypotension and hypothermia. Furthermore, naloxone has a very short duration of action (30-120 minutes depending on route of administration), so it is important that people know that in situations when naloxone is warranted, they still need to immediately seek medical treatment in a healthcare facility. If they do not seek medical attention, the naloxone will wear off and the person could rapidly develop life-threatening respiratory depression.

There are two new FDA approved naloxone products that are currently available, Narcan® nasal spray (4mg/0.1mL) and an auto-injector called Evzio® (0.4mg/0.4mL). In October 2016, a new strength of Evzio was approved by the FDA, 2mg/0.4mL, but it will not be available until early 2017. The difference in the concentrations of naloxone is due to differences in bioavailability among the different routes of administration. The bioavailability of a drug delivered via the nares will be less than that delivered intramuscularly or intravenously, therefore, a larger dose is required. Narcan nasal spray has an onset of action of about 8-13 minutes, while Evzio begins to work in 2-5 minutes. In recent years, the price of naloxone products has increased exponentially due to increased demand. At CVS, the cost of the injectable form is around \$45, while the nasal spray sells for \$90.

“In Alabama specifically, recent laws have been passed that remove criminal and civil liability for physicians, dentists, pharmacists, and nurses who administer or dispense naloxone.”

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Under the standing order in Alabama, pharmacists may dispense naloxone in a retail pharmacy via the following process. The requestor of naloxone must complete a form stating the factual basis for why they need the naloxone and sign the form stating that they have been counseled. The pharmacist must provide basic instructions on how to recognize an opioid overdose and administer naloxone. The pharmacist must also explain that once an opioid overdose has occurred the responder should call 911, begin rescue breathing, and administer

naloxone. These records must be kept by the pharmacy. The standing order for naloxone will expire each year, but can be renewed until it is approved as an over-the-counter medication. An example of the standing order for Alabama can be found at the following website:

<http://c.ymcdn.com/sites/www.aparx.org/resource/resmgr/Docs/NaloxoneStandingOrder.pdf>

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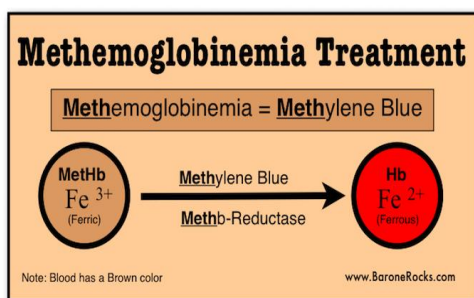


Aczone Gel 7.5%- Topical Treatment for Acne Vulgaris

Aczone® (dapson) is a topical antibiotic gel approved for the treatment of acne vulgaris in people 12 years and older. Oral dapsone has been available for over 70 years and has been used to treat leprosy and other skin conditions. Oral dapsone can cause hemolytic anemia and peripheral neuropathy. The primary toxic effects are due to its P-450 metabolites. Dapsone metabolites oxidize the ferrous iron hemoglobin complex to the ferric state, resulting in methemoglobinemia. These metabolites can sulfate the pyrrole hemoglobin ring in an irreversible reaction, resulting in sulfhemoglobinemia. Finally, oxidative stress with depletion of glutathione may contribute to hemolysis. When the drug was approved, it was thought that the topical form wasn't associated with these toxicities because very little of the drug is absorbed systemically. The systemic exposure from Aczone Gel, 7.5% is expected to be about 1% of that from a 100 mg oral dose. Topical formulation was approved in the US based on two randomized, vehicle-controlled studies. The studies demonstrated that the concentrations of dapsone and N-acetyl dapsone remain low and do not accumulate over time once steady state is reached. Since Aczone's approval, cases of methemoglobinemia, with resultant hospitalization, have been reported postmarketing in association with twice daily dapsone gel, 5%, treatment. In one case reported in March 2014, a 19-year-old female

presented with blue lips and fingers to the emergency department. She was treated with a single 100-mg dose of intravenous methylene blue and within 30 minutes, the cyanosis and symptoms had completely resolved.

In February 2016, the FDA approved 7.5% gel for a once- a-day application and discontinued the Aczone 5% twice-a-day application. In the drug's prescribing information, it states, *Patients with glucose-6-phosphate dehydrogenase deficiency or congenital or idiopathic methemoglobinemia are more susceptible to drug-induced methemoglobinemia. Avoid use of Aczone Gel, 7.5% in those patients with congenital or idiopathic methemoglobinemia. Signs and symptoms of methemoglobinemia may be delayed some hours after exposure. Initial signs and symptoms of methemoglobinemia are characterized by a slate grey cyanosis seen in e.g., buccal mucous membranes, lips, and nail beds. Concomitant use of Aczone Gel, 7.5% with drugs that induce methemoglobinemia such as sulfonamides, acetaminophen, acetanilide, aniline dyes, benzocaine, chloroquine, dapsone, naphthalene, nitrates and nitrites, nitrofurantoin, nitroglycerin, nitroprusside, pamaquine, para- aminosalicylic acid, phenacetin, phenobarbital, phenytoin, primaquine, and quinine may increase the risk for developing methemoglobinemia.*



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