Emergent Therapies in Toxicology: High Dose Insulin and Lipid Rescue

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Introduction
Poisoning and overdoses involving calcium-channel blocker (CCB), beta-blocker (BB), and tricyclic antidepressants (TCA) poisonings are associated with significant morbidity and mortality and may be refractory to standard treatment. In this article, we review two new therapies, high dose insulin euglycemia therapy (HIE) and lipid rescue, for use when standard treatments fail.

High Dose Insulin Euglycemia Therapy (HIE)

Toxicity of Calcium Channel Blockers and Beta-Blockers
Overdoses of calcium channel blockers (CCB) and beta-blockers (BB) may produce hypotension and bradycardia, and in severe overdoses, conduction disturbances and cardiovascular shock. Calcium channel blockers hinder the ability of calcium to enter cells by antagonizing voltage-sensitive calcium channels. This effect is seen most prominently in the myocardial cells but also in the β-cells of the pancreas and smooth muscle resulting in impaired myocardial conduction and contractility and hyperglycemia. Beta blocker toxicity is similar to CCB toxicity but without hyperglycemia. Propranolol exerts additional toxicity through sodium channel blockade, and it and other lipophilic beta-blockers may produce seizures and more pronounced CNS depression.

Mechanism of Action of High Dose Insulin Euglycemia Therapy
Insulin likely provides benefit by enhancing glucose uptake in the myocardium. While under normal circumstances, the heart uses fatty acid oxidation to meet its energy requirements; under stressed conditions, the heart prefers glucose. Insulin increases inotropy and promotes vasodilation, which may restore cardiac output and improve critical organ perfusion. This mechanism only occurs at supratherapeutic insulin doses.

Treatment and Dosing Recommendations
High dose insulin euglycemia therapy (HIE) is an off-label use often initiated in conjunction with or after traditional treatments such as fluid resuscitation, atropine, glucagon, and vasopressors. The UPCC recommends HIE along with traditional supportive measures in patients with evidence of depressed myocardial activity. There are currently no standard dosing recommendations, but doses of regular insulin range from 0.1 units/kg/hr IV to 0.3 units/kg/hr IV. The UPCC recommends a bolus of 1 unit/kg regular insulin followed by an infusion of 0.5 units/kg/hour. Reassess patient’s cardiac function in 15-30 minutes and increase infusion to 1-2 units/kg/hour if no improvement in 30 minutes. Dextrose should be infused to maintain a blood glucose of 100-200 mg/dL. Contact the UPCC to receive a copy of our Fast Fax for help in managing a specific patient.

See Appendix: Table 1 Safety/Adverse Effects
Hypoglycemia may occur; however HIE therapy is generally well tolerated. One case review reported hypoglycemic events in five of twelve patients receiving HIE. In another case series of seven patients who received HIE, no patients experienced hypoglycemia. Insulin therapeutic errors with minimal hypoglycemic events occurred in three case reports. Engebretsen et al described one episode of hypoglycemia (57 mg/dL) in a patient inadvertently given insulin 16.7 units/kg/h. No hypoglycemic events were reported by Place et al or Stellpflug et al; however, large dextrose requirements (485 grams over 36 hours) were needed to maintain euglycemia. Hypokalemia may also occur as insulin shifts potassium (cont. on pg. 3)
**What Do We Know About e-Cigarettes?**

E-cigarettes are devices that are designed to deliver nicotine or other substances in vapor form. They essentially consist of 2 pieces: 1) rechargeable heating element and 2) replaceable cartridge. The safety and efficacy of e-cigarettes have not been fully studied at this time.

The FDA has conducted some limited studies on a sampling of these products. Significant quality control issues were found. Some labeled as having no nicotine contained nicotine and several with the same label emitted markedly different amounts of nicotine.

The lack of studies raises the following concerns:
- How much nicotine or other chemicals are being inhaled during use?
- What are the potential risks of using e-cigarettes?
- Are there any benefits associated with these products?

There are too many unknowns at this time to understand the safety and potential value of these products.

As e-cigarettes have grown in popularity, the Utah Poison Control Center has seen a rapid rise in pediatric poisoning exposures to these products. From 2012 to 2013, pediatric poisoning exposures to e-cigarettes had increased 350%, while poisoning exposures to regular cigarettes increased 35%. Symptoms from poisoning can include drooling, vomiting, agitation, cardiac arrhythmia, and convulsions.

Many products come in a variety of candy flavorings, making them appealing to children. Even a small amount of liquid in a spent cartridge can cause toxicity in a child. If these products are used around children, it is important to keep all parts out of reach.

**Antidotes for Methotrexate Toxicity**

by Thomas G. Martin, MD, MPH

Medical Director & Paul Hinckley, PharmD 2014 Candidate

Methotrexate poisonings are uncommon but may be quite serious or even lethal. Methotrexate (MTX) works by reversibly inhibiting dihydrofolate reductase and causing cell death by preventing DNA and RNA synthesis. Leucovorin is a reduced derivative of folic acid that is biologically active and supplies the necessary tetrahydrofolate co-factor for DNA and RNA synthesis that is blocked by MTX. Leucovorin and levoeleucovorin (Fusilev®, L-isomer) are used as rescue therapy with high dose MTX chemotherapy to prevent toxicity and spare non-cancerous cells from MTX’s toxic effects. Leucovorin, levoeleucovorin and glucarpidase (Voraxaze®) are also antidotes for methotrexate (MTX) toxicity.

When used as a rescue agent, leucovorin is administered 24 hours after treatment with high dose MTX to save healthy cells without reducing the antitumor activity of MTX. In the case of a MTX overdose, leucovorin is administered as soon as possible. For the treatment of an acute MTX overdose, 1 mg of leucovorin is given for every mg of MTX, every 6 hours, until the serum MTX concentration is < 0.01 µmol/L in those not on MTX and < 0.05 – 0.1 µmol/L in those on MTX for chemotherapy. Because of the calcium content of the preparation, the infusion rate in adults should not exceed 160 mg/minutes. Higher doses of leucovorin may be warranted if the patients renal function is poor or worsening or serum levels of MTX are not declining. Levoeleucovorin is an alternative to leucovorin. The dose is ½ the dose of leucovorin. Leucovorin should not be given intrathecally. One death has been reported in a child after intrathecal injection.

**Glucarpidase (Voraxaze®)**

Glucarpidase is indicated for the treatment of patients who develop toxic MTX concentrations (>1 µmol/L) due to impaired renal clearance. Glucarpidase is a recombinant enzyme (carboxypeptidase G2) that is cloned from *Pseudomonas*. Glucarpidase lowers MTX concentrations by rapidly hydrolyzing extracellular MTX into inactive metabolites (DAMPA and glutamate). This allows for non-hepatic metabolism and extra renal clearance of MTX. Glucarpidase has been available under compassionate use since 1993 and gained FDA approval in January 2012.

Glucarpidase decreases serum MTX concentrations within 15 minutes of infusion, thus reducing organ toxicity. Leucovorin rescue is indicated with glucarpidase, however it should not be given within 2 hours of the glucarpidase infusion (before or after) as it is a substrate of glucarpidase. The dose is 50 U/kg infused intravenously over 5 minutes. Glucarpidase has also been used as an antidote for an inadvertent intrathecal MTX (IT) overdose at a dose of 2000 units IT, as soon as possible. The acquisition cost of glucarpidase is $26,775 per 1000-unit vial.

**Outreach Education**

**Antidotes for Methotrexate Toxicity**

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**References**

2. Inc. RI. Glucarpidase (Voraxaze) Full Prescribing Information. BTG International Inc.; 2013:11.
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intracellularly. In one case report, two patients treated with HIE had potassium concentrations < 3.5 mEq/mL, and in another report, eight patients had potassium concentrations < 3.0 mEq/mL. No significant arrhythmias were recorded in either case series.

Lipid Rescue

Lipophilic Drug Toxicity

Lipid emulsion is used as a component of total parenteral nutrition and for the prevention and treatment of essential fatty acid deficiency (EFAD). Lipid rescue is used off-label in the treatment of local anesthetic-induced cardiac toxicity and for lipophilic drug overdose, unresponsive to conventional resuscitation. Lipid rescue first proved useful in reversing systemic toxicity associated with bupivacaine in animal studies and eventually in humans. A number of case reports have documented the benefit of lipid rescue in the treatment of calcium channel blocker beta blocker, tricyclic antidepressant and other lipophilic drug poisonings. Intralipid® 20% is the concentration most commonly used for treating acute toxicities in the US.

Mechanism of Action of Lipid Rescue

Lipid emulsions form a lipid partition in the serum and likely act as a “lipid sink.” It is thought that lipophilic drugs are extracted from the plasma and tissues into the lipid sink, thereby reducing toxicity by decreasing the concentration of drug at the active site.

Lipid rescue may also improve myocardial fatty acid oxidation by increasing fatty acid uptake by the mitochondria and improving ATP synthesis. Lipid rescue may also stabilize the myocardial membrane and increase ionotropy by promoting calcium entry via voltage-dependent calcium channels.

TOXINS IN THE NEWS

FDA regulates dietary supplement products as well as supplement ingredients. FDA is responsible for taking action against any dietary supplement found to be unsafe. Last year FDA initiated several recalls involving supplements and provided safety alerts on many others. The most serious recalls involved the following products:

- Maxiloss Weight Advanced Softgels, PerfectBody Solutions, and Burn 7: FDA testing found these products contain sibutramine. Sibutramine is a serotonin-norepinephrine reuptake inhibitor approved in 1997 for management of obesity and removed from the market in 2010 for safety reasons.
- Oxy Elite Pro, Jack3D, and VERSA-1 (any supplement containing dimethylamylamine (DMAA)): DMAA is an amphetamine derivative most commonly found in supplements promising weight loss, muscle building, and performance enhancement. It is quite dangerous and has been associated with a variety of cardiovascular problems: shortness of breath, tightening of the chest, and even heart attack in young persons. Given the known biological activity of DMAA, the ingredient may be particularly dangerous when used with caffeine. Other synonyms for DMAA include methylhexanamine, 1,3-DMAA, 1,3-dimethylamylamine, 1,3-dimethylpentylamine, amino-4-methylhexane, 2-hexanamine, 4-methyl-2-hexanamine, 4-methyl-2-hexylamine, 4-methyl-(9CI), dimethylamylamine, geranamine, methylhexanamine, methylhexenamine, pelargonium graveolens extract, and geranium extract. Oxy Elite Pro and VERSA-1 replaced their products with aegeline, which is not an FDA approved ingredient and has been associated with serious liver damage. Users are urged to discard any remaining products containing DMAA.

FDA is unable to test and identify all products marketed as dietary supplements that have potentially harmful ingredients. Consumers are cautioned to check with their health care provider before starting any new supplement. If someone experiences negative side effects from a supplement they should check with their health care provider or call the poison control center at 1-800-222-1222.

Check out this FDA fact sheet for more information about dietary supplements.

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www.utahpoisoncontrol.org

Treatment and Dosing Recommendations

Supporting literature and clinical experience have led to guidelines for the use of lipid rescue in poisoning emergencies unre sponsive to conventional resuscitation. Use of lipid rescue therapy should not replace standard ACLS procedures. The American College of Medical Toxicology’s (ACMT) guideline is a modification of previously published guidelines and recommends lipid rescue in patients with serious hemodynamic instability, with or without cardiac arrest, from a drug with a high degree of lipid solubility. A large volume of distribution and positive partition constant (log P) predict higher lipid extraction efficiency. ACMT recommends an initial bolus of Intralipid® 20% 1.5 mL/kg IV over 2-3 minutes, followed by 0.25 mL/kg/min IV for maintenance.

Safety/Adverse Effects

Lipid rescue is generally well tolerated. The most common adverse events include pancreatitis (increased amylase levels, increased lipase levels) and interferences with a variety of laboratory tests due to lipemia. A rare case of bronchospasm has been reported. Intralipid® 20% is contraindicated if a patient has hyperlipidemia, any disturbance of normal fat metabolism, acute pancreatitis, or severe allergies to eggs.
Emergent Therapies


Table 1: Insulin Doses Used in Case Reports/Reviews

<table>
<thead>
<tr>
<th>Reference (Year)</th>
<th>Age (Yr)</th>
<th>CCB/BB Ingested</th>
<th>Highest Insulin Dose Used</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Boyer et al (2001)</td>
<td>34</td>
<td>amlodipine</td>
<td>0.5 units/kg/h</td>
<td>Survived</td>
</tr>
<tr>
<td></td>
<td>48</td>
<td>diltiazem ER</td>
<td>0.5 units/kg/h</td>
<td>Survived</td>
</tr>
<tr>
<td>Engebretsen (2008)</td>
<td>32</td>
<td>amlodipine&lt;sup&gt;a&lt;/sup&gt; metoprolol</td>
<td>16.7 units/kg/h&lt;sup&gt;c&lt;/sup&gt;</td>
<td>Survived</td>
</tr>
<tr>
<td>Herbert et al (2001)</td>
<td>58</td>
<td>verapamil</td>
<td>Unknown</td>
<td>Died</td>
</tr>
<tr>
<td>Marques et al (2003)</td>
<td>75</td>
<td>diltiazem&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.5 units/kg/h</td>
<td>Survived</td>
</tr>
<tr>
<td>Meyer et al (2003)</td>
<td>13</td>
<td>verapamil SR</td>
<td>0.1 units/kg/h</td>
<td>Survived</td>
</tr>
<tr>
<td>Morris-Kukoski et al (2000)</td>
<td>5 mo</td>
<td>nifedipine</td>
<td>1 unit/kg/h</td>
<td>Survived</td>
</tr>
<tr>
<td>Place et al (2000)</td>
<td>49</td>
<td>verapamil SR</td>
<td>10 unit/kg bolus&lt;sup&gt;c&lt;/sup&gt;</td>
<td>Survived</td>
</tr>
<tr>
<td>Rasmussen et al (2003)</td>
<td>36</td>
<td>amlodipine&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.4 units/kg bolus</td>
<td>Survived</td>
</tr>
<tr>
<td>Stellpflug et al (2010)</td>
<td>48</td>
<td>nebivolol&lt;sup&gt;c&lt;/sup&gt;</td>
<td>21.8 units/kg/h&lt;sup&gt;c&lt;/sup&gt;</td>
<td>Survived</td>
</tr>
<tr>
<td>Stellpflug et al (2010)</td>
<td>30</td>
<td>amlodipine metoprolol</td>
<td>10 units/kg/h</td>
<td>Survived</td>
</tr>
<tr>
<td>Yuan et al (1999)</td>
<td>37</td>
<td>amlodipine&lt;sup&gt;b&lt;/sup&gt; atenolol</td>
<td>0.5 units/kg/h</td>
<td>Survived</td>
</tr>
<tr>
<td></td>
<td>14</td>
<td>verapamil SR</td>
<td>0.5 units/kg/h</td>
<td>Survived</td>
</tr>
<tr>
<td></td>
<td>31</td>
<td>verapamil SR</td>
<td>0.1 units/kg/h</td>
<td>Survived</td>
</tr>
<tr>
<td></td>
<td>36</td>
<td>verapamil SR</td>
<td>0.3 units/kg/h</td>
<td>Survived</td>
</tr>
<tr>
<td></td>
<td>50</td>
<td>verapamil SR&lt;sup&gt;c&lt;/sup&gt;</td>
<td>1 unit/kg/h</td>
<td>Survived</td>
</tr>
</tbody>
</table>

<sup>a</sup> Table adapted from Shepherd et al.<sup>1</sup>; <sup>b</sup> Co-ingestants in addition to CCB or BB; <sup>c</sup> Therapeutic error

Table 2. Lipid Rescue Adverse Events

<table>
<thead>
<tr>
<th>Reference</th>
<th>Intoxicant</th>
<th>Total Dose of Intralipid®</th>
<th>Adverse Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cave et al&lt;sup&gt;12&lt;/sup&gt;</td>
<td>ropivicaine</td>
<td>300 mL</td>
<td>Bronchospasm</td>
</tr>
<tr>
<td></td>
<td>olanzapine, ethanol, lithium</td>
<td>1000 mL</td>
<td>Elevated amylase levels</td>
</tr>
<tr>
<td></td>
<td>propranolol, methocarbamol</td>
<td>1000 mL</td>
<td>Laboratory interference</td>
</tr>
<tr>
<td>Levine et al&lt;sup&gt;14&lt;/sup&gt;</td>
<td>amitriptyline</td>
<td>1.5 mg/kg x 2 0.25 mg/kg/min x 30 min</td>
<td>Elevated lipase, possible pancreatitis, laboratory interference</td>
</tr>
<tr>
<td>West et al&lt;sup&gt;14&lt;/sup&gt;</td>
<td>amlodipine</td>
<td>2000 mL</td>
<td>Laboratory interference</td>
</tr>
<tr>
<td>Bucklin et al&lt;sup&gt;11&lt;/sup&gt;</td>
<td>bupropion</td>
<td>4000 mL</td>
<td>Elevated lipase and amylase, possible pancreatitis, laboratory interference</td>
</tr>
</tbody>
</table>

ALERTS

After an FDA warning to the public not to use it, Pro ArthMax, a dietary supplement for joint, muscle and arthritic pain has been withdrawn from market. It contains undeclared active NSAIDS, which can cause adverse effects or allergic reactions in sensitive individuals.

The following OTC male sexual enhancement products: Boost Ultra, XZone Gold, Sexy Monkey, Triple Miracle Zen Platinum, Magic for Men, “New” Extenze, and New XZen Platinum have been voluntarily recalled. These products were found to contain undeclared sildenafil and/or tadalafil, which may interact with nitrates and may lower blood pressure to dangerous levels.

NATIONAL POISON PREVENTION WEEK

MARCH 16-22, 2014

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National Poison Prevention Week was held March 16-22nd 2014. Awareness of the poison problem and poison prevention messages were promoted throughout the state. Over 88,000 education materials were sent out in conjunction with this event and hundreds of people were reached via presentations, health fairs, radio and TV interviews, and newspaper articles during the month of March.

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Utah Poison Control Center