Resident Journal Review

Development in Clinical Toxicology: Use of Intralipid Emulsion and High-Dose Insulin Therapy

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Introduction

There are few antidotes in clinical toxicology, especially with regards to some of the most commonly used medications including calcium channel blockers, beta-blockers, and peripheral anesthetics. Morbidity and mortality rates are high and supportive care is often ineffective. Intralipid and high-dose insulin therapy are two exciting developments in clinical toxicology. This review of the literature explores the evidence behind these new treatment options for beta-blocker and calcium channel blocker toxicity, as well as anesthetic overdoses.


Beta-blocker and calcium channel blockers are common medications that can result in both intentional, and unintentional, overdoses. The high morbidity and mortality associated with these overdoses is largely secondary to cardiovascular toxicity. Recent data suggests that early use of high dose insulin (HDI) may be an effective treatment strategy for beta-blocker and calcium channel blocker poisonings.

Historically, initial treatment for poisonings included gastric decontamination along with crystalloid fluids in an attempt to counteract hypotension, bradycardia, and cardiogenic shock. Glucagon is often recommended as an antidote to beta-blocker toxicity due to its inotropic effect. It can also; however, cause vomiting and with it a risk of aspiration. Pressor support, while increasing blood pressure, also increases myocardial demand in the setting of cardiogenic shock. Calcium supplementation only has variable efficacy, especially in severe intoxications. Finally, atropine can reverse bradycardia, but is a short-lived option.

Insulin has three main effects as an antidote to beta-blocker and calcium channel blocker toxicity. First, insulin causes vasodilation at the pre-capillary and capillary bed level, thereby decreasing systemic resistance and increasing cardiac output. Second, insulin enhances the intracellular transport of glucose, which is particularly beneficial to a stressed myocardium. And lastly, high concentrations of insulin increase coronary blood flow and inotropy without increasing cardiac oxygen demand (unlike pressors).

This particular review collated data from an online search for relevant articles from 1975-2010. In addition, they manually searched for relevant abstracts in Clinical Toxicology from 1996-2010. Seventy-two relevant articles were considered, none of which were clinical trials.

Several experimental studies that have demonstrated favorable outcomes with high dose insulin therapy were included. Kline et al., used dog models with verapamil poisoning. Dogs were treated with either saline, epinephrine, glucagon, calcium chloride, or high dose insulin. Survival rates were 0/6, 4/6, 3/6, 3/6, and 6/6, respectively. Krukenkamp et al., also used a canine model treating propranolol toxicity with insulin. The study showed insulin reversed myocardial depression to 80 +/-2% of baseline cardiac function. Kerns et al., compared insulin, glucagon, and epinephrine for propranolol poisoning in dogs over 240 minutes. Overall survival rates were 6/6, 4/6, and 1/6, which were significantly higher in the insulin treatment. Holger et al., compared high dose insulin to vasopressin and epinephrine. In this study, insulin decreased SVR while increasing cardiac output. Interestingly, vasopressin together with epinephrine increased MAP and SVR initially, followed by steady decline until death. Five of five insulin dogs survived while 0/5 of pressor dogs survived leading to early study termination. Multiple studies have demonstrated that pressors either have no effect or an antagonistic effect on clinic outcomes when used with insulin therapy for beta-blocker and calcium-channel-blockers intoxications.

The clinical protocol proposed in this review is dependent on an initial normal saline infusion. Prior to infusing insulin, serum glucose should be measured and supplemented if less than 200. Most clinicians recommend giving a 1U/Kg insulin bolus followed by a .5-1U/Kg/hour infusion. The infusion rate can be increased by 2U/Kg/hour every 10 minutes to a maximum of 10U/Kg/hour while monitoring for clinical improvement. This should be initiated early in therapy for the greatest results, not as salvage after other failed interventions. Patients should be monitored by clinical parameters of perfusion (skin color, warmth, urine output, mental status, and peripheral pulses). Since insulin increases capillary perfusion, effects may manifest beyond solely an increase in MAP or SBP.

Insulin is inexpensive and relatively easy to manage. Common adverse effects from high dose insulin therapy are hypoglycemia and electrolyte disturbances, mainly hypokalemia. In all reviewed case reports, no long-term sequelae from these aforementioned effects were documented. Dextrose infusion should be used to prevent hypoglycemia. Glucose should be checked every 10 minutes, and then every 30-60 minutes once stable. Potassium levels should initially be monitored hourly, and then every 6 hours once stable. Potassium supplementation is recommended for levels below 2.8-3.0. Magnesium and phosphorous should also be repleted as necessary. At this time, there are no recommendations on how to taper or stop insulin therapy once cardiac function has rebounded.

This study has a number of limitations. As evidenced by the fact that the authors were unable to identify any clinical trials using HDI for beta-blocker or calcium channel blocker toxicity, there is a need for higher quality research in this area in humans rather than animals. The authors

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also do not specify the inclusion or exclusion criteria they used, likely
due to overall lack of quality studies.

Despite the limited evidence, the use of HDI for beta-blocker and calci-
um channel blocker poisoning demonstrates promising results in animal
studies and case reports, and may represent a favorable alternative to
conventional therapies.

Greene S, Gawarammana I, Wood DM, Jones Al, Dargan Pi. Relative

This study was a prospective observational study to assess adverse
reactions associated with hyperinsulinemia/euglycaemia (HIET) in cal-
umium channel blocker (CCB) poisoning. CCB poisoning has significant
vascular toxicity. As mentioned previously, there are case reports
and animal studies that suggest HIET may be an effective treatment for
these ingestions, but human experimental trials are limited. Researchers
note that clinicians may fear instituting HIET for fear of unknown clinical
safety.

In this study, researchers prospectively collected data from seven
patients considered to have severe CCB toxicity (SBP <90mmHg and
requiring ICU) that were treated with HIET, as advised by the poisons
center in the South of England from 2004-2006. Patients were also
treated conventionally with IV fluids, inotropes, calcium, and glucagon.
Glucose and potassium levels were monitored every 30 minutes, and
then every one to two hours once stable. Supplemental IV potassium
was administered to keep patients in low-normal range. Fifty percent
dextrose was administered as needed, along with 5% or 10% IV dex-
trose infusions. Three of the seven patients were loaded with 1unit/kg
of an IV short acting insulin bolus. All were given maintenance insulin
infusions of 0.5 units/kg/hour, titrated to a maximum of 2 units/kg/hour
to maintain a SBP >100mmHg. All three patients that received the initial
bolus experienced a significant sustained rise in BP>10mmHg within the
first 60 minutes of HIET. HIET was given within seven hours of presen-
tation and less that 12 hours from time of ingestion in the three bolus
patients, but administration was delayed for some of those who did not
receive an initial bolus. One patient died. Of note, there were no clini-
cally significant episodes of hypokalemia, arrhythmias, or hypoglycemia
recorded.

There were many limitations to this study including: small sample size,
lack of randomization, and limited patient demographic data. Also,
each patient ingested different medications (i.e., verapamil, diltiazem,
alpha blockers) and then were given various amounts of other standard
treatments (i.e., Ca, glucagon, various inotropes). It is apparent that
this study cannot be used to evaluate the overall efficacy of HIET, but it
is interesting to note that there were no adverse effects from hypokale-
mia or hypoglycemia. However, HIET poses serious potential risks and
should only be administered in an ICU setting with close monitoring.
Incidentally, researchers comment that the three patients who received
the initial insulin bolus were documented to have had a more significant

elevation of BP. They note that HIET failures in previous cases were
related to late administration of insulin and argue that the maximal CCB-
induced systemic insulin resistance occurs within the first 24 hours of
ingestion. They therefore argue that HIET should be administered imme-
diately (after glucose and potassium monitoring). More studies looking
at efficacy and clinical outcomes with systematic design need to be per-
formed to guide indications, dosing protocols, and special circumstances
for the use of HIET in CCB toxicity.


This is a review article of current evidence supporting the use of intrave-
nous lipid emulsion (IVLE) as an antidote to local anesthetic (LA) toxicity.
To date, literature on this topic is limited to animal studies and human
case reports. However, this is a promising treatment option for cardiac
arrest secondary to local anesthetic toxicity, which tend to be resistant to
standard resuscitation protocols such as ACLS.

Local anesthetics are thought to function by reversibly binding sodium
canals. They also deplete ATP by inhibiting complete oxidation of
fatty acids. Peripheral nerve blocks have a relatively high frequency of
systemic toxicity, with a rate of approximately 0.1%. Moderate signs

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of LA toxicity include CNS excitation, cardiac arrhythmias, contractile depression, and conduction block. Severe toxicity presents as seizures, hypotension, bradycardia, ventricular arrhythmias, and cardiac collapse. Severity of toxicity correlates with serum concentrations.

There are four proposed mechanisms of action in which IVLE can be used to reverse LA toxicity. First, IVLE functions as a “lipid sink” that extracts LAS from the plasma. Second, IVLE inhibits the mitochondrial metabolism of lipids, thus decreasing tissue acidosis and carbon dioxide production during myocardial ischemia. Thirdly, IVLE may reverse the LA-induced delivery of fatty acids to the mitochondria, thereby allowing for more ATP production. And lastly, fatty acids (in IVLE) activate calcium and potassium channels, which are blocked in LA-induced cardiotoxicity.

Formal dose-ranging studies have not been performed in humans. All of the human case studies below used IVLE 20%. Weinberg and colleagues developed a website using extrapolated information to make dosing recommendations. They recommend IVLE 20% as a bolus of 1.5mL/kg over one minute followed by infusion of 0.25mL/kg/min for 30-60 minutes (and increase to 0.5mL/kg/min if hypotension). They recommend re-bolus every three to five minutes with a total of 8mL/kg if necessary. (Lipidrescue.org).

**Animal Studies**

Study 1 bottom line: Pretreatment with IVLE increases the median lethal dose and concentration of bupivacaine tolerated. Resuscitation with IVLE increases the lethal dose of bupivacaine. Male rats were pretreated with saline, IVLE 10%, 20%, or 30%, followed by bupivacaine 0.75% administration until subjects had 10 seconds of asystole. The lethal dose was found to be higher in subjects pretreated with a higher concentration of IVLE (17.8, 27.6, 49.8, and 82mg/kg respectively with p value <0.0001). Differences in bupivacaine levels were also statistically significant (93.3μg/mL in the saline group vs. 212μg/mL in IVLE group). In the second arm of the study, subjects were given various bupivacaine doses and then resuscitated with either IVLE or saline. The lethal dose (LD50) was 18.5mg/kg in the IVLE group vs. 12.5mg/kg in the saline group.

Study 2 bottom line: IVLE effectively resuscitated male hounds with cardiovascular collapse induced by bupivacaine administration. Hounds were given bupivacaine to induce BP <30mmHg and HR <10bpm, followed by either a saline or IVLE 20% bolus and infusion. None from the saline group returned to NSR or maintained a mean BP >20 mmHg, meanwhile all of the IVLE subjects had a return to NSR within five minutes and after 30 minutes both a near-normal BP and EKG.

Study 3 bottom line: After isolated rat hearts received bupivacaine, IVLE significantly hastened the dissociation of bupivacaine from myocardial tissue compared to buffer (control) solution when myocardial tissue samples were taken at interval times.

**Human case reports**

Case 1: A 58 y/o man who received 40mL of LA (20mL mepivacaine 1.5% and 20mL bupivacaine 0.5%) afterwards developed seizures and asystole. The patient initially did not respond to ACLS, but had return of spontaneous circulation following a 100mL bolus of 20% IVLE followed by infusion. He had no neurologic deficits or signs/symptoms of IVLE adverse effects. Cardiac catheterization later showed total occlusion of the RCA and reduced LVEF. Authors postulated that his cardiac disease predisposed him to LA toxicity.

Case 2: An 84 y/o woman who underwent a brachial plexus block for Dupuytren’s contracture repair inadvertently received ropivacaine 1% instead of 0.5% and proceeded to have a tonic-clonic seizure followed by asystole. After 10 minutes of ACLS without regaining a pulse, she received 10mL of IVLE 20% followed by 0.2mL/kg/min infusion and developed a wide complex tachycardia, and then regained a pulse. She was extubated after three hours with full recovery.

Case 3: A 75 y/o woman who underwent lumbar plexus block using 20mL of levobupivacaine 0.5% developed convulsions with EKG changes. She then received a 100mL bolus of IVLE 20% during resuscitation. After 10 minutes, her vital signs and EKG were within normal limits. Authors concluded that IVLE might be useful for management of even suspected LA toxicity.

Case 4: An 18 y/o 38-week pregnant woman presented for induction of labor and was given an epidural with lidocaine, bupivacaine, and fentanyl through the epidural catheter. The patient became unresponsive with twitching of her extremities and face. She was given two boluses of 50mL IVLE 20% followed by a 300mL infusion and returned to consciousness within 30 seconds. The patient and her neonate were both discharged four days later without complications.

Conclusion: These human case reports show successful use of IVLE for presumed LA toxicity involving bupivacaine, mepivacaine, ropivacaine, and levobupivacaine. There exists a recommended dosing regimen, but formal dose ranging studies still need to be performed.

**Cave G, Harvey M. Intravenous lipid emulsion as antidote beyond local anesthetic toxicity: A systematic review. Academic Emergency Medicine 2009;16:815-824.**

There has been a lot of attention focused on the potential benefit of IVLE in cardiac arrest secondary to lipophilic drugs. The objective of this systematic review was to determine the efficacy of IVLE in animal models of poisoning and describe the outcomes associated with IVLE therapy in poisoned humans.

A systematic review of the literature was carried out to answer the question, “Does the evidence support administration of IVLE as an antidote in lipophilic drug toxicity, beyond that of local anesthetics?” The electronic databases PubMed, OVID, and EMBASE identified 145 potentially relevant articles. Two reviewers selected and divided articles into animal and human studies. Ultimately, 14 relevant animal studies, one human study, and four human case reports were chosen to be included.

The animal studies demonstrated that IVLE improved hemodynamic
markers when administered in the setting of toxicity from lipophilic drugs such as cyclic antidepressants, verapamil, and propranolol. IVLE had no effect on atenolol toxicity, a hydrophilic drug. Most of these studies, however, were designed to show efficacy alone and were not compared to other established antidotal therapies. The single controlled human study found a statistically non-significant 14% increase in plasma levels of amitriptyline and nortriptyline levels in patients receiving a five-hour infusion of lipid suspension when compared to a saline control. This was a small study, n=4, and subjects were in a pharmacologic steady state as opposed to an acute ingestion. The one controlled human study in this field is not generalizable to an acute tricyclic poisoning. In the four human case reports, IVLE seemed to benefit patients toxic from bupropion/lamotrigine, verapamil/atenolol, atenolol alone, and sertraline/quetiapine. All four cases showed an initial improvement in hemodynamic markers within minutes of administering IVLE; however, they all had significant limitations. In theory, basic science supports the use of IVLE in humans, but does not establish clinical efficacy. Based on limited animal and human data, the expected benefit of IVLE may range from limited to life preserving. That said, IVLE has been associated with adverse effects such as allergic reactions, hyperthermia, thrombocytopenia, hypercoagulability, pancreatitis, and hepatitis when administered as a component of total parenteral nutrition. Human cases of lipophilic drug toxicity are rare, and therefore unlikely to be studied in a randomized prospective controlled fashion. Based on this systematic review, IVLE may be helpful in potentially lethal overdoses from highly lipophilic cardiotoxic medications. Administration of IVLE in such settings should therefore occur in accordance with established antidotal therapies and after early consultation of poison centers. Additional studies and systematic reporting of human case reports are necessary to confirm IVLE as an effective antidote. Conclusion Intraavenous lipid emulsion and high-dose insulin euglycemic therapy are two exciting developments in the field of clinical toxicology. Like many studies in clinical toxicology, the limitations are abundant. With that in mind, many of the animal studies and published case reports have demonstrated quite dramatic results. The administration of these two promising therapies should be considered early on in conjunction with other established antidotal therapies, especially with guidance from local poison centers.