## Title

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TOXICOLOGY INVESTIGATION

# Utilization of Hyperinsulinemia Euglycemia and Intravenous Fat Emulsion Following Poison Center Recommendations

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**Abstract** Hyperinsulinemia euglycemia (HIE) and intravenous fat emulsion (IFE) may be beneficial in the treatment of calcium channel (CCB) and beta receptor (BB) antagonist toxicity. Many poison control centers (PCC) now recommend use. Healthcare providers may be unfamiliar with these treatments and may not institute them despite recommendations. We sought to determine how often HIE and IFE are recommended by a statewide PCC in CCB and BB toxicity, how often those recommendations are implemented, and whether a faxable information sheet increased adherence. All cases of CCB and BB exposure from January 2005–July 2011 where insulin or "other therapy" was coded were reviewed. Exclusion criteria included an incomplete PCC record, miscoding, and insulin administration as other than cardiovascular drug antidotal therapy. There were 215 CCB or BB exposures initially identified using the search criteria. HIE was recommended in 71 cases and started in one case prior to PCC recommendation. HIE was subsequently used in 30 cases after PCC recommendation (42 %). IFE was recommended by the PCC in 30 cases and implemented 10 times (33 %). In six cases, both HIE and IFE were implemented after recommendation. There was no statistical difference when recommendation was made via telephone or by faxable information sheet for HIE or IFE. HIE and IFE are two therapies that are potentially beneficial in the treatment of BB and CCB toxicity. Current national organization guidelines for use are limited. Exploration of reasons for not following recommendations and additional efforts to improve clinician education regarding HIE and IFE may be required to increase the utilization of these potentially lifesaving antidotes.

**Keywords** Hyperinsulinemia euglycemia · Intravenous fat emulsion · Calcium channel antagonist toxicity · Beta-adrenergic receptor antagonist toxicity

## Introduction

Calcium channel (CCB) and beta-adrenergic receptor (BB) antagonists cause significant morbidity and mortality in overdose [1]. Hyperinsulinemia euglycemia (HIE) and intravenous fat emulsion (IFE) are two interventions that may be beneficial in the treatment of CCB and BB overdose [2, 3]. Many poison control centers (PCC) are now recommending their use following overdose of BB and CCB [4, 5]. The goal of this study was to determine how often HIE and IFE were recommended by a statewide PCC for CCB and BB intoxications, how often those recommendations were implemented, and whether the use of a faxable treatment protocol influenced provider adherence to PCC recommendations.

## Methods

After Institutional Review Board review and approval, case records from a state PCC database (Visual Dotlab, Madera,

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CA) were queried for all cases of CCB and BB exposure occurring between January 2005 and January 2011 in which "insulin" or "other therapy" was coded. The case free-text areas were then reviewed to determine that HIE and/or IFE were recommended as antidotal therapy by poison center staff and whether by telephone or faxable information sheet. Patient age, gender, route of exposure, which CCB or BB was involved, presence of other co-ingestants, other interventions (atropine, calcium, glucagon, vasopressors, intravenous fluids) administered, outcome, and whether HIE or IFE was implemented at doses recommended by PCC were recorded. Exclusion criteria included incomplete PCC records (missing data of interest), miscoded cases (not a CCB, BB, or therapies not actually administered), or insulin administered as other than cardiovascular drug antidotal therapy. All records were reviewed by four authors (MD, SL, HD, DB). Discrepancies were discussed, free-text notes were reviewed to corroborate all coded data, and consensus was agreed upon.

A faxable sheet containing dosing for HIE and IFE and rationale for use was available and utilized at PCC staff discretion in responding to provider calls. Separate sheets were utilized for HIE or IFE, respectively. Fisher's exact test was performed to compare adherence to recommendations when an information sheet was sent versus telephone recommendation for antidotal therapy alone.

## Results

There were 215 CCB or BB exposures identified using the search criteria. All patients had an oral route of exposure. The PCC recommended HIE as antidotal therapy in 71 cases. All recommendations for HIE or IFE were made after administration of other traditional therapies for BB or CCB toxicity (See Table 1). HIE was subsequently implemented in 30 cases at the PCC recommended dose (30/71, 42 %). IFE was recommended by the PCC in 30 cases and implemented 10 times (10/30, 33 %). HIE was implemented in one case prior to PCC recommendation, and in no case was IFE started prior to discussion with PCC (See Figs. 1 and 2).

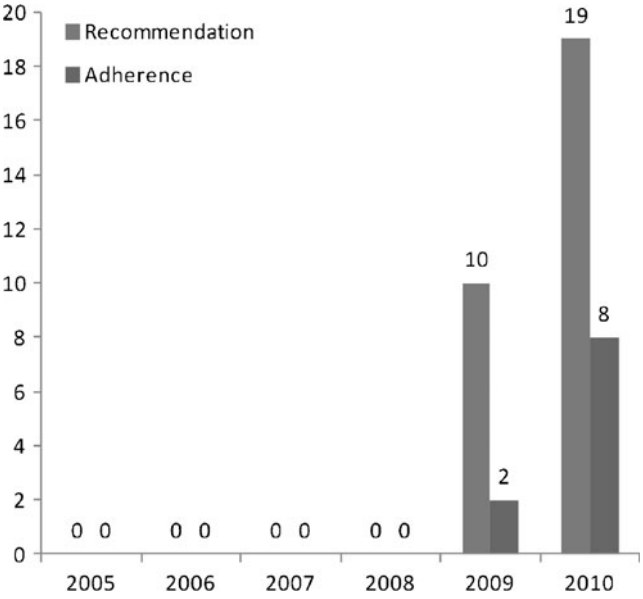


**Fig. 1** IFE recommendation and adherence by year

The use of a faxable information sheet describing dosing and rationale for use did not improve provider adherence to recommendation (Fisher's exact test >0.05) (See Table 2).

## Discussion

The use of IFE and HIE as antidotal therapy in BB and CCB poisonings has been gaining in popularity. Since the first published review in the emergency medicine literature describing the use of HIE in the treatment of BB and CCB toxicity appeared in the medical literature in 2004 [6], there have been a large number of additional published articles suggesting a beneficial use of this therapy. We chose to include cases from January 2005 forward to reflect the appearance of this review article. However, there were no recommendations or implementation of IFE prior to 2009 in the present retrospective chart review.

In 2011, Cave et al. conducted a systematic literature review using the PubMed, Embase, and Ovid databases for

**Table 1** Therapies administered prior to PCC recommendation

| | Atropine | AC | Calcium | IV fluid | Pressors | Glucagon | WBI |
|---|---|---|---|---|---|---|---|
| Therapies administered prior to recommendation for HIE | | | | | | | |
| BB (*N*=12) | 6 | 5 | 2 | 6 | 11 | 12 | 0 |
| CCB (*N*=43) | 8 | 16 | 31 | 28 | 33 | 37 | 11 |
| BB/CCB (*N*=16) | 5 | 4 | 10 | 14 | 16 | 16 | 1 |
| Therapies administered prior to recommendation for IFE | | | | | | | |
| BB (*N*=8) | 4 | 0 | 0 | 7 | 6 | 6 | 0 |
| CCB (*N*=13) | 3 | 4 | 11 | 12 | 7 | 12 | 4 |
| BB/CCB (*N*=5) | 2 | 1 | 4 | 5 | 4 | 4 | 1 |

*BB* beta-adrenergic receptor antagonist ("beta blocker"), *CCB* calcium channel blocker, *AC* activated charcoal, *IV* intravenous, *WBI* whole bowel irrigation

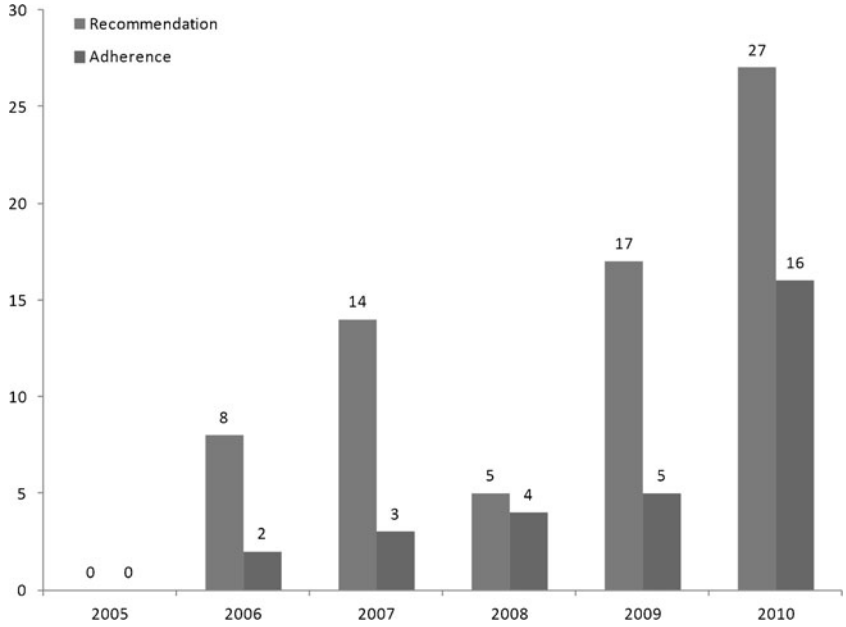


**Fig. 2** HIE recommendation and adherence by year

all published peer-reviewed cases and clinical studies on the use of IFE as antidotal therapy in humans for local anesthetic and nonlocal anesthetic toxicity [3]. Two abstracts describing IFE in the treatment of CCB and BB were published in 2008 [7, 8]. Five case descriptions were published in 2009 [9–12] while six case descriptions were published in 2010 [13–18]. All case reports described by Cave all involving cardiovascular drug toxicity received other therapies including glucagon, calcium, and vasopressors prior to IFE.

Engebretsen et al. conducted a similar systematic review of Medline, Embase, TOXNET, and Google scholar for articles on the use of HIE in the treatment of BB and CCB toxicity in 2011 [2]. The authors found 72 articles demonstrating potential benefit of this therapy. The authors further conclude that HIE should be considered initial therapy in both BB and CCB toxicity based on these animal studies and human case reports [2]. The recommendation for HIE as initial therapy in BB and CCB is not always implemented in clinical practice. All human cases described by Engebretsen received other therapies including glucagon, calcium, and vasopressors prior to HIE. HIE and IFE continue to be seen by many emergency and critical care providers as "rescue or salvage" therapy. Despite a growing body of published literature suggesting benefit of these therapies, there remain very limited formal guidelines regarding the use of IFE and HIE in the management of cardiovascular drug-poisoned patients or what constitutes appropriate use.

**Table 2** Influence of faxable protocol on provider adherence to recommendation

| | Faxable protocol | Telephone recommendation |
|---|---|---|
| Hyperinsulinemia euglycemia (HIE) | | |
| Given | 8 | 22 |
| Not given | 12 | 29 |
| | | Fisher's exact test: $p=1$ |
| Intravenous fat emulsion (IFE) | | |
| Given | 5 | 5 |
| Not given | 8 | 12 |
| | | Fisher's exact test: $P=0.7$ |

The American College of Medical Toxicology (ACMT) position statement on the use of IFE states, "… that there are no standard of care requirements to use or not to use IFE. However, in circumstances where there is serious hemodynamic, or other instability from a xenobiotic with a high degree of lipid solubility, LRT (lipid rescue therapy) is viewed as a reasonable consideration for therapy, even if the patient is not in cardiac arrest." [19]. IFE is also recommended in the 2010 Advanced Cardiac Life Support guidelines for "cardiac arrest secondary to lipophilic Beta Blockers and Calcium Channel Blockers, when other conventional resuscitative therapies have failed." [20]. The ACMT does not currently have a position statement on the use of HIE.

In the present retrospective chart review, the number of recommendations per year for HIE and IFE following BB and CCB overdose demonstrated an increase between 2005 and 2011. Implementation by treating providers following recommendations also showed a temporal increase. The most marked increase in both number of recommendations and adherence to recommendation was seen in 2010. The reasons for not following PCC recommendations were not examined in the present study. These therapies are relatively

new, and clinicians may not be aware of the rationale for use or dosing of these therapies. While intuitively appealing, the use of an information sheet containing dosing and rationale for use of HIE and IFE did not demonstrate an improvement in clinician adherence when compared to telephone recommendations alone. This suggests that reasons for nonadherence may be more than clinician lack of knowledge or awareness of these therapies.

The relatively low rate of use of HIE and IFE seen in the present chart review is consistent with previous reports of clinicians not always adhering to PCC recommendations with regard to antidotal therapy. For example, Mycyk et al. described a 64 % use of fomepizole following poison center recommendation in the treatment of methanol or ethylene glycol toxicity [21]. We were unable to find previous studies describing clinician implementation of PCC recommendations regarding HIE or IFE in the treatment of BB or CCB toxicity.

This is a retrospective descriptive analysis of clinician use of HIE and IFE following PCC recommendation. It is limited to the information available in a poison control system database. As such, it is not possible to accurately determine the efficacy of the interventions. Additionally, as standards of care for these therapies have not been clearly described, the appropriateness of PCC recommendation for HIE or IFE was not examined in the present study; however, they were in agreement with the limited published guidelines currently available. Errors may have been made in data entry at the time of the initial call to the poison control center. There may be additional cases where HIE or IFE was performed for BB and CCB exposures that were not called into the poison control system or were not identified due to a lack of appropriate coding. The results presented may not reflect these additional instances of use which may distort the true frequency of IFE or HIE use following BB and CCB toxicity. The content and indications for use of the faxable information sheet were left to the discretion of the staff at the four poison centers in our state; however, dosing recommendations were consistent: HIE (0.5–1 unit/kg/h) and IFE (1.5 ml/kg bolus followed by 0.25 ml/kg/min for 30–60 min). Utilization of the faxable information sheet was overall low limiting the power of the statistical test. Post hoc power analysis revealed a power of less than 10 % to detect a difference with an alpha of 0.05. Standardized and more liberal use may have demonstrated an improvement in clinician adherence to recommendations following faxable protocol.

## Conclusion

PCC recommendations for HIE and IFE use and implementation following recommendation have increased since 2005. However, clinicians are still not universally following PCC treatment recommendations in BB and CCB poisonings regarding HIE and IFE use. Distribution of a faxable information sheet did not improve adherence when compared to telephone recommendations alone. Gaining additional insight into clinicians' reluctance to follow PCC recommendations may improve future efforts to educate providers regarding these potentially lifesaving antidotes.

**Conflict of Interest** The authors have no conflicts of interest.

## References


1. Bronstein AC, Spyker DA, Cantilena LR Jr, Green JL, Rumack BH, Dart RC (2011) 2010 Annual report of the American Association of Poison Control Centers' National Poison Data System (NPDS): 28th annual report. Clin Toxicol (Phila) 49(10):910–941
2. Engebretsen KM, Kaczmarek KM, Morgan J, Holger JS (2011) High-dose insulin therapy in beta-blocker and calcium channel-blocker poisoning. Clin Toxicol (Phila) 49(4):277–283
3. Cave G, Harvey M, Graudins A (2011) Intravenous lipid emulsion as antidote: a summary of published human experience. Emerg Med Australas 23(2):123–141
4. Christian MR, Pallasch EM, Wahl M, Mycyk MB (2011) Lipid Rescue 911: a survey of poison center medical directors regarding intravenous fat emulsion therapy. Clin Toxicol (Phila) 49(6)
5. Lulek-Starosta K (2012) High-dose insulin with supplemental dextrose and potassium (HDIDK) infusions for beta-blocker and calcium channel blocker overdose. Michigan Pharmacists Association. http://michiganpharmacists.org/news/article.php?x=2525. Accessed April 3, 2012
6. DeWitt CR, Waksman JC (2004) Pharmacology, pathophysiology and management of calcium channel blocker and beta-blocker toxicity. Toxicol Rev 23(4):223–238
7. Dolcourt B, Aaron C (2008) Intravenous fat emulsion for refractory verapamil and atenolol induced shock: a human case report. Clin Toxicol (Phila) 46:619–620
8. Harchelroad F, Palma A (2008) Efficacy and safety of intravenous lipid therapy in a beta blocker overdose. Clin Toxicol (Phila) 46:634
9. Meehan T, Gummin D, Kostic M, Cattapan S, Waghray R, Bryant S (2009) Beta blocker toxicity successfully treated with intravenous fat emulsion: a case series. Clin Toxicol (Phila) 47:735, Abstract
10. Oakes J, Piquette C, Barthold C (2009) Successful use of intravenous lipid as adjunctive therapy in a severe calcium channel antagonist poisoning. Clin Toxicol (Phila) 47:755–756, Abstract
11. Carr D, Boone A, Hoffman R, Martin K, Ahluwalia N (2009) Successful resuscitation of a carvedilol overdose using intravenous fat emulsion. Clin Toxicol (Phila) 47:710, Abstract
12. Young A, Velez L, Kleinschmidt K (2009) Intravenous fat emulsion therapy for intentional sustained release verapamil overdose. Resuscitation 80:591–593
13. West P, McKeown N, Hendrickson R (2010) Iatrogenic lipid emulsion overdose in a case of amlodipine poisoning. Clin Toxicol (Phila) 48:293–296
14. Stellpflug S, Harris C, Engebretsen K, Cole J, Holger J (2010) Intentional overdose with cardiac arrest treated with intravenous

fat emulsion and high dose insulin. Clin Toxicol (Phila) 48:227–229
15. Hillyard S, Barrera-Groba C, Tighe R (2010) Intralipid reverses coma associated with zopiclone and venlafaxine overdose. Eur J Anaesthiol 27:582–583
16. Cooper G, Dyas J, Krishna C, Thompson J (2010) Successful use of intravenous fat emulsion in severe poisoning following ingestion of lipid soluble drugs. Clin Toxicol (Phila) 48:298, Abstract
17. Dean P, Ruddy P, Marshall S (2010) Intravenous lipid emulsion in propranolol overdose. Anaesthesia 65:1149–1150, Letter
18. Montiel V, Gougnard T, Hanston P (2011) Diltiazem poisoning treated with hyperinsulinemic euglycemia therapy and intravenous lipid emulsion. Eur J Emerg Med 18(2):121–123
19. Position Statement ACMT (2011) Interim guidance for the use of lipid resuscitation therapy American College of Medical Toxicology. J Med Toxicol 7:81–82
20. Vanden Hoel TL, Morrison LJ, Shuster M (2010) Cardiac arrest in special situations. Circulation 122:S829–S861
21. Mycyk MB, DesLauriers C, Metz J, Wills B, Mazor SS (2006) Compliance with poison center fomepizole recommendations is sub-optimal in cases of toxic alcohol poisoning. Am J Ther 13(6):485–489