Original Article

Before and After Study of Pharmacists' and Students' Knowledge of Two Novel Antidotes: High-Dose Insulin Euglycemia and Intravenous Fatty Acid Emulsion 20%

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Abstract

Purpose: To assess pharmacists' and students' knowledge of high-dose insulin euglycemia (HIE) and intravenous fatty acid emulsion 20% (IFE) and to see whether it improved after an educational intervention.

Methods: A survey to assess the knowledge about the use of HIE and IFE as antidotes was e-mailed to practicing pharmacists, pharmacy residents, and students prior to and following an educational intervention. Fact sheets on the antidotes were developed in conjunction with the New York City Poison Control Center and were used as the educational intervention in this study. The impact of exposure to the intervention was measured by comparing the number of correct responses per question on the pre- and posttests and the mean pre- and posttest scores using chi-square and *t* tests, respectively.

Results: Most respondents felt either not at all or only somewhat comfortable with managing a toxicologic emergency. There was a statistically significant difference in mean scores on the pretest and posttest (2.9 vs 5.45; *P* = .001) and for the number of participants giving correct responses for each question before and after education: 52.4% of respondents answered "I don't know" to the questions prior to education versus 21.2% after education (*P* < .001). Fewer respondents felt not at all comfortable managing a toxicologic emergency after the educational intervention (42.4 vs 50.3%; *P* < .001).

Conclusion: Pharmacists and students reported little comfort in managing toxicological emergencies in general and have limited baseline knowledge about these agents. Educational interventions can significantly improve knowledge. Prior familiarity with these newer antidotes should reduce delays in their administration in an emergency.

Key Words—antidotes, fact sheets, knowledge, pharmacists, survey

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The lack of clinical experience with antidotes and unfamiliarity with methods to prevent or manage adverse effects related to their use can contribute to significant delays in administration. In certain scenarios, there can even be omission of administration in the management of severely poisoned patients for whom such antidotes are indicated.¹ Several studies have reported that hospital pharmacies have inadequate stocks of antidotes available.²⁻⁶ Administration and dosing errors have also been reported in the literature.^{7,8} With new dosing strategies being introduced, use in special populations, expanded indications for established antidotes, and the reassessment and expansion of off-label indications for other medications, knowledge of antidotes remains paramount.¹ High-dose insulin euglycemia (HIE) and intravenous fatty acid emulsion 20% (IFE) are 2 novel antidotes that are being utilized with increased frequency in the emergency department (ED). HIE is used to treat calcium channel and beta blocker overdose. The 2012 Annual Report of the American Association of Poison Control Centers' National Poison Data System reported 10,691 single exposures to beta blockers.⁹ Of these exposures, 4,306 required treatment in a health care facility and 13 resulted in death. Also reported were 5,076 single exposures to calcium channel blockers, 2,286 of which required treatment in a health care facility and 24 of which resulted in death. Insulin was used in a total of 1,996 cases. It is presumed that HIE was used in many of those cases. IFE is used to treat cardiovascular toxicity associated with local anesthetic toxicity. Local anesthetic toxicity has been reported to occur as frequently as 1:1000 peripheral nerve blocks. However, of those, only about 44% involved both central nervous system and cardiac manifestations.¹⁰ The purpose of this study was to assess the baseline knowledge of pharmacists and students of these novel antidotes and to see whether it improved after an educational intervention.

METHODS

This before and after study assessed the knowledge of the novel antidotes, HIE and IFE, following exposure to an educational intervention. The impact of exposure to the educational intervention was measured by comparing pre- and posttest scores. The study protocol was approved by the institutional review board of St. John's University.

A 36-question survey instrument consisting of multiple-choice questions was uploaded to SurveyMonkey (www.surveymonkey.com), and an invitation including a brief explanation of the research

project and a link to the survey was sent via e-mail. The survey instrument was original in design, as no other surveys have been developed on this topic. Closed-ended questions were constructed when applicable to provide standardized data that would be used in qualitative analysis. Questions assessing knowledge of the antidotes included, but were not limited to, case-based and true and false type. Each question included an option to respond as "I don't know." When the number of correct responses was tallied, any response that included "I don't know" was counted as incorrect. The survey was developed by the junior investigator, and content validity was assessed by the 2 senior investigators. Face validity was assessed by 10 research volunteers and pharmacy interns. Questions were revised and reformatted to ensure that they were clear, were not misleading, and did not include elements of instrumentation or response bias (eAppendix 1). Contact e-mail addresses were compiled for all possible study participants, who were identified as currently paid members (as of January 2013) of the American College of Clinical Pharmacy (ACCP) (including student members) and all residency program directors, directors of pharmacy, and program contacts for postgraduate year 1 and year 2 pharmacy residency programs in all phases of accreditation by the American Society of Health-System Pharmacists (ASHP).

Completion of the presurvey waiver, which stated that the survey responses would be kept confidential and that data would be reported only in aggregate, served as consent to participate in the study. The initial instrument was sent via e-mail on January 29, 2013, and results were collected through September 2013. Reminder e-mails were sent biweekly to individuals who did not complete the survey.

Fact sheets on the antidotes were developed in conjunction with the New York City Poison Control Center and were used as the educational intervention in this study. The fact sheets included information such as off-label indications and other uses of the antidotes, information about the proposed mechanism of action of the antidote in specific toxicological emergencies, dosing, adverse effects, contraindications, and monitoring parameters (eAppendices 2 and 3). The database was reviewed weekly to identify participants who had completed the initial survey. Once the initial survey was completed, the participant was e-mailed the fact sheets and had 1 month to review it. After a month had passed, each participant who had received the fact sheets was e-mailed a posttest, which was identical to the pretest.

The data were summarized using descriptive statistics, percentages for all categorical variables, and medians with lower and upper ranges for all continuous variables. The chi-square test was used to compare the number of correct responses per question on the pre- and posttests. The chi-square test was also used to determine the percent of respondents who felt not at all comfortable managing a toxicologic emergency before and after the educational intervention. The *t* test was used to compare mean scores on the pre- and posttests. The overall score could range from 0 (*did not answer any of the knowledge questions correctly*) to 9 (*answered all of the knowledge questions correctly*). All responses were included in the statistical analyses. Levels of significance were tested at $P < .05$. Analyses were conducted using the IBM SPSS (version 19) software system (IBM Corp., Armonk, NY).

RESULTS

The survey was e-mailed to 13,019 members of ACCP and 2,018 contacts from the ASHP Residency Directory; 122 e-mails bounced, 280 opted out, and 11 did not agree to the terms and conditions of the study. There were 2,271 participants who completed at least the first demographic question.

As seen in **Table 1**, the majority of respondents identified themselves as pharmacists, living in the South, and practicing in a hospital setting. More than half are affiliated with a residency program and about a quarter currently or have previously worked in an ED. Most respondents felt either not at all or only somewhat comfortable with managing a toxicologic emergency. Less than one-third reported being involved in the management of toxicologic emergencies, with about half of those reporting ever managing a toxicologic emergency with either IFE or HIE. Pretest respondents reported gaining most of their knowledge about antidotes during school, while posttest respondents reported primary literature.

There was a statistically significant difference in mean scores on the pretest and posttest (2.9 vs 5.45; $P = .001$) and for the number of participants giving correct responses for each question before and after education, as seen in **Figure 1**. Residents scored the highest scores on the pretest (mean score of 3.69 for 173 residents vs mean score of 3.08 for 1,296 pharmacists vs mean score of 1.46 for 266 students; $P = .001$). ED pharmacists scored higher on the pretest compared to staff and other clinical pharmacists (mean score of 5.62 for 162 ED pharmacists vs mean

score of 3.05 for 526 clinical pharmacists vs mean score of 2.62 for 112 staff pharmacists; $P = .001$). Students had the greatest increase in scores from pretest to posttest (increase of 4.05 correct answers for 59 students, increase of 2.39 correct answers for 383 pharmacists, and increase of 1.8 correct answers for 54 residents; $P = .006$). On average, 52.4% of respondents answered "I don't know" to the questions prior to education versus 21.2% after education ($P < .001$) (**Figure 2**). Fewer respondents felt not at all comfortable managing a toxicologic emergency after the educational intervention (42.4% vs 50.3%; $P < .001$).

DISCUSSION

This is the first study to assess pharmacists' and students' knowledge of novel antidotes. We assessed their knowledge by examining their responses to 9 multiple-choice questions. We demonstrated that pharmacists and students had limited knowledge of the antidotes at baseline, but more respondents answered the questions about IFE correctly. Their knowledge increased after an educational intervention as evidenced by a greater number of respondents answering the questions correctly and fewer answering "I don't know." Two similar studies have been published in the emergency medicine literature.

Wood et al conducted a before and after study in which they administered a survey to medical staff in general medicine, emergency medicine, and pediatrics after they attended either a 1-hour or 2-day clinical toxicology teaching course.¹¹ Participants were questioned about their knowledge of and whether they had read any of the gut decontamination consensus guidelines. They were then asked to indicate which methods of gut decontamination (induced vomiting, gastric lavage, activated charcoal, multidose activated charcoal, and whole bowel irrigation), if any, they felt would be appropriate for 6 clinical scenarios of acute poisoning. For each correct answer, they received 1 point and the maximum number of points they could receive was 6. Sixty-nine general and emergency medicine physicians and 23 pediatricians participated in the study. Only 34 (37%) doctors had heard of all methods of gut decontamination and only 3 (3.3%) doctors had read all the guidelines. The mean (*SD*) score for all doctors completing the case scenarios of acute poisoning was 2.67 (1.5), pediatricians 3.78 (1.59), and general/emergency medicine physicians 2.3 (1.28) ($P < .0001$). The mean (*SD*) score was 3.48 (0.87) ($n = 21$) at the commencement of the 2-day course and 4.94 (0.73) ($n = 19$) at the end ($P < .001$).

Table 1. Demographic data of survey respondents (N = 3,013)

Demographics	Pretest n/N (%)	Posttest n/N (%)
<i>Title of person completing the survey</i>		
Pharmacist	1,715/2,272 (75.5)	588/741 (79.4)
Clinical	874/1,709 (51.1)	318/587 (54.2)
Faculty	219/1,709 (12.8)	76/587 (12.9)
Clinical Coordinator	122/1,709 (7.1)	42/587 (7.2)
Director	94/1,709 (5.5)	31/587 (5.3)
Manager	94/1,709 (5.5)	29/587 (4.9)
Staff	94/1,709 (5.5)	53/587 (9.0)
Other	138/1,709 (8.1)	38/587 (6.5)
Resident	218/2,272 (9.6)	83/741 (11.2)
PGY1	134/221 (60.6)	50/83 (60.2)
PGY2	87/221 (39.4)	33/83 (39.8)
<i>Specialty</i>		
Critical care	26/85 (30.6)	13/33 (39.4)
Ambulatory care	13/85 (15.3)	2/33 (6.1)
Emergency medicine	10/85 (11.8)	6/33 (18.2)
Cardiology	5/85 (5.9)	0/33 (0)
Infectious diseases	5/85 (5.9)	0/33 (0)
Pediatrics	5/85 (5.9)	3/33 (9.1)
Internal medicine	4/85 (4.7)	3/33 (9.1)
Oncology	4/85 (4.7)	1/33 (3.0)
Geriatrics	3/85 (3.5)	1/33 (3.0)
Drug information	2/85 (2.4)	0/33 (0)
Nutrition support	2/85 (2.4)	0/33 (0)
Psychiatry	2/85 (2.4)	2/33 (6.1)
Solid organ transplant	2/85 (2.4)	1/33 (3.0)
Medication use safety	1/85 (1.2)	0/33 (0)
Pharmacogenetics	1/85 (1.2)	0/33 (0)
Health system pharmacy practice administration	0/85 (0)	1/33 (3.0)
Student	339/2,272 (14.9)	70/741 (9.4)
1 st professional year	23/336 (6.8)	2/70 (2.9)
2 nd professional year	57/336 (16.9)	12/70 (17.1)
3 rd professional year	90/336 (26.8)	18/70 (25.7)
4 th professional year	166/336 (49.4)	38/70 (54.3)

Table 1. Demographic data of survey respondents (*N* = 3,013) (CONT.)

<i>Location</i>		
South	793/2,272 (34.9)	257/741 (34.8)
Midwest	661/2,272 (29.1)	228/741 (30.9)
Northeast	406/2,272 (17.9)	141/741 (19.1)
West	401/2,272 (17.6)	112/741 (15.2)
<i>Practice setting</i>		
Hospital	1,545/2,257 (68.5)	548/738 (74.3)
Other	393/2,257 (17.4)	121/738 (16.4)
Community/retail pharmacy	229/2,257 (9.9)	47/738 (6.4)
Poison Control Center	6/2,257 (0.3)	3/738 (0.4)
<i>Total no. of ED visits</i>		
<10,000	75/1,207 (6.2)	26/439 (5.9)
10,000-20,000	84/1,207 (7.0)	40/439 (9.1)
20,001-30,000	72/1,207 (6.0)	30/439 (6.8)
30,001-40,000	113/1,207 (9.4)	50/439 (11.4)
40,001-50,000	126/1,207 (10.4)	31/439 (7.1)
50,001-60,000	166/1,207 (13.8)	56/439 (12.8)
60,001-70,000	108/1,207 (8.9)	43/439 (9.8)
70,001-80,000	101/1,207 (8.4)	33/439 (7.5)
80,001-90,000	89/1,207 (7.4)	28/439 (6.4)
90,001-100,000	62/1,207 (5.1)	25/439 (5.7)
>100,000	211/1,207 (17.5)	77/439 (17.5)
Affiliated with a residency program	1,057/1,709 (61.8)	373/587 (63.5)
Currently working in an ED	192/1,206 (15.9)	83/439 (18.9)
<i>Years working in an ED</i>		
<1 years	48/192 (25.0)	13/83 (15.7)
1-3 years	73/192 (38.0)	38/83 (45.8)
4-7 years	58/192 (30.2)	24/83 (28.9)
8-10 years	8/192 (4.2)	5/83 (6.0)
>10 years	5/192 (2.6)	3/83 (3.6)
Ever worked in an ED	248/1,441 (17.2)	99/495 (20.0)
<i>Comfort with managing a toxicologic emergency</i>		
Not at all	1,088/2,161 (50.3)	309/728 (42.4)
Somewhat	752/2,161 (34.8)	310/728 (42.6)
Comfortable	253/2,161 (11.7)	87/728 (12.0)
Very comfortable	68/2,161 (3.1)	22/728 (3.0)

Table 1. Demographic data of survey respondents (N = 3,013) (CONT.)

Involved in the management of toxicologic emergencies	636/2,161 (29.1)	230/661 (34.8)
Ever managed a toxicologic emergency with IFE	308/2,176 (14.2)	92/660 (13.9)
Ever managed a toxicologic emergency with HIE	398/2,176 (18.3)	102/660 (15.5)
Source of knowledge of antidotes		
Gained as a student	1,020/2,161 (47.2)	273/728 (37.5)
Primary literature	904/2,161 (41.8)	300/728 (41.2)
Internet	674/2,161 (41.2)	271/728 (37.2)
Textbooks	643/2,161 (29.8)	219/728 (30.1)
CE lectures	611/2,161 (28.3)	241/728 (33.1)
Read "Antidotes for Toxicological Emergencies: A Practical Review" article ^a	295/2,161 (13.7)	203/728 (27.9)

Note: CE = continuing education; ED = emergency department; HIE = high-dose insulin euglycemia; IFE = intravenous fat emulsion 20%; IV = intravenous; PGY = postgraduate year.

^aMarraffa JM, Cohen V, Howland MA. Antidotes for toxicological emergencies: a practical review. *Am J Health Syst Pharm.* 2012;69:199-212.

Figure 1. Impact of education on knowledge of antidotes. HIE = high-dose insulin euglycemia; IFE = intravenous fatty acid emulsion 20%.

Figure 2. Impact of education on participant ability to answer each question. HIE = high-dose insulin euglycemia; IFE = intravenous fatty acid emulsion 20%.

Lidder et al¹² designed a survey to determine adult internal medicine and emergency physicians' knowledge of the appropriate use and routes of administration of various antidotes in the management of recreational drug toxicity. Medical staff of all grades in internal and emergency medicine were recruited before attending 1 of 3 clinical toxicology training sessions. Participants were asked to indicate whether the antidote/treatment and route of administration specified for 9 clinical scenarios of acute recreational drug toxicity were correct or not. A score of 1 point was given for each correct answer. A total of 42 doctors of all grades in general and emergency medicine attending 3 clinical toxicology training sessions completed the survey. The mean (*SD*) score was 5.4 (1.1) and the median (interquartile range [IQR]) was 6 (5-7). The percentage of answers that were correct for the various groups of clinical scenarios were 68.3%, 81%, 28.6%, and 70.2% for opioid toxicity, benzodiazepine toxicity, 3,4-methylenedioxy-methamphetamine (MDMA)-induced serotonin toxicity, and cocaine toxicity, respectively. Participants were more likely to record an answer of "unsure or don't know" for the use of cyproheptadine in MDMA-induced serotonin toxicity (28.6%) compared with

the use of the antidote in the other scenarios (opioid toxicity, cocaine toxicity, and benzodiazepine toxicity) (1.4%; $P < .001$).

In this study, most respondents felt either not at all or only somewhat comfortable with managing a toxicologic emergency, whereas about one-third are responsible for doing so in their current positions. After education, the number of respondents who felt not at all comfortable decreased significantly. This finding highlights the value of continuing education and the need to keep abreast of emerging literature to maximize potential benefits while minimizing the potential for adverse or unwanted effects.

This study and its findings have several limitations. First, we had a 15% response rate, which is below what has been reported as the typical response rate for electronic surveys. However, we feel that the sample size in this study was large and diverse enough to garner generalizable results. Second, we used survey questions that we developed. Even though we attempted to use techniques to minimize bias and misunderstanding, some may still have existed in the final draft of the survey. The survey was designed to allow respondents to answer "I don't know." This is contrary to real life situations where pharmacists

would come to a conclusion after conducting adequate research on the topic, even if they were unsure. The survey instructions did not ask participants to refrain from looking up the answers. However, based on the low pretest scores, it is not likely that participants utilized additional resources. Additionally, the fact sheets were e-mailed to participants after they completed the pretest; they had 1 month to review them prior to receiving an e-mail prompting them to complete the posttest. The degree or frequency at which the fact sheets were reviewed prior to completion of the posttest is not known.

The remainder of this discussion will provide a brief overview of the antidotes assessed in this survey to improve pharmacists' familiarity with HIE and IFE.

High-Dose Insulin Euglycemia

High-dose insulin euglycemia (HIE), sometimes referred to as high-dose insulin (HDI), is an antidote used to treat the hypotension or shock due to cardiac dysfunction (bradycardia, conduction delay, and negative inotropy) and peripheral vasodilation seen in calcium channel blocker and beta blocker poisoning.^{13,14} The mechanism of HIE in beta blocker and calcium channel blocker poisoning falls into 3 categories: (1) increased inotropy, (2) increased intracellular glucose transport, and (3) vascular dilatation.¹⁵ In calcium channel blocker overdose, insulin also increases plasma levels of ionized calcium and improves the hemodynamic state.¹⁶ In calcium channel blocker-induced shock, the heart cannot use carbohydrates effectively because of calcium channel blocker-induced inhibition of pancreatic insulin release with hypoinsulinemia and an acquired insulin resistance. Furthermore, depressed cardiac output reduces effective delivery of insulin and glucose. Most clinicians recommend an initial insulin bolus of 1 unit/kg followed by a 0.5 to 1 unit/kg/h continuous IV infusion. The IV infusion rate may be increased by 2 units/kg/h every 15 minutes to a maximum of 10 units/kg/h if no increase in cardiac output or clinical improvement is seen. There is often a delay of 15 to 40 minutes before an increase in cardiac contractility is observed.¹⁶ Blood glucose levels must be checked at least once every 15 to 30 minutes and 0.5 g/kg of dextrose followed by a dextrose infusion delivered as D25W or D50W at 0.5 g/kg/h may be administered to maintain blood glucose in the upper normal range. Up to 20 to 30 g/h may be needed in adults. Some patients with hyperglycemia related to calcium channel blocker toxicity do not require

glucose supplementation during insulin infusions.^{13,17} Special attention is required in patients with altered mental status, due to either poor hemodynamic conditions or to co-ingestion of sedative drugs, in whom clinical signs of hypoglycemia may be masked.¹³ Potassium concentrations should be checked every hour during insulin titrations and then every 6 hours once stable. It is recommended that potassium be supplemented once concentrations fall below 2.8 to 3.0 mEq/L.¹⁵ Hypoglycemia and hypokalemia are the most common adverse effects seen with HIE. Although serum potassium concentrations may at times fall below normal laboratory ranges, this change reflects the shifting of potassium from the extracellular to intracellular space that occurs as a result of the action of insulin. Patients maintain normal total body potassium stores and do not experience true deficiency unless they have other reasons for potassium loss.¹⁷

IV Fatty Acid Emulsion 20%

Lipid emulsion therapy has been associated with positive outcomes when used as an antidote in resuscitation from lipophilic drug-induced cardiovascular collapse.¹⁸⁻²⁰ Although its mechanism of action as an antidote is not completely understood, there are currently 3 possible mechanisms that have been postulated. IFE is thought to create a pharmacological sink for fat-soluble drugs. In the blood, fat emulsion exists as small fat droplets that provide a lipid compartment separate from the aqueous compartment into which lipophilic compounds may dissolve. By creating a serum lipid partition, the effective concentration of the lipophilic drug available to tissues, and in particular the heart, is lessened. Other mechanisms include overcoming fatty acid transport blockade by local anesthetic drugs and restoring myocyte function by increasing intracellular calcium.^{19,21} Desired outcomes are the return of spontaneous circulation or improved blood pressure.²² Current guidelines from the American Heart Association and European Resuscitation Council recommend 1.5 mL/kg of 20% long-chain fatty acid emulsion as an initial bolus, repeated every 5 minutes until cardiovascular stability is restored.^{23,24} After the patient is stabilized, some articles suggest a maintenance infusion of 0.25 mL/kg/min for at least 30 to 60 minutes. A maximum cumulative dose of 12 mL/kg has been proposed.^{23,24} Lipid emulsions have been associated with adverse effects including allergic reaction, hyperthermia, thrombocytopenia, hypercoagulability, antineutrophil activity, pancreatitis, and elevated liver enzymes

when infused as components of balanced parenteral nutrition regimens. Such adverse effects are likewise conceivable following use in resuscitation, as well as lipemia and pulmonary toxicity.^{19,25}

HIE and IFE are novel antidotes that are gaining increased usage, as data to support their use in toxicological emergencies accumulates. Pharmacists' and students' reported limited knowledge in using HIE and IFE prior to an educational intervention. Fact sheets sent to the recipients following the first survey improved both knowledge of their use and comfort in their administration. It is hoped that prior familiarity with these new antidotes will reduce delays in administration in an emergency.

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