Treatment of Calcium Channel Blocker Poisoning: Should We Reprioritize Our Potpourri of Treatment Options?

Answers to the September 2013 Journal Club Questions

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Editor's Note: *You are reading the 35th installment of* Annals of Emergency Medicine *Journal Club. This Journal Club refers to the Levine et al*[1] *article published in the September 2013 edition. Information about Journal Club can be found at http://www.annemergmed.com/content/journalclub. Readers should recognize that these are suggested answers. We hope they are accurate; we know that they are not comprehensive. There are many other points that could be made about these questions or about the article in general. Questions are rated "novice," (NOV) "intermediate," (INT) and "advanced (ADV) so that individuals planning a journal club can assign the right question to the right student. The "novice" rating does not imply that a novice should be able to spontaneously answer the question. "Novice" means we expect that someone with little background should be able to do a bit of reading, formulate an answer, and teach the material to others. Intermediate and advanced questions also will likely require some reading and research, and that reading will be sufficiently difficult that some background in clinical epidemiology will be helpful in understanding the reading and concepts. We are interested in receiving feedback about this feature. Please e-mail journalclub@acep.org with your comments.*

DISCUSSION POINTS

1. Levine et al[1] describe a single center's experience treating patients poisoned with a calcium channel blocker (CCB). CCBs are a familiar group of medications that have been used in the United States market since the 1970s. CCBs are used in the management of a spectrum of clinical conditions. Their utility stems from the ubiquitous nature of the calcium channel throughout the body. Commercially available CCBs in the United States block the L-type voltage-sensitive channels.

NOV A. The authors discuss how there are 3 different classes of CCBs: phenylalkylamines (verapamil), benzothiazepines (diltiazem), and dihydropyridines (amlodipine, nicardipine, etc). Discuss the differences in the clinical effects between these different classes when given in therapeutic doses.

INT B. What mechanism of action allows the specificity of the class of CCBs to bind to the myocardium versus the vascular smooth muscle? How does the selectivity and clinical effect of each medication change in supratherapeutic dosing?

ADV C. The pharmacokinetics of a drug may be described as "what the body does to the drug." Many medical Web sites will report the drug's half-life. How does the knowledge of a drug's half-life affect the anticipated management of the poisoned patient? According to CCB's pharmacokinetics, would you expect extracorporeal elimination to enhance removal of the drug?

ADV D. The differential diagnosis of a poisoned patient who presents with hypotension and bradycardia includes CCBs, β-blockers, and imidazoline analogues such as clonidine. What clinical clues may assist with the differentiation among these classes of medications in an overdose scenario? How does the mechanism of action of receptor blockade versus channel blockade affect the treatment paradigm?

2. This study is a retrospective chart review of 48 cases of CCB poisoning collected during 25 years from a single, tertiary care, regional referral center for poisoned patients.

INT A. Discuss some of the limitations associated with performing chart reviews on poisoned patients. How might these limitations affect the generalizability of these results to another population of poisoned patients? What additional limitations might affect the reliability of the data, given that they were accumulated during 25 years? How might these limitations affect the authors' conclusions?

INT B. How did the authors define the study population? Why did they require documentation of verapamil or diltiazem in urine by gas chromatography/mass spectrometry for inclusion yet also review charts of 12 patients lacking documentation of urine confirmation? What additional data may have more accurately defined the population of CCB-poisoned patients, as well as the severity of the poisoning?

3. Levine et al[1] conclude "that management with high-dose vasopressors without hyperinsulinemic euglycemia is not detrimental, given complete recovery in all but 1 patient. [W]e recommend the use of initial fluid challenges and vasopressors as first choices in supporting blood pressure and treating shock caused by verapamil and diltiazem toxicity."

(ADV) A. The management of CCB poisoning includes a variety of approaches. Describe how the following treatments are theorized to counter the toxic effects of CCBs. (1) Calcium. Specifically contrast the differences between calcium chloride and calcium gluconate in reference to the available calcium in each formulation, risks of administration, and possible routes of administration. (2) Insulin with glucose. Why are high doses of insulin (nondiabetic doses) thought to be beneficial? (3) Glucagon. (4) Vasopressor and inotropes. How would the class of CCB ingested in an overdose influence the initial choice of vasopressor?

(INT) B. Describe the complications of high-dose vasopressor therapy. What information would be helpful to discern whether the incidence of complications reported in this study is less than expected or at expected levels?

(INT) C. How were the possible complications of high-dose vasopressor therapy defined in this study? How were all subjects evaluated for these possible complications of the high-dose vasopressor therapy?

4. A novel therapy being introduced in the management of various overdoses such as verapamil poisoning is intravenous lipid emulsion (ILE) therapy.

(INT) A. What is the proposed mechanism of action of ILE as a treatment modality? What are the theoretical risks associated with its use? How might a drug's pharmacokinetics such as its volume of distribution predict whether ILE could be beneficial as a treatment modality?

(ADV) B. Given the mechanism of action of CCBs on the metabolic capacity on the heart, what are other proposed mechanisms of action that ILE may provide in the improvement of cardiovascular parameters in the setting of a CCB poisoning?

(INT) C. Discuss how a researcher might design a study to investigate whether ILE is a safe and effective treatment in patients with acute CCB poisonings. Would a prospective, randomized controlled trial necessarily be the most efficient initial investigation? Discuss potential problems associated with conducting such a trial in acutely poisoned patients.

ANSWER 1

Q1. Levine et al[1] describe a single center's experience treating patients poisoned with a calcium channel blocker (CCB). CCBs are a familiar group of medications that have been used in the United States market since the 1970s. CCBs are used in the management of a spectrum of clinical conditions. Their utility stems from the ubiquitous nature of the calcium channel throughout the body. Commercially available CCBs in the United States block the L-type voltage-sensitive channels.

Q1.a The authors discuss how there are 3 different classes of CCBs: phenylalkylamines (verapamil), benzothiazepines (diltiazem), and dihydropyridines (amlodipine, nicardipine, etc). Discuss the differences in the clinical effects between these different classes when given in therapeutic doses.

Although the target for all CCBs is the calcium (Ca^{2+}) channel, in therapeutic doses, each class of CCBs has targeted effects. The phenylalkylamines (verapamil) and benzothiazepines (diltiazem) act preferentially on the L-type Ca^{2+} channels in the myocardium. At therapeutic levels, these medications slow the spontaneous depolarization of the sinoatrial node, leading to negative chronotopy. They reduce conduction through the atrioventricular (AV) node, leading to negative dromotropy. Thus, these 2 classes of CCBs are used as a primary therapy for tachydysrhythmias, such as atrial fibrillation and atrial flutter. Verapamil has moderate vasodilatory effects on vascular smooth muscle, both peripherally and on the coronary vasculature, and causes a decrease in systemic blood pressure. Both are negative inotropes; however, diltiazem has fewer vasodilatory and negative inotropic effects than verapamil.

Dihydropyridines (amlodipine, nicardipine, nifedipine, etc) also act on the L-type voltage-gated Ca^{2+} ion channels, but have greater effect on peripheral vasculature than myocardium. Their predominant therapeutic effect is through relaxation of the vascular smooth muscle, resulting in arteriole vasodilation and a decrease in systemic blood pressure. They are therefore considered therapeutic for conditions such as essential hypertension. This class of CCBs has little or no effect on the sinoatrial and AV nodes when received in therapeutic doses.

Q1.b What mechanism of action allows the specificity of the class of CCBs to bind to the myocardium versus the vascular smooth muscle? How does the selectivity and clinical effect of each medication change in supratherapeutic dosing?

Voltage-sensitive L-type Ca^{2+} channels mediate influx of Ca^{2+} for myocytes, sinoatrial node, AV node, and vascular smooth muscle. The pharmacologic differences between the 3 classes of CCBs are determined by slight variation in their binding to the α 1c subunit of the L-type Ca^{2+} channels. Verapamil has a higher affinity for myocardial Ca^{2+} channels. Verapamil's blockade also increases with the frequency of the Ca^{2+} channel opening. Thus, verapamil has a greater affinity for pacemaker cells. Diltiazem has less effect on the myocardial Ca^{2+} channels than verapamil. Dihydropyridines have less affinity than the other classes of CCBs for the myocardial Ca^{2+}channels at therapeutic dosing. Dihydropyridines preferentially bind to Ca^{2+} channels that have less negative membrane potential. Vascular smooth muscle has a resting membrane potential around –60 to –70 mV, which is less negative than the resting membrane potential of myocytes, which is in the –90 mV range.

As the dosing of the CCB increases, the selectivity of the CCB declines. In overdoses, each class of CCBs will have exaggerated clinical effects that are an extension of their therapeutic effects; however, the higher the dose, the less the selectivity of the CCB for their preferred Ca^{2+} channel.

Q1.c The pharmacokinetics of a drug may be described as "what the body does to the drug." Many medical Web sites will report the drug's half-life. How does the knowledge of a drug's half-life affect the anticipated management of the poisoned patient? According to CCB's pharmacokinetics, would you expect extracorporeal elimination to enhance removal of the drug?

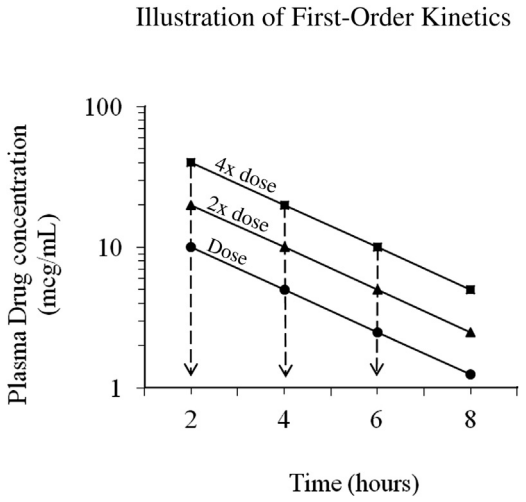

Figure 1. This simplified illustration of the concept of first-order kinetics assumes complete absorption and distribution before 2 hours. Serial plasma levels of the xenobiotic are plotted every 2 hours for 3 different initial doses. The plot shows that regardless of dose or time, the slopes of the lines (decay rate), when plotted on a logarithmic y-axis, are constant; the hallmark of 1st order kinetics. Said another way, the half-life, the time it takes for the plasma concentration to decrease 50%, is constant, in this case, about 2 hours as shown by the equal spacing of the dashed lines.

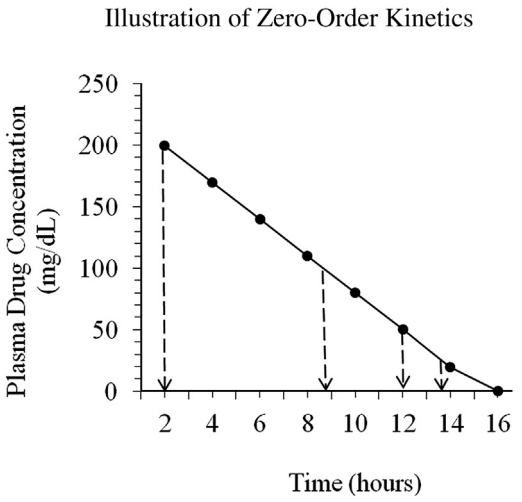

Figure 2. This simplified illustration of the concept of zero-order kinetics assumes complete absorption and distribution before 2 hours. Serial plasma levels of a theoretical xenobiotic every 2 hours are plotted assuming a clearance of 15 mg/dL per hour. The dotted lines are drawn at values 200, 100, 50, and 25 and the distance between them is the half-life. In contrast to Figure 1, they are not equally spaced illustrating that in zero order kinetics only a set amount of xenobiotic is cleared per time unit.

Pharmacokinetics include the absorption, distribution, and elimination of the xenobiotic. They are calculated with mathematical models after administration of the xenobiotic. Elimination of the xenobiotic by the body may occur because of biotransformation of the xenobiotic or excretion from the body in an unchanged form. Using traditional compartmental modeling, elimination may be described as first order when the rate of the reaction is proportional to the concentration of the xenobiotic. The kinetics are described as zero order if the elimination is a set amount of the xenobiotic per time unit. Half-life is the time needed for the plasma concentration of the xenobiotic to decrease by 50%. As illustrated in Figure 1, the half-life is constant in first order kinetics. Zero-order kinetics result in a variable half-life, depending on the plasma concentration of the xenobiotic as illustrated in Figure 2.

The pharmacokinetic information provided in most references is based on therapeutic dosing. In overdose, the pharmacokinetics may change. Time until absorption may be delayed because of the ingestion of a large amount of drug or ingestion of an extended-release formulation. In this setting, half-life may be prolonged because there is continued absorption of drug that may exceed or match the clearance. Thus, the plasma levels do not decline in the typical fashion observed with therapeutic dosing. As the route of elimination becomes saturated, the kinetics of elimination may also change from first-order to zero-order kinetics, thus further modifying the half-life. Half-life of the parent compound also does not take into account that some xenobiotics have active metabolites that prolong the clinical or toxic effects. In addition, the time of the half-life does not correspond with resolution of toxicity. The half-life indicates the time when the measured level decreases by half, not when the body burden of drug is below toxic levels.

CCBs are highly protein bound, and only the "free" or unbound drug is available to bind to the Ca^{2+} channel. The volume of distribution varies by class, with verapamil having a volume of distribution of 5.5 L/kg and diltiazem of 5.3 L/kg. Nifedipine has a much smaller volume of distribution. When extracorporeal elimination techniques are considered, the xenobiotic must have a low volume of distribution (hence in the vascular compartment), have low protein binding (so large amounts of free drug are available for removal), and be a small molecule that easily crosses membranes. The CCBs do not have a pharmacokinetic profile that would predict effective removal by extracorporeal techniques.

Q1.d The differential diagnosis of a poisoned patient who presents with hypotension and bradycardia includes CCBs, β-blockers, and imidazoline analogues such as clonidine. What clinical clues may assist with the differentiation among these classes of medications in an overdose scenario? How does the mechanism of action of receptor blockade versus channel blockade affect the treatment paradigm?

The poisoned patient who presents with hypotension and bradycardia provides a diagnostic dilemma about which type of xenobiotic is the culprit; however, there are some clinical clues that can assist in prioritizing the differential diagnosis. On physical examination, the pupillary findings may provide an initial clue. Clonidine and imidazoline analogues cause miosis in

the overdose setting. In addition, central nervous system depression is manifested early after an overdose of imidazoline; thus, this class of xenobiotics may mimic an acute opioid poisoning. With CCBs and β-blockers, miosis is not a typical finding; however, lipophilic β-blockers such as propranolol may cause sedation and coma in the absence of cardiovascular collapse.

An initial review of the bradycardia may provide clues. Because of their effect on the sinoatrial and AV nodes, CCBs and β-blockers can present with high-degree AV blocks (from first- to third-degree), as well as escape rhythms. Clonidine does not have direct action on the nodal tissue in the heart and will typically cause sinus bradycardia and is less likely to cause a second- or third-degree AV nodal blockade.

Pronounced hyperglycemia would support CCBs as the primary culprit. CCBs inhibit release of insulin from β-islet cells in the pancreas, causing hyperglycemia. β-Blockers and other medications do not have a similar effect on insulin. Hypoglycemia may be identified in β-blocker poisonings, although this is a less common presentation in adult patients. A stress response may increase the serum glucose level after any overdose, as well as underlying comorbidities such as uncontrolled diabetes mellitus.

The response to high-dose naloxone may also delineate between the different types of xenobiotics that cause hypotension and bradycardia. High-dose naloxone may improve the hypotension and mental status of a patient with acute poisoning from clonidine.[2] Naloxone does not have any specific effect for β-blocker or CCB overdose.

However, even with these techniques, clinicians must maintain a broad differential during the evaluation and management of these patients because, unfortunately, many overdose patients have coingestants.

Although both CCBs and β-blockers exert their clinical effects by altering Ca^{2+} entry into cells, they do so by different mechanisms. When activated, β receptors trigger a downstream cascade of secondary messengers that result in influx of Ca^{2+} through L-type channels. β-Blockers inhibit the initial step in this process by blocking the receptor. However, activation of those same secondary messengers (G-proteins, cyclic adenosine monophosphate) can occur through medications such as glucagon, which "bypass" the β receptor. CCBs, however, block the final step in the pathway (the L-type Ca^{2+} channel).

ANSWER 2

Q2. This study is a retrospective chart review of 48 cases of CCB poisoning collected during 25 years from a single, tertiary care, regional referral center for poisoned patients.

Q2.a Discuss some of the limitations associated with performing chart reviews on poisoned patients. How might these limitations affect the generalizability of these results to another population of poisoned patients? What additional limitations might affect the reliability of the data, given that they were accumulated during 25 years? How might these limitations affect the authors' conclusions?

Case series are a common way of presenting data on acute poisonings. The difficulty with use of retrospective chart review is that the data of interest may not be in the medical record (ie, reporting bias). Such case series are prone to recall and surveillance bias in that poisoned patients and the clinicians who treat them might be more likely to remember and inquire about specific exposures that might not be recalled or reported in nonpoisoned patients. Investigators who are not blinded to the outcome may search the medical records more thoroughly for specific exposures in cases than controls, resulting in further bias.

During a 25-year period, there have been changes in the ability to monitor the patient, nursing care, ventilator techniques, and the degree of supportive care. A patient who presented 25 years ago may have had different "supportive care" than a patient who presented in the last 2 to 3 years. One strength of the study is that it was conducted in a single institution, and the authors provided direct patient care and would be cognizant of some of the changes in care over time; however, such changes are hard to identify and adjust for the effect on the outcome of interest. As a result of these limitations, this study is not conclusive; rather, it generates questions for hypotheses for future studies.

Q2.b How did the authors define the study population? Why did they require documentation of verapamil or diltiazem in urine by gas chromatography/mass spectrometry for inclusion yet also review charts of 12 patients lacking documentation of urine confirmation? What additional data may have more accurately defined the population of CCB-poisoned patients, as well as the severity of the poisoning?

The study population was a convenience sample of subjects aged 14 years and older who were treated for verapamil or diltiazem poisoning by the toxicology service. Verification of exposure to verapamil and diltiazem was confirmed by gas chromatography/mass spectrometry of urine samples obtained from the subjects. Of the 63 subjects with medical records (records of 6 subjects could not be located), 12 did not have results for the chromatography and spectrometry. Of the 48 subjects who had confirmation of diltiazem or verapamil in the urine, the presence of coingestants was common, with 38 of the 48 having at least 1 coingestant, 8 of whom also had exposure to a β-blocker.

The confirmation of the presence of verapamil and diltiazem was important to define the population; however, this does not confirm that the exposure resulted in the disease, particularly with coingestants such as β-blockers. Remember that a case series may suggest an association between an exposure and an outcome but cannot establish the validity of this relationship. The coingestants were not provided for the individual cases and may make it impossible to determine whether the cardiovascular collapse was due to CCB exposure. The sensitivity of chromatography and spectrometry was not provided to determine which additional xenobiotics may have been present in the urine but not identified, such as imidazole derivatives. One laboratory value that correlates with severity of CCB poisoning is the degree of hyperglycemia. Levine et al[3] published a retrospective review of acute verapamil and

diltiazem poisonings in a total of 40 patients. The serum glucose concentrations correlated with the severity of toxicity from the CCB for the composite outcomes of inhospital mortality, need for a pacemaker, or need for vasopressors. Documentation of the glucose levels in the case series by Levine et al[1] may have further corroborated the severity of the CCB poisoning.

ANSWER 3

Q3. Levine et al[1] conclude "that management with high-dose vasopressors without hyperinsulinemic euglycemia is not detrimental, given complete recovery in all but 1 patient. [W]e recommend the use of initial fluid challenges and vasopressors as first choices in supporting blood pressure and treating shock caused by verapamil and diltiazem toxicity."

Q3.a The management of CCB poisoning includes a variety of approaches. Describe how the following treatments are theorized to counter the toxic effects of CCBs. (1) Calcium. Specifically contrast the differences between calcium chloride and calcium gluconate in reference to the available calcium in each formulation, risks of administration, and possible routes of administration. (2) Insulin with glucose. Why are high doses of insulin (nondiabetic doses) thought to be beneficial? (3) Glucagon. (4) Vasopressor and inotropes. How would the class of CCB ingested in an overdose influence the initial choice of vasopressor?

In addition to basic resuscitative measures, the treatment algorithm for CCB poisoning involves multiple pharmacologic therapies. Unfortunately, no individual pharmacologic intervention has provided consistent success in reversal of the cardiovascular collapse.

1. Ca^{2+} has generally been an initial treatment in CCB-poisoned patients, given a dose-dependent improvement in cardiac output in an animal model.[4] Although there are inconsistent data to establish an effective dose in humans, intravenous administration of Ca^{2+} is hypothesized to increase the transmembrane gradient, which may overcome the competitive antagonism of the CCB and drive more Ca^{2+} intracellularly through Ca^{2+} channels that are still functional. There are 2 forms of Ca^{2+} salts available: calcium chloride and calcium gluconate. Calcium chloride has approximately 3 times the available Ca^{2+} compared with the gluconate formulation when similar weights are used. However, calcium chloride may cause significant tissue injury if it extravasates through a vessel, so administration through central venous access is usually recommended.
2. Insulin is beneficial by a variety of mechanisms. It has a direct, positive inotropic effect on the heart while increasing Ca^{2+} entry into the cell. Insulin also plays an important role in carbohydrate metabolism. During drug-induced shock, the heart preferentially uses carbohydrates (such as glucose) as its energy source. Insulin aids the heart in absorbing glucose during these states and therefore improves myocardial contractility. The dose of insulin used for CCB poisonings has ranged from 0.1 to 1 to 2 units/kg per hour intravenously. Higher dosing has been reported as well. Maintaining euglycemia during these infusions provides an appropriate amount of energy stores for the heart while preventing the negative effects of hypoglycemia.[5]
3. Glucagon is classically used as a first-line "antidote" in β-blocker poisoning because it bypasses the β receptors to activate the same secondary messengers. Even though CCB inhibition occurs downstream of the glucagon binding site, glucagon may be beneficial because of its direct myocardial inotropic actions, presuming that not all of the Ca^{2+} channels are blocked.[6]
4. Vasopressors are the hallmark of treatment for hemodynamically compromised patients. The literature reports cardiovascular benefit with most of the typical pressors; however, failures have also been published. Targeting the cause of the hypotension (negative inotropy versus peripheral vasodilation) is a reasonable strategy. The initial selection of a vasopressor, however, can be tailored to the class of CCB ingested. For instance, dihydropyridines selectively affect the peripheral vasculature, so medications that have more α_1 agonist activity are logical choices. The difficulty is that the optimal dose of vasopressors in the setting of CCB or polypharmacy poisoning is not known, and the article by Levine et al[1] brings this question to light, given the maximal infusion rates administered to patients as outlined in Table 2 in the article by Levine et al.[1]

Q3.b Describe the complications of high-dose vasopressor therapy. What information would be helpful to discern whether the incidence of complications reported in this study is less than expected or at expected levels?

The complications from high-dose vasopressor therapy are typically related to the vasoconstriction of vessels with resultant ischemia of tissue. As a result, complications such as myocardial ischemia, mesenteric ischemia, limb or digit necrosis, or acute tubular necrosis leading to renal failure may occur. The risk for developing these complications is also influenced by the health of the patient before initiation of the vasopressors. Dysrhythmias may also occur because of enhanced β-adrenergic activity by some vasopressors.

Levine et al[1] reported the frequency of possible ischemic events in the study population. They assumed that all possible complications were listed in the medical records. There is difficulty in determining whether these ischemic events may have been related to the vasopressor therapy or were caused by the poor perfusion to the target organ as a result of the cardiovascular effects of the overdose. Having an idea of the "typical" complication rate of vasopressors would allow comparison to the data in this study to determine whether the frequency of vasoconstrictive complications exceeded that observed in other uses of vasopressors. Unfortunately, most trials involving comparisons of vasopressor agents have been performed in subjects with septic shock, and complication rates for these patients may not be generalizable to the overdose population.

Q3.c How were the possible complications of high-dose vasopressor therapy defined in this study? How were all subjects evaluated for these possible complications of the high-dose vasopressor therapy?

The vasopressors were defined as drugs that provide cardiovascular support through α- or β-adrenoceptor agonism. The endpoints of complications from the vasopressor therapy were defined for acute tubular necrosis (creatinine level greater than 1.5 mg/dL for at least 2 days and urine sodium level greater than 40 mEq/L or a written diagnosis of acute tubular necrosis by a nephrologist) and the ischemic complications of extremities, heart, intestines, brain, or kidneys. Of the 48 subjects who had confirmation of exposure to verapamil or diltiazem, 41 required therapy, and of these, 33 were treated with vasopressors. Five of these patients met the definition of possible ischemic events, but whether these patients are inclusive of the 4 patients who had an inhospital cardiac arrest is not clear. According to Table 3, each of the 5 had some element of ischemia on presentation, so their outcomes may be related to injury from hypoperfusion. The duration of the elevated creatinine level is not described and may not have been available, given the retrospective nature of the study. The data are not clear about whether all subjects had evaluations that would have led to a diagnosis of an ischemic complication. In addition, the technology and laboratory markers for certain diagnoses such as myocardial infarction have evolved during the 25 years of the study.

ANSWER 4

Q4. A novel therapy being introduced in the management of various overdoses such as verapamil poisoning is intravenous lipid emulsion (ILE) therapy.

Q4.a What is the proposed mechanism of action of ILE as a treatment modality? What are the theoretical risks associated with its use? How might a drug's pharmacokinetics such as its volume of distribution predict whether ILE could be beneficial as a treatment modality?

ILE is the rapid infusion of lipid emulsion 20% in the attempt to improve the hemodynamics of an acutely poisoned patient. It was initially described in the anesthesiology literature as a treatment modality for local anesthetic toxicity, particularly bupivacaine. ILE is not approved by the Food and Drug Administration for this indication, and the dose of ILE for this purpose is not well defined, although recommendations have been published.[7]

Although the exact mechanism of ILE is not clear and is probably multifactorial, the focus of many studies has been the lipophilicity of ILE and the ability to provide a "lipid sink" for redistribution of the toxicant from the receptor/cell site to the intravascular volume space. Animal studies have suggested that clinical parameters improve when the toxicant redistributes into the blood compartment after administration of ILE. This suggests a redistribution of the toxicant out of the tissue compartment and presumably away from the site of action (receptor, channel, etc). Potential risks from administration of ILE include hypersensitivity syndromes, phlebitis, fat emboli syndrome, and lung injury (usually described in ICU patients who advertently receive large doses of ILE used for nutrition support).

Volume of distribution is a calculated number representing the proportion of dose of the xenobiotic relative to the plasma concentration. The lipid sink model of ILE would suggest that xenobiotics with a higher volume of distribution would be more likely to redistribute into the plasma after the administration of the ILE. The theoretical benefit of the lipid sink model assumes that the intoxicant exerts less toxicity when located in the plasma compartment. Further studies are needed to determine the efficacy of ILE in human poisonings and better define the dosing model because it may not be the same for all xenobiotics.

Q4.b Given the mechanism of action of CCBs on the metabolic capacity on the heart, what are other proposed mechanisms of action that ILE may provide in the improvement of cardiovascular parameters in the setting of a CCB poisoning?

The myocardium prefers to use fatty acids for its energy needs when it is in a nonstressed state. In the setting of poisoning from β-blockers and CCBs, the myocardium switches to carbohydrates as its energy source. In the setting of a stressor, the liver will initiate glycogenolysis to release more glucose into the body; however, insulin release is inhibited by the CCBs. They may also inhibit phosphatidyl inositol 3-kinase mediated glucose transport into cells. Verapamil inhibits intracellular processing of fatty acids. Thus, in the setting of CCBs, there are multiple mechanisms by which the myocardium does not have adequate substrates for metabolism.

ILE provides fatty acids that may be used by the myocardium, which may contribute to improve hemodynamic performance.[7] In addition, the fatty acids may increase intracellular Ca^{2+}concentration by activating voltage-gated Ca^{2+} channels. ILE may augment this process because this has been demonstrated in isolated myocytes using long-chain fatty acids.[8]

Q4.c Discuss how a researcher might design a study to investigate whether ILE is a safe and effective treatment in patients with acute CCB poisonings. Would a prospective, randomized controlled trial necessarily be the most efficient initial investigation? Discuss potential problems associated with conducting such a trial in acutely poisoned patients.

Although the randomized controlled trial is considered the criterion standard for experimental investigations, this study design is generally not practical for studying the acute management of human poisonings. Many of the human data are reported from observational studies that are descriptive, such as case reports and case series. The reporting of case reports and case series may generate questions for further study but does not determine causality. Cross-sectional studies may be helpful to determine prevalence but are not helpful in determining efficacy in treatment of disease.

Analytic studies may also be observational in their design, such as cohort studies or case-control studies. Although a cohort study may provide more robust evidence of association, many poisonings have small sample sizes so a case-control study may be more feasible.

The enrollment of subjects for a trial examining an aspect of poisoning is usually a convenience sample (whoever presents to

the hospital with a poisoning) with uncontrolled dosing and time of ingestion relative to time of presentation to a health care facility. In addition, potential subjects may ingest more than 1 class of xenobiotic, leading to a mixed toxidrome. As a result, there are many confounders that would dilute the certainty of conclusions. Trials would have to be multicenter because patients of a specific poisoning present in small numbers to individual institutions. The sample size needed to treat to determine whether the null hypothesis can be rejected can be large. Determining the outcome of choice can also be challenging. When the outcome is survival or death, large numbers of subjects are required because the incidence of death is low in the noninterventional group. Surrogate markers may be used for outcomes, but great care must be taken not to introduce bias.

Trials of comparison of an intervention (ILE, vasopressors) against a "control" group that receives the standard of care therapy are difficult because investigators must then agree on what the standard of care therapy should be for that toxicant. As observed with CCBs, the approach can be quite varied. Historical controls are sometimes used in toxicology; however, the outcome must be easily defined because surrogate outcomes may be influenced by treatments, including the type of "supportive care" that is received. The influence of the complexity and degree of supportive care can be of a greater magnitude than the intervention. A registry of cases may also generate hypotheses; however, these are only as robust as the accuracy of the data entered into the registry.

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