Relatively New Antidotes: Fomepizole, Octreotide, and Hyperinsulinemia Therapy

Robert J. Hoffman, MD

Mustafa Al-Chiabi, MD

Maria Ho, DO

Beth Israel Medical Center, Department of Emergency Medicine, New York, New York, USA

Corresponding Author:
Robert J. Hoffman, MD,
Email: rjhoffman@pol.net

Reprints not available.

Abstract

In the past decade, several antidotes have been developed as therapy for specific poisonings. Herein we review three relatively new antidotes, fomepizole for toxic alcohol poisoning, octreotide for sulfonylurea-induced hypoglycemia, and hyperinsulinemia therapy for calcium channel blocker poisoning

Fomepizole, also known as 4-methylpyrazole, is a competitive inhibitor of alcohol dehydrogenase used to prevent metabolism of ethylene glycol and methanol to their respective toxic metabolites. Octreotide is a somatostatin analog that inhibits pancreatic insulin release, preventing hypoglycemia associated with sulfonylurea ingestions. Hyperinsulinemia therapy is beneficial in treating the cardiovascular depression from calcium channel blocker toxicity in which hypoinsulinemia plays a critical role in cardiac dysfunction.

Although these antidotes have been used for a relatively short time, the available evidence attesting to their efficacy and safety and superiority to alternative antidotes is highly encouraging. As a result, these antidotes are recommended for consideration as first-line agents with other initial therapies for their respective indicated poisonings

Keywords: Ethylene glycol, Methanol, Sulfonylurea, Calcium channel, Blocker, Antagonist, Poisoning, Toxicity, Fomepizole, Octreotide, Insulin, Antidote

Introduction

The following is a review of antidotal treatments for specific poisonings. Although these antidotes have not been in general use for a long period of time, the available evidence about their efficacy is extremely encouraging. Based on this evidence, each of the following antidotes should be considered for administration as first-line agents with other initial therapies for their respective indicated poisonings.

Fomepizole for Toxic Alcohol Poisoning

Fomepizole, also known as 4-methylpyrazole, acts as a competitive inhibitor of alcohol dehydrogenase. In cases of toxic alcohol ingestion, fomepizole prevents the formation of the toxic metabolites of ethylene glycol and methanol. Additional suggested uses for fomepizole include treatment of poisoning with butoxyethanol, butanediol, diethylene glycol, or propylene glycol, as well as treatment of the disulfiram/ethanol reaction or the similar acetaldehyde accumulation in alcohol-sensitive patients.

Ingestion of toxic alcohols initially produces an elevated osmolar gap that progressively diminishes as a concomitant and inverse elevation of anion gap and metabolic acidosis occurs. During this period of metabolic acidosis, the toxic metabolites exert damage on their respective target tissues as well as causing systemic toxicity.

Ethylene glycol is a common constituent of antifreeze and de-icing solutions. The accessibility of ethylene glycol, its intoxicating properties, and its sweet taste may result in the ingestion of ethylene glycol as a substitution for ethanol in alcohol abusing patients.

The oxidation of ethylene glycol to glyoxylate, and subsequently to oxalate, results in the conversion of pyruvate to lactate and in the production of lactic acidosis. Oxalate precipitates with calcium to form calcium oxalate crystals, which appear primarily in the renal tubules. The deposition of these crystals in the proximal renal tubules results in the development of renal failure.

Almost all cases of acute methanol toxicity result from ingestion, though rare cases of inhalation or dermal toxicity are reported. Methanol is widely available as an antifreeze agent in windshield wiping fluid and as a fuel for camp stoves and chafing dishes. Methanol is metabolized in a sequential fashion principally in the liver. Alcohol dehydrogenase is the primary enzyme responsible for the oxidation of methanol to formaldehyde. The oxidation of formaldehyde to formic acid is facilitated by formaldehyde dehydrogenase. At physiological pH, formic acid dissociates to formate and a hydrogen ion. The magnitude of acidosis correlates with formic acid accumulation and the decrease in plasma bicarbonate closely parallels the increase in the plasma formic acid concentration, hence the acidosis seen early in the clinical course is caused by formic acid production. Ocular toxicity is caused by formic acid directly and not by the metabolic acidosis that accompanies its accumulation. However, the acidosis increases toxicity by favoring the undissociated form of formic acid that diffuses more easily into retinal cells. There it binds to cytochrome oxidase, exerting a similar effect as cyanide and resulting in histotoxic hypoxia and depleting retinal and optic nerve ATP. MRI and CT scans and pathological findings at autopsy show signs of edema and necrotic damage to the basal ganglia of the brain, specifically the putamen, and hemorrhages in the subcortical white matter (1).

Since the 1940s, the traditional treatment for toxic alcohol ingestion has been the therapeutic administration of ethanol. Ethanol acts as a competitive inhibitor of alcohol dehydrogenase, thus preventing the formation of the toxic metabolites of ethylene glycol and methanol. The disadvantages of ethanol therapy include difficulty of preparation, dosing and monitoring. A 5% ethanol solution is a hyperosmolar solution (950mOsmol/L) that also may cause osmotic dehydration and venous irritation. It may also cause pancreatitis and gastritis. Ethanol infusions are commonly associated with adverse side effects ranging from mild inebriation to major toxicity inducing cardiovascular collapse and death.

Fomepizole should be administered as soon as possible after suspected ethylene glycol or methanol ingestion. Proposed indications for the use of fomepizole are listed in **Table 1**.

Serum fomepizole concentrations in excess of 0.8 mg/L provide constant inhibition of alcohol dehydrogenase as shown in human volunteer and animal studies (2,3). Brent et al. (4) reported a case series of 11 patients with methanol poisoning that utilized a loading dose of fomepizole of 15 mg/kg followed by intravenous doses

Table 1: Protocol for fomepizole therapy for toxic alcohol poisoning (9).

1. Assess for corroborating evidence of toxic alcohol ingestion, including:

   i. A documented plasma methanol / ethylene glycol concentration > 20 mg/dL or

   ii. Documented recent history of ingesting toxic amounts of methanol/ethylene glycol and osmolal gap >10 mOsm/kg H_2O or

   iii. A history or strong clinical suspicion of methanol/ethylene glycol poisoning and at least two of the following criteria: arterial pH < 7.3; serum bicarbonate < 20 meq/L; osmolal gap > 10 mOsm/kg H2O. With respect to ethylene glycol, the presence of urinary oxalate crystals is an additional criterion. In cases of suspected methanol poisoning, the presence of ophthalmologic abnormalities.

2. If any of the preceding criteria are met, administer fomepizole.

   i. A loading dose of 15 mg/kg followed by intravenous doses of 10 mg/kg every 12 hours for the first four doses.

   ii. Subsequently, higher doses of 15 mg/kg every 12 hours are administered.

3. In cases of hemodialysis, dosing is as follows:

   i. Dose at the beginning of hemodialysis

      a. If < 6 hours since last dose, administer none.

      b. If > 6 hours since last dose, give next scheduled dose.

   ii. During hemodialysis administer dose every 4 hours.

   iii. At the time that dialysis is completed

      a. If < 1 hour since last dose, administer no additional dose

      b. If 1-3 hours since last dose, administer 50% of the next scheduled dose.

      c. If > 3 hours since last dose, administer the next scheduled dose.

   iv. When off hemodialysis, administer maintenance doses at regular 12 hour intervals.

of 10 mg/kg every 12 hours for the first four doses with is then increased to 15 mg/kg every 12 hours. Monitoring of fomepizole concentrations for clinical reasons is unnecessary. Fomepizole dosing is continued until the ethylene glycol or methanol concentration is undetectable or less than 20 mg/dL and the patient is asymptomatic with a normal arterial pH (5). Fomepizole does not diminish ocular, renal, and metabolic toxicity of the toxic alcohols that have already been metabolized by ADH - it only prevents metabolism and does not impact on whatever quantity of toxic alcohol that is already converted to toxic metabolite. Hemodialysis may be necessary because the toxic alcohol has already been partially metabolized or because the half-life of methanol is too long to wait for natural clearance in patients treated with fomepizole. Methanol poisoned patients might require a full week on fomepizole therapy before the blood methanol level is non-toxic.

Hemodialysis should be considered for the following conditions:

- Significant metabolic acidosis <7.25–7.30.
- Abnormalities of vision
- Deteriorating vital signs despite intensive supportive care
- Renal failure, or
- Electrolyte imbalance unresponsive to conventional therapy.

A serum methanol/ethylene glycol concentration >50 mg/dL.

Fomepizole dose not cause CNS depression, and thus will not interfere with the evaluation of a patient who has ingested other substances with CNS depressant activity. Use of fomepizole in children offers the advantage of avoidance of hypoglycemia or free water excess commonly associated with ethanol infusions in children. It additionally avoids the creation of a prolonged state of inebriation in children who receive ethanol.

Fomepizole is devoid of most of the side effects encountered with ethanol therapy, and as such is overwhelmingly safer to administer. It is also easier to administer than ethanol and has a longer duration of action, requiring less frequent dosing. It has a standardized and less complicated dosing regimen that does not require direct observation and frequent blood monitoring, thus reducing intensive care unit costs. In the U.S., fomepizole is an extremely costly drug. A package of 4 vials distributed for use in a single patient is several thousand dollars. Methanol intoxication can be particularly expensive due to the long half-life of methanol when

alcohol dehydrogenase is blocked with fomepizole, and such therapy can easily cost more than US $10,000.

The most commonly reported adverse effects were headache (12%), nausea (11%) and dizziness (7%). Case reports have temporally associated eosinophilia and skin rash (6,7). In addition, following the administration of fomepizole, transient mild elevation of serum hepatic transaminase concentrations that lasted 1-2 weeks have been observed (8). This is more commonly seen with prolonged dosing. The main contraindication to using fomepizole is any known hypersensitivity to fomepizole or any pyrazole compounds.

Octreotide for Sulfonylurea Hypoglycemia

Sulfonylurea agents are widely used as therapy for type 2 diabetes. Hypoglycemia is the most common adverse effect of therapeutic doses of sulfonylureas. Ingestion of these agents may cause severe hypoglycemia resulting in permanent neurologic disability or even death.

Ingestion of even a single tablet by a nondiabetic patient may result in profound hypoglycemia, particularly in children (11).

Sulfonylurea agents produce hypoglycemia by facilitating release of insulin from pancreatic beta islet cells (12). Treatment of sulfonylurea-induced hypoglycemia has traditionally included administration of dextrose and frequent monitoring of serum blood glucose levels. Administration of parenteral dextrose expectedly results in a release of pancreatic insulin in response to hyperglycemia, and use of dextrose to treat sulfonylurea-induced hypoglycemia is a well-documented cause of recurrent, prolonged hypoglycemia (13). Glucagon is not recommended for routine use in cases of sulfonylurea-induced hypoglycemia because it acts as an insulin secretagogue. Because of its propensity to cause hypotension (14), nausea and vomiting as well as its relatively poor efficacy as an antihypoglycemic agent, diazoxide should be avoided in cases of sulfonylurea-induced hypoglycemia.

Most cases of sulfonylurea-induced hypoglycemia occur within 6-12 hours, though hypoglycemia may occur as late as 12-16 hours after ingestion. After ingestion of multiple tablets, the onset of hypoglycemia is typically unchanged but the duration of symptoms may be drastically prolonged. Many of the commonly used sulfonylurea drugs are long acting, which allows them to be dosed once daily but causes prolonged illness in toxicity. In therapeutic dosing, chlorpropamide may have a duration of action of 60 hours and glyburide, glipizide,

glimepiride, and tolazamide may have a duration of action of 24 hours. In overdose, these agents act longer. The duration of action will also be prolonged in patients with diminished ability to hepatically metabolize or renally excrete sulfonylureas.

Octreotide is a synthetic analogue of somatostatin, an endogenous human hormone. Octreotide inhibits secretion of numerous hormones, including insulin, glucagon, and others, and is used for a variety of endocrine and gastrointestinal indications. Octreotide inhibits pancreatic release of insulin, and this effect is the basis of its use in cases of sulfonylurea-induced hypoglycemia. Administration of octreotide in cases of sulfonylurea-induced hypoglycemia prevents rebound hypoglycemia that results from parenteral dextrose administration. Since 1993, octreotide has been recognized as an efficacious and pathophysiologically sensible treatment for sulfonylurea-induced hypoglycemia (15).

Use of octreotide prevents hypoglycemia and reduces or eliminates the necessity for repeated administration of glucose, also reducing the frequency of repeated serum glucose measurements necessary (16). Additionally, it may obviate the need for central venous access used to administer concentrated glucose solutions.

The most frequently recommended dosing of octreotide for sulfonylurea-induced hypoglycemia is 1 mcg/kg to a maximum of 50 mcg/dose administered subcutaneously every 8 hours (17,18). The adverse effects reported from this manner of octreotide use include local discomfort at the injection site, nausea, and abdominal discomfort.

In any case of known or suspected sulfonylurea ingestion, rapid bedside assessment of the serum glucose concentration should be conducted. If hypoglycemia is present it should be treated immediately with parenteral dextrose. If hypoglycemia is not present, the patient may be fed glucose and carbohydrate-rich food, but parenteral dextrose should not be administered prophylactically as it complicates and prolongs management. Because hypoglycemia may occur late after ingestion, it is necessary to assess serum glucose concentration on an hourly basis for a minimum of 12-16 hours after sulfonylurea ingestion, particularly in a child.

Patients treated with parenteral dextrose should also be treated with octreotide. After initial treatment with octreotide, glucose monitoring should occur at 30-minute intervals for one hour. Thereafter, glucose monitoring may be delayed to intervals of every 2-4 hours. The duration of octreotide therapy should be based on the type of sulfonylurea ingested and the dose of the sulfonylurea. After discontinuation of octreotide therapy, the patient should undergo serum glucose measurements every hour for 8-12 hours. In practice, this would require assessment of serum glucose concentrations beginning 8 hour after the last dose of octreotide and continuing for 8-12 hours. The rationale for this is that when octreotide is not suppressing insulin release, it is possible for the patient to experience prompt and severe hypoglycemia. Recurrence of hypoglycemia at that time should not be considered a failure of octreotide therapy but rather insufficient duration of therapy with octreotide. If hypoglycemia recurs, prompt therapy with parenteral dextrose and octreotide should be administered. Generally, octreotide therapy is required for a minimum of 2-3 doses (16-24 hours) followed by a period of observation after octreotide discontinuation. Prolonged hypoglycemia lasting up to 7 days have been reported (19).

Octreotide is a highly efficacious, well tolerated, and easy to administer antidote recommended for routine use in cases of sulfonylurea-induced hypoglycemia. Patient-to-patient variation in type and quantity of sulfonylurea ingested as well as response to toxicity results in variation in duration of octreotide therapy necessary.

Table 2: Protocol for octreotide therapy in treatment of sulfonylurea-induced hypoglycemia

1. Measure blood glucose at the bedside

   i. If glucose <60 in adult or < 40 in a child, administer 0.25 mg/kg of dextrose to a maximum of 1 ampoule of D50. If possible, feed the patient glucose and carbohydrate-rich food.

   ii. Reassess the blood glucose at least every 30 minutes for one hour after octreotide administration.

   iii. If glucose is above these cutoff levels, oral administration of glucose/carbohydrate rich foods is appropriate.

2. If parenteral dextrose is required due to hypoglycemia, administer octreotide.

   i. 1 mcg/kg to a maximum dose of 50 mcg administered subcutaneously.

   ii. Repeat octreotide administration every 8 hours.

   iii. At lease 2-3 doses (16-24 hours) of octreotide should be administered

3. When discontinuation of octreotide is attempted:

   i. 8 hours after the last octreotide administration, resume measuring blood glucose on an hourly basis.

   ii. This should continue for 8-12 hours.

   iii. If hypoglycemia recurs, administer parenteral dextrose and resume octreotide therapy.

Hyperinsulinemia/Euglycemia Therapy for Calcium Channel Blocker Toxicity

Calcium channel blocker (CCB) toxicity may be associated with bradycardia, cardiac conduction delay, hypotension, hypoinsulinemia, hyperglycemia and elevation of serum lactate (20). This is particularly true for the conduction modulating calcium channel blockers verapamil and diltiazem as opposed to newer dihydropyridine agents such as nifedipine, amlodipine and others that primarily cause hypotension. The clinical features of toxicity are the result of blockade of L-type calcium channels in myocardial, vascular smooth muscle, and beta-islet pancreatic cells. Traditional therapy of CCB toxicity has focused on the life threatening cardiovascular effects. Current therapies include administration of intravenous fluids, atropine, glucagon, parenteral calcium, and pressors including dopamine, dobutamine, and norepinephrine. These therapies are largely ineffective in severely poisoned patients.

In recent years, animal data and a growing body of clinical experience in humans has led to support and advocacy of high-dose insulin/euglycemia (HIE) therapy for calcium CCB toxicity (21-23). Due to the ineffectiveness of other therapies and the striking benefit of HIE therapy, HIE therapy in considered a treatment that should be administered "early in the treatment of…CCB toxicity" (20). The most comprehensive case series of the phenomenon has demonstrated survival without sequelae of verapamil overdoses with the highest recorded serum verapamil levels for which HIE therapy was initiated due to failure of standard therapies (24).

The precise mechanism by which HIE therapy is beneficial in CCB toxicity is poorly defined. Hypoinsulinemia appears to be a critical factor in CCB toxicity, and it is presumed that counteraction of this is the method by which HIE is effective (25). In an unstressed state of aerobic metabolism, myocytes rely on free fatty acid oxidation for energy. In shock states including CCB toxicity, myocytes rely on glucose utilization for energy. Utilization of glucose by myocardial tissue is presumed to be compromised during hypoinsulinemia. As inotropy, chronotropy, and peripheral vascular resistance progressively deteriorate, myocardial perfusion progressively deteriorates in a cycle of worsening perfusion of tissue ultimately leading to hemodynamic compromise, shock, and death.

Administration of HIE therapy improves inotropy and peripheral vascular resistance and has been anecdotally demonstrated to improve cardiac ejection fraction. The positive inotropic effect of insulin has been demonstrated in both humans and animal models. Typically in cases of CCB toxicity, HIE therapy results in improved arterial blood pressure and pH. Other symptoms, including bradycardia, heart block, and conduction delay do not routinely respond to HIE therapy. These beneficial effects of HIE therapy may not be evident until 30-60 minutes after therapy is initiated, and other therapies may be required until HIE is effective. Although there is significant animal evidence attesting to the efficacy of HIE therapy for CCB toxicity, human data is limited to case series in which this therapy has been instituted. As a result there is variation in recommended protocols for HIE therapy advocated by toxicologists.

The two largest case series of HIE therapy for CCB toxicity suggest that insulin dosing of 0.5 units/kg/hour is appropriate. Our treatment recommendations are to begin therapy with an initial bolus of insulin, 1 unit/kg, followed by the infusion at a dose of 0.5 units/kg/hour. Infusion dosing may be increased as high as 1 unit/kg/hour or decreased to as low as 0.2 units/kg/hour depending on clinical response. It is important to remember that the full clinical response to HIE therapy may not be evident until a full hour after initiation.

Administration of insulin in HIE therapy must be accompanied by dextrose infusion to maintain euglycemia. After initiation of insulin therapy, assessment of the serum glucose by bedside measurement should occur. The necessity for an initial bolus of glucose depends on the serum glucose measurement. If a patient has a serum glucose greater than 200 mg/ dL, the initial bolus of glucose may be withheld. If the serum glucose is less than 200 mg/dL, an initial glucose bolus of 0.5-1 g/kg should accompany the initial insulin bolus, thereafter a glucose infusion rate of 1 g/kg/hour is initiated and may be titrated as needed to maintain euglycemia. When titrating insulin and glucose infusions in HIE therapy, titration of insulin infusion is manipulated for clinical effect counteracting the deleterious cardiovascular depression of CCB toxicity and titration of glucose infusion is simply to maintain euglycemia. Any downward titration of glucose infusion should be accompanied by assessment of the serum glucose every 30 minutes for 4 hours. It is of the utmost importance to monitor serum glucose frequently, particularly at the initial stages of HIE therapy.

Hypokalemia is a benign side effect of HIE therapy. A drop in serum potassium is of theoretical benefit in CCB toxicity by mechanism of prolonging ventricular myocyte action potential plateau. Hyperkalemia is noted to worsen ventricular function in animal models of verapamil toxicity. It is unlikely that there is any need for potassium supplementation, but in lieu of more comprehensive data we recommend that clinicians consider potassium supplementation for patients with serum potassium less than 2.5 mEq/L.

Duration of HIE therapy required for CCB toxicity will vary, but a range of 9-49 hours with a mean infusion time of 27 hours has been reported. Duration of HIE therapy appears to correlate with the severity of the patient's condition based on the dose ingested, the arterial blood pressure, and the degree of acidemia. Discontinuation of HIE therapy is typically based on maintenance of stable blood pressure for a degree of time considered adequate. The duration of therapy must be decided upon on a case-by-case basis until further evidence is available, but having an initial plan to administer HIE therapy for 24 hours followed by an observation period of one day is appropriate. Patients have been documented to develop hypotension after discontinuation of HIE therapy, though this is not typical. When hypotension has recurred, it has not developed abruptly. It is surmised that the high doses of insulin used saturate insulin receptors and create an excess of circulating insulin. As a result, the physiologic effects persist for hours and taper slowly as insulin dissociates from receptors and is metabolized. Failure of HIE therapy has been reported, but in this circumstance the therapy was administered extremely late in the course of poisoning (26). This case suggests that HIE therapy should not be delayed until other therapies have failed, but should be administered concomitantly.

Toxicologists authoring numerous case series, reviews, and toxicology texts advocate HIE therapy as adjunctive therapy in the treatment of CCB. We concur with authors suggesting that HIE therapy be initiated early in CCB toxicity. Further studies will determine if HIE therapy should be advanced to initial therapy for CCB toxicity.

Table 3: Protocol for hyperinsulinemia/euglycemia treatment of calcium channel antagonist poisoning

1. Measure blood glucose at the bedside

   i. If glucose <200, administer 0.25 mg/kg of dextrose to a maximum of 1 ampoule of D50.

   ii. During the first hour of insulin infusion, reassess the blood glucose every 15 minutes and hourly thereafter.

2. Administer regular insulin as an intravenous bolus (1 U/kg).

   i. Continue an infusion of 0.5- 1U/kg/hour. Begin with the lower dosage and increase after one hour if there is insufficient response. A recommended infusion is an insulin solution of 500 U insulin in 500 mL of normal saline with a concentration of 1 U/mL.

3. Assess the serum potassium concentration on an hourly basis during insulin infusion. Supplement potassium if serum concentration < 2.5 mEq/dL.

References

1. Kuteifan K, Oesterle H, Tajahmady T, Gutbub AM, Laplatte G. Necrosis and haemorrhage of the putamen in methanol poisoning shown on MRI. Neuroradiology 1998;40:158-160
2. Jacobsen D, Sebastien CS, Blomstrand R, McMartin KE. 4-methylpyrazole: A controlled study of safety in healthy human subjects after single, ascending doses. Metab Clin Exp Res 1988;12:516-522
3. McMartin KE, Headstroem KG, Tolf BR, Ostling-Wintzell H, Blomstrand R. Studies on the metabolic interactions between 4-methylpyrazole and methanol using the monkey as an animal model. Arch Biochem Biophys 1980;199:606-614
4. Brent J, McMartin KE, Phillips S, Aaron C, Kulig K. Fomepizole for the treatment of methanol poisoning. NEJM 2001;244:424-429
5. Antizol (fomepizole) formulary booklet. Orphan Medical, Inc., Minnetonka, MN 1997
6. Borron SW, Megarbane B, Baud FJ. Fomepizole in treatment of uncomplicated ethylene glycol poisoning. Lancet 1999;354:831
7. Baud FJ, Bismuth C, Garnier R, et al. 4-methylpyrazole may be an alternative to ethanol therapy for ethylene glycol intoxication in man. J Toxicol Clin Toxicol 1987;24:463-483
8. Jacobsen D, Sebastian CS, Barron SK, Carriere EW, McMartin KE. Effects of 4-methylpyrazole, Methanol/Ethylene Glycol Antidote in Healthy Humans. J Emerg Med 1990;9:455-461
9. Barceloux DG, Bond R, Krenzelok EP, Cooper H, Vale, JA: American Academy of Clinical Toxicology Ad Hoc Committee on the Treatment Guidelines for Methanol Poisoning. Clin Toxicol 2002;40(4):415-446
10. Jeffries DB, Volans GN. Self poisoning in diabetic patients. Hum Toxicol 1983;2:345-348
11. Harrigan RA, Nathan MS, Beattie P. Oral agents for the treatment of type 2 diabetes mellitus: pharmacology, toxicity, and treatment. Ann Emerg Med 2001;38:68-78
12. Gerich JE. Oral hypoglycemic agents. N Engl J Med 1989;321:1231-1245
13. Krentz, AJ, Boyle PJ, Justice KM, et al. Successful treatment of severe refractory sulfonylurea-induced hypoglycemia with octreotide. Diabetes Care 1993;16:184-186
14. Koch-Weser J. Diazoxide. N Eng J Med 1976;294:1271-1274
15. Boyle PJ, Justice K, Krentz AJ, Nagy RJ, Schade DS. Octreotide reverses hyperinsulinemia and prevents hypoglycemia induced by sulfonylurea overdoses. J Clin Endocrinol Metab 1993;76:752-756
16. McLaughlin SA, Crandall CS, McKinney PE. Octreotide: an antidote for sulfonylurea-induced hypoglycemia. Ann Emerg Med 2000;36:133-138
17. Carr R, Zed PJ. Octreotide for sulfonylurea-induced hypoglycemia following overdose. Ann Pharmacother 2002;36:1727-1732
18. Howland MA. Octreotide. In: Goldfrank LR, Flomenbaum N, Lewin NA, Howland MA, Hoffman RS, Nelson LS, eds. Goldfrank's Toxicologic Emergencies, 7th ed. New York, NY. McGraw Hill; 2002:611-613
19. Bui L, Adler D, Keller KH. Prolonged octreotide infusion to treat glyburide-induced hypoglycemia. [abstract] J Toxicol Clin Toxicol 2000;38:576
20. De Roos F. Calcium Channel Blockers. In: Goldfrank LR, Flomenbaum N, Lewin NA, Howland MA, Hoffman RS, Nelson LS, eds. Goldfrank's Toxicologic Emergencies, 7th ed. New York, NY. McGraw Hill 2002:762-774
21. Boyer EW, Shannon M, Treatment of calcium-channel-blocker intoxication with insulin infusion. N Engl J Med 2001;344:1721-1722
22. Boyer EW, Duic PA, Evans A. Hyperinsulinemia/euglycemia therapy for calcium channel blocker poisoning. Ped Emerg Care 2002;18:36-37
23. Morris-Kukosi C, Biswas A, Parra M, et al. Insulin "euglycemia" therapy for accidental nifedipine overdose. Toxicol Clin Toxicol 2000;38:577
24. Yuan TH, Kerns WP 2nd, Tomaszewski CA, Ford MD, Kline JA. Insulin-glucose as adjunctive therapy for severe calcium channel antagonist poisoning. J Toxicol Clin Toxicol 1999;37:463-474
25. Kline JA, Leonova E, Raymond RM, Beneficial myocardial metabolic effects of insulin during verapamil toxicity in the anesthetized canine. Crit Care Med 1995;23:1251-1263
26. Herbert J, O'Malley C, Tracey J, et al. Verapamil overdosage unresponsive to dextrose/insulin therapy. J Toxicol Clin Toxicol 2001;39:293-294