



The New York State Poison Centers

TOXICOLOGY

LETTER

COMPRISING THE NEW YORK CITY AND UPSTATE NEW YORK POISON CENTERS

A Compounded Problem

Ross Sullivan MD, Senior Fellow in Medical Toxicology, Upstate NY Poison Center, Syracuse, NY

Case

An 18 month old male previously healthy child was found by his mother unresponsive with gasping respirations. Emergency medical services was called and in the Emergency Department (ED), vital signs included : pulse 57 beats per minute, blood pressure 74/35 mmHg, respiratory rate 21 breaths per minute, with an oxygen saturation of 98% on a non-rebreather. Fingertick glucose returned at 105 mg/dL. Physical examination was significant for: no response to deep painful stimuli, pinpoint pupils and hyporeflexia. The patient's mental status remained unchanged, but his respiratory effort deteriorated further requiring endotracheal intubation. Laboratory results were non-contributory, and an electrocardiogram revealed only sinus bradycardia.

Upon questioning, the mother described applying ointment for a diaper rash approximately 20 minutes before the symptoms started. She used a single pump of a prescription ointment that her husband received from a compounding pharmacy for neck pain.

What makes transdermal drug delivery so appealing?

Transdermal drug preparations are ubiquitous, and are used to treat acne, skin infections, hemorrhoids, pruritis, pain, blood pressure, and many other conditions. Dermal preparations are very appealing due to the multitude of conditions treated, the ease of use, and a general thought that they are free of the adverse effects common after the use of systemic medications.

How do dermal drug delivery systems work?

Skin is a barrier that exists to keep body water in and micro-organisms and noxious chemicals out. The skin consists of three main layers: the epidermis, the dermis, and subcutaneous tissues. The epidermis also has multiple layers. The superficial layers of the epidermis, the stratum corneum, provide almost all the skin's protective properties. The stratum corneum is made up of keratin, which consists of dead skin cell remnants and fibrous proteins that overlap in layers. Most drug absorption is transcellular, or a solute movement across an epithelial cell layer through the cells, and it is unlikely that noticeable absorption occurs between cells or through sweat pores and hair follicles.¹ In addition, transdermal absorption occurs via a passive diffusion, in a concentration-dependent process. The magnitude of diffusion will depend on the integrity and also physical properties of the applied drug. Drugs with low molecular weight (below 800 daltons) with a high water and lipid solubility (drugs with high lipophilicity and hydrophilicity are desired as the layers of the skin have both lipid and hydrophilic layers) show the greatest penetration.¹

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Program Announcements ♦♦

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What are some types of transdermal medication delivery systems and what characteristics do they have?

The efficacy, tolerability, and application properties of topical medications are often related to the base (a mixture of components with various properties, most notably polarity) used. Interactions between the base, skin, and drug will influence the effect of the preparation and release of the drug.² The base of a product has a few essential properties, including polarity, hydrophilicity, and lipophilicity.

Lotions are often liquid suspensions, or a powder in a water-in-oil mixture. They possess low viscosity, and most often have low oil content. Gelling agents are sometimes added to enhance viscosity just enough to keep lotions in a readily apply-able state. Lotions have low drug penetration properties.²

Creams are multiphase preparations consisting of a lipophilic phase and an aqueous phase (emulsion). Creams are usually oil in water, or water in oil. In either case, the water content is usually less than 60% of the emulsion. Creams have moderate oil component and drug penetration properties.²

Ointments are semi-solid preparations in which solids or liquids may be dispersed. Ointments can be water-in-oil emulsion, with water content less than 40%. Some typical bases for ointments include petrolatum, paraffin's, vegetable oils, and animal fats. Ointments have high oil content and high drug penetration properties.²

Gels are semi-solid preparations that consist of a solid component, which forms a matrix, and a liquid component that exists within the solid matrix. The liquid phase is usually water or alcohol, and often contains additives like propylene glycol, glycerol, or sorbitol.² Oil content is high for gels as is its drug penetration properties.

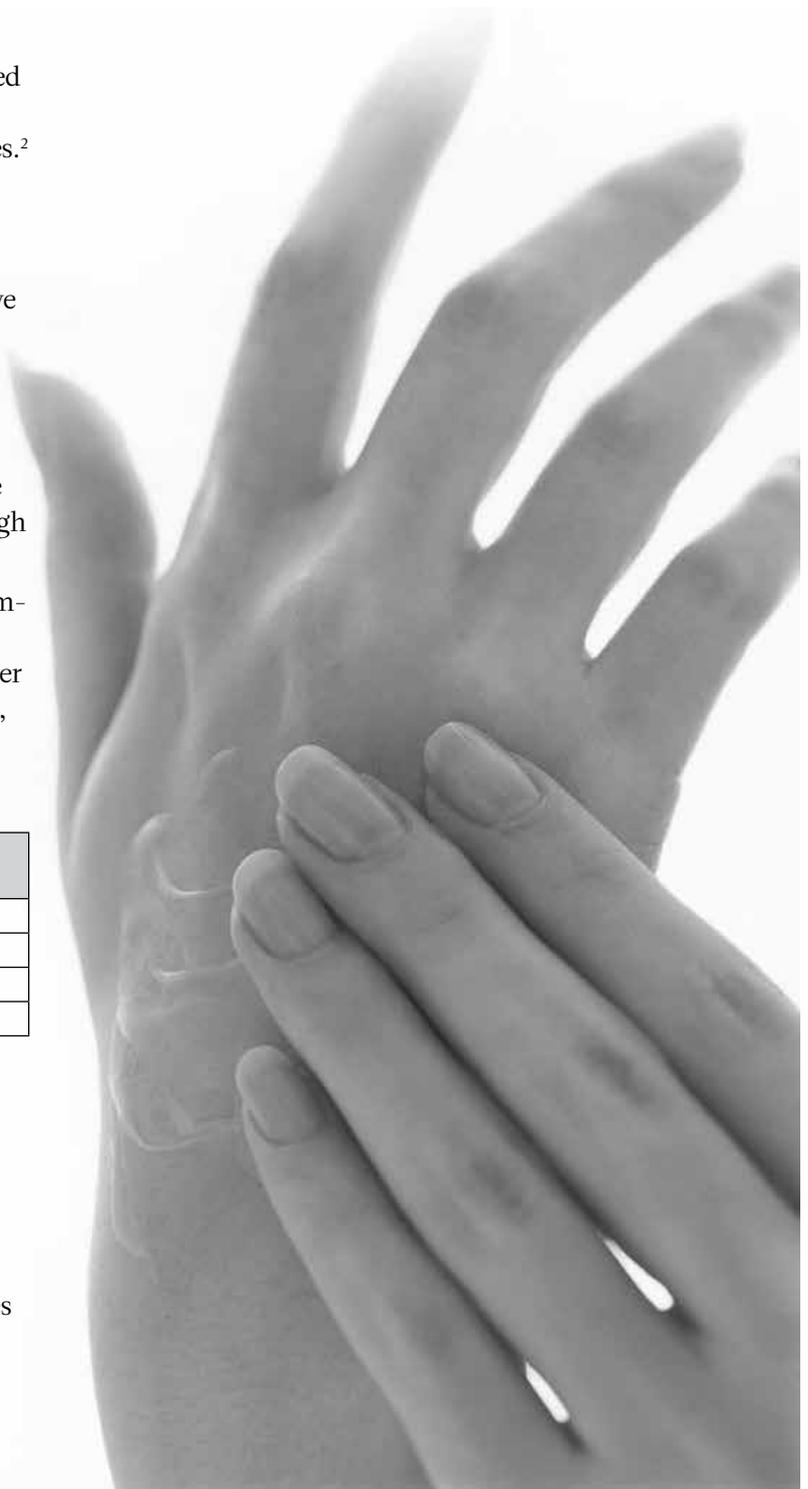
Type of base	Water Content	Oil Content	Drug Penetration
Lotion	++++	+	+
Cream	+++	++	++
Ointment	++	+++	+++
Gel	+	++++	++++

Transdermal patches are another topical delivery system. Patches contain an occlusive backing, a reservoir of drug, a microporous membrane, and an adhesive. The microporous membrane is less permeable to the drug than is the skin and therefore, is able to release the drug in a controlled and consistent way.¹ This form of delivery is touted to be convenient, requires less frequent dosing than oral preparations, produces more predictable and constant blood concentrations, can be taken by vomiting patients, and can be removed at once (although drug may still be left in the skin).¹

Case Continuation

The patient was transported to a pediatric intensive care unit (PICU). The patient's father brought in the compounded ointment. Each pump consisted of the following: Ketamine 100mg, Clonidine 2mg, Gabepentin 60mg, Mefenamic acid 10mg, Imipramine 30mg, and Lidocaine 10mg.

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Inadvertent Intravenous Epinephrine Administration

Fiona M. Garlich, M.D. and Lewis Nelson, M.D.

Case Summary:

A 2 year-old girl with a history of mild, intermittent asthma is brought to the Emergency Department via ambulance with difficulty breathing and hives after eating a cashew. She vomits once and has a near syncopal episode en route. Upon arrival to the ED, she is in acute respiratory distress, with wheezing, stridor, and tachypnea to a respiratory rate of 40/min. An urticarial rash is noted. The remainder of her vital signs include: HR, 130/min; BP, 90/62 mm Hg; T, 99°F oxygen saturation, 98% on 4L O₂ via facemask.

Epinephrine 0.15 mg of 1:1,000 concentration is prepared for intramuscular administration for a diagnosis of anaphylaxis. However, the epinephrine is inadvertently administered intravenously. The patient subsequently develops tachycardia (heart rate in the 180s/min) and hypertension (blood pressure of 120/70 mmHg).

What is the mechanism of action of epinephrine?

Epinephrine, or adrenaline, is a catecholamine that is produced endogenously in the adrenal medulla. As a medication, epinephrine is administered parenterally as treatment for anaphylaxis and cardiac arrest. Its clinical utility is based on its activity at alpha- and beta- adrenergic receptors (beta >> alpha). Alpha-1 agonism in the peripheral vasculature results in vasoconstriction. Stimulation of beta-1 receptors in the myocardium increases chronotropy and inotropy, leading to increased heart rate and contractility, respectively. Stimulation of beta-2 receptors causes smooth muscle relaxation that in the peripheral vasculature induces vasodilation, and in the bronchioles causes bronchodilation. This forms the basis for the use of nebulized or aerosolized epinephrine as treatment for bronchoconstriction.

How is epinephrine dosing calculated?

Injectable epinephrine is available in two concentrations, 1:10,000 for intravenous use and 1:1,000 for intramuscular use. Epinephrine is unusual in its labeling because it is formulated as an unconventional dilution ratio of one thousand instead of as the more conventional percent (per one hundred) concentration. Since epinephrine was introduced before the enactment of the 1938 Food, Drug and Cosmetic Act, it does not fall under current FDA labeling standards.⁴ The antiquated dilution formulation represents the volume of aqueous solution in milliliters into which 1,000 mg of epinephrine is dissolved. For example, a solution labeled as 1:1,000 represents 1,000 mg / 1,000 mL or 1 mg/mL, of epinephrine. Thus, the formulation intended for intravenous use is 10 fold more dilute than that intended for IM administration.

What are the indications and recommended doses for epinephrine administration?

According to the American Heart Association Guidelines, anaphylaxis should be treated by administration of epinephrine, 0.3 to 0.5 mg of the 1:1000 concentration IM in an adult

(0.3 to 0.5 mL), and 0.01 mg/kg of 1:1000 IM in a child (up to the adult dose).¹ Subcutaneous epinephrine administration is no longer recommended due to the achievement of more rapid peak plasma concentrations of epinephrine when administered intramuscularly in the thigh.^{8,9} This can be repeated every 5-15 minutes until clinical improvement is demonstrated. For patients who do not respond, and who demonstrate evidence of anaphylactic shock, with refractory hypotension and signs of hypoperfusion, epinephrine should be administered intravenously at a dose of 0.1 mg (adults) or 0.01 mg/kg (children; up to the adult dose) of the 1:10,000 concentration via slow IV infusion over 5 minutes. During cardiac arrest, epinephrine is administered via IV bolus at a dose of 1 mg (adults) or 0.01 mg/kg (children; up to the adult dose) of 1:10,000 concentration (up to adult doses). Epinephrine can also be administered continuously via intravenous infusion at doses of 2-10 mcg/min as a second-line therapy for shock or unstable bradycardia.

Indication	Epinephrine Dose
Anaphylaxis	adult 0.3 to 0.5 mg of 1:1,000 IM in thigh child 0.01 mg/kg of 1:1,000 IM in thigh (up to 0.3 mg)
Anaphylactic shock (refractory)	adult 0.1 mg of 1:10,000 IV over 5 minutes child 0.01 mg/kg 1:10,000 IV over 5 minutes (up to 0.1 mg)
Cardiac arrest	adult 1 mg of 1:10,000 IV push child 0.01 mg/kg of 1:10,000 IV push

What are the factors that contribute to dosing errors with epinephrine?

Confusion concerning the appropriate dose, formulation, and route of administration of epinephrine is common. Many hospital "crash carts" stock epinephrine in the intravenous formulation that is only appropriate for cardiac arrest, causing confusion or delay when a patient with anaphylaxis requires the more concentrated formulation for intramuscular delivery. Furthermore, many physicians understandably have difficulty with complex dose calculations and conversions, and this may be magnified under stressful conditions. In a survey of 150 hospital physicians, half were unable to correctly convert doses of epinephrine from a dilution to mass concentration.⁶ Physicians may not have adequate insight into the appropriate dose and concentration for anaphylaxis. In another survey of 253 radiologists in 26 U.S. and Canadian hospitals, no physician was able to give the correct dose, concentration, and route of epinephrine administration. Of those surveyed, 17% would have administered an epinephrine overdose.⁶

Inappropriate route of administration (IV vs IM) can occur when there is miscommunication between team members caring for a critically ill patient. A retrospective review of patients admitted with anaphylaxis at a single institution

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Inadvertent Intravenous Epinephrine Administration

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over a 5 year period identified a 2.4% incidence of potentially life-threatening complications from inappropriate epinephrine administration.⁴ Two of their reported cases involved the inadvertent intravenous administration of a dose and concentration of epinephrine intended for IM use. The causes of these errors were multifactorial, and were attributed to inadequate physician knowledge, lack of IM doses in emergency crash carts, complicated dose calculations involving ratios and decimal points, and lack of adequate communication between physicians and nurses. In a survey of inpatient pharmacies, only 1 of 7 responding hospitals had epinephrine available in prefilled syringes for IM administration, as is appropriate for anaphylaxis.⁴ Inappropriate intravenous epinephrine administration can also occur with infusion pump malfunction in the setting of continuous infusion.⁵

What adverse effects are associated with inadvertent overdose of epinephrine?

Tachycardia and hypertension occur following intravenous administration of inappropriately high doses of epinephrine. In many patients with acute exposures, these effects can resolve spontaneously without evidence of end-organ effects. Epinephrine is rapidly metabolized and has a short half life of approximately two minutes. However, prolonged cardiovascular toxicity has been described in both adult and pediatric populations, especially when exposure is prolonged by continuous infusion.

Case examples from the literature:

A 23 year-old woman presented with anaphylaxis and was erroneously given two doses of epinephrine 1 mg (1:10,000) as an IV bolus, instead of by slow infusion. She developed cardiogenic shock with severe left ventricular dysfunction (ejection fraction of 15%) and pulmonary edema requiring intubation. She returned to normal cardiac function after four days.⁴

A 33 year-old woman was erroneously given epinephrine 0.3 mg (1:1,000) IV instead of IM. She subsequently developed a right coronary artery dissection that was treated with intracoronary stenting.⁴

A five year-old boy developed acute myocardial ischemia, as evidenced by elevated cardiac enzymes, ECG changes, decreased left ventricular systolic function, and pulmonary edema, after epinephrine was erroneously given intravenously instead of subcutaneously.² Ventricular dysrhythmias in children receiving excessive doses of subcutaneous epinephrine as treatment for asthma are described.³

An 18-year-old man receiving continuous epinephrine infusion for septic shock developed tachycardia to 198 beats/min, hypertension to 250/188 mm Hg, pulmonary edema, and myocardial damage as evidenced by ECG changes and elevated cardiac enzymes. It was determined that electromagnetic interference from a nearby cell phone caused a malfunction of the infusion pump, resulting in the delivery of an excess 10.5 mg of epinephrine over a period of 1.4 minutes.⁵

What are some therapeutic considerations for iatrogenic epinephrine overdose?

Management priorities in epinephrine overdose, as with any critically ill patient, are control of airway, breathing, and circulation. Continuous cardiac monitoring and frequent blood pressure measurements should be instituted. An ECG should be examined for myocardial ischemia. For patients with evidence of myocardial ischemia, end-organ hypoperfusion, cardiac failure, pulmonary edema, or persistent severe hypertension or tachycardia, the administration of an antidote should be considered. Phentolamine, a non-selective alpha-antagonist, can be administered intravenously at doses of 5 mg for adults and 1 mg for children to reverse peripheral and coronary artery vasoconstriction. A short-acting, cardioselective beta-1 adrenergic antagonist such as esmolol may be considered for refractory tachycardia, though this should be rarely needed. Beta blockade should be avoided without the concomitant administration of phentolamine or another vasodilator to avoid the dangers of unopposed alpha adrenergic agonism.

Case Conclusion:

An ECG shows sinus tachycardia with normal intervals without evidence of ischemia. Throughout this time, the patient receives IV diphenhydramine and methylprednisolone as secondary treatment for anaphylaxis, along with normal saline. Her stridor and respiratory distress improve rapidly, and over a four hour observation period her tachycardia and hypertension resolve. She is admitted overnight for observation, and is discharged the following day without sequelae.

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Series Editor: Lewis S. Nelson, MD

ABCs of CCBs

Hong K. Kim, MD, MPH, Lewis S. Nelson, MD, FACEP, FACMT, and David Jang, MD

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Cardiovascular medications are a leading cause of death from drug exposures. What steps can be taken in the ED to prevent fatality? Find out in this case of a woman who took undetermined quantities of several agents.

Case

A 69-year-old woman with a history of hypertension and depression presents to the emergency department after ingesting unknown quantities of amlodipine, atenolol, and thioridazine 3 to 5 hours earlier. The patient's vital signs are as follows: blood pressure (BP), 135/62 mm Hg; heart rate, 50 beats/min; respiratory rate, 18 breaths/min; temperature, 97.9°F. Her oxygen saturation is 95% on room air, and her blood glucose level is 181 mg/dL. Other examination findings are unremarkable, except for lethargy. One hour after her initial presentation, a repeat BP is 67/40 mm Hg and her heart rate is 44 beats/min. The ECG shows normal sinus rhythm.

Are all calcium channel blockers the same?

In 2010, cardiovascular drugs were the fifth leading class of drugs associated with referrals to poison control centers and the second leading drug exposure-related cause of death in adults (following analgesics), with 128 reported fatalities.¹ Calcium channel blockers (CCBs) were responsible for 40% of all cardiovascular drug-associated fatalities, followed by β -blockers and cardioactive steroids (such as digoxin).¹ Among the CCBs, amlodipine was responsible for the largest number of fatalities (24), followed by diltiazem and verapamil. This is quite distinct from just a decade ago, when the majority of CCB overdose fatalities were due to verapamil and diltiazem.²

There are three classes of CCBs: dihydropyridines (eg, nifedipine and amlodipine), phenylalkylamines (verapamil), and benzothiazepines (diltiazem). The nondihydropyridines—verapamil and diltiazem—bind to the L-type calcium channels in the myocardium, nodal tissue (sinoatrial and atrioventricular nodes), and vascular smooth muscles. Verapamil has the most potent effect on the myocardium, followed by diltiazem. In contrast, dihydropyridines bind calcium channels preferentially in vascular smooth muscle due to their enhanced binding at less negative membrane potentials: the resting potential for smooth muscle is -70 mV versus -90 mV for myocardium.³ Thus, they are potent peripheral vasodilators and have limited effect on the myocardium even following substantial overdose. This likely accounts for their relative safety in overdose, despite the apparently paradoxical prior statement about their increasing involvement in poisoning deaths.

What are the expected clinical findings in CCB overdose? How can one differentiate CCB overdose from β -blocker overdose?

Patients with CCB or β -blocker overdose may initially be deceptively asymptomatic and hemodynamically stable. However, immediate attention is critical, as cardiovascular collapse can develop rapidly. In general, patients who ingest immediate-release formulations develop clinical signs within 2 hours,

whereas the onset of toxicity can be delayed for 6 hours, or even longer, with exposure to sustained-released formulations.

Patients with dihydropyridine CCB overdose typically develop profound hypotension with a prominent reflex tachycardia, and this latter finding clearly distinguishes this class of CCBs from the nondihydropyridines. Despite impressive vital sign abnormalities (hypotension and bradycardia), particularly with verapamil or diltiazem, patients may maintain an alert mental status. This is postulated to be related to inhibition of the neuronal calcium ion entry that causes neuronal dysfunction.⁴

β -Blockers tend to produce less prominent vital sign abnormalities but are associated with altered mental status (since they do not block neuronal calcium channels). In most healthy people at rest, the cardiovascular effects of a therapeutic dose of a conventional β -blocker, such as metoprolol, are minimal. Only with cardiovascular stress, such as with exercise or anxiety, does the β -blocker's ability to block endogenous sympathetic stimulation manifest (as a lack of tachycardia).

Due to different effects on pancreatic release of insulin, CCBs, regardless of class, typically cause hyperglycemia in overdose, while β -blockers cause hypoglycemia, albeit less predictably. Diverse ECG changes can occur following overdose with either CCBs or β -blockers and do not help differentiate between the two types of agents. However, the dihydropyridines generally produce only sinus tachycardia and have little direct myocardial effect.

What are the initial steps in managing a patient with a mixed β -blocker/CBB overdose?

Following the initial assessment and implementation of standard supportive care, the need for gastrointestinal decontamination should be considered. Most awake and clinically stable patients should receive activated charcoal at a dose of 1 g/kg orally. Whole bowel irrigation (WBI) with polyethylene glycol solution (1 to 2 L/h orally) should generally be used in patients who ingest sustained-released β -blockers or CCBs. By enhancing gastrointestinal elimination of sustained-release agents, WBI can decrease the enteric absorption of the drug. Both activated charcoal and WBI should be deferred in patients with decreased gastric motility or hemodynamic instability.⁵

Patients with hypotension who fail to respond to intravenous saline should receive intravenous calcium salts to increase the Ca^{2+} concentration external to the blocked calcium channel. Calcium administration improves cardiac inotropy and electrical conduction and improves hypotension in patients with both β -blocker and CCB poisoning; for the latter, calcium is an essential antidote. However, this effect is short-lived due to the rapid dissipation of this enhanced transmem-

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brane Ca^{2+} concentration gradient. Thus, repeat bolus dosing may be required. Although calcium chloride contains three times more calcium ion than calcium gluconate (13.4 vs 4.3 mEq in a standard 10-mL dose), the latter is generally used due to safety considerations. The recommended initial bolus dose is 30 mL IV of 10% calcium gluconate (or 10 mL of 10% calcium chloride). This bolus can be repeated every 15 to 20 minutes as needed, up to three to four doses, without concern for systemic hypercalcemia.

Inotropes target the β_1 -adrenergic receptors in the myocardium, while vasopressors bind to the β_1 -adrenergic receptors in the peripheral vascular smooth muscle. Among the available inotropic and vasopressor agents, norepinephrine is preferred due to its direct action on the adrenergic receptors. Dopamine, an agent that stimulates norepinephrine release, has unpredictable effects in a severely poisoned patient and is best avoided. Vasopressin works via G protein-coupled V_1 receptors in the peripheral vasculature, with minimum effect on inotropy. In theory, vasopressin may be useful in reversing the peripheral effects of dihydropyridine toxicity, but the clinical evidence is limited.

Glucagon is the initial therapy of choice in patients with β -blocker poisoning.⁶ Glucagon increases inotropy (more than chronotropy) by increasing cAMP (cyclic adenosine monophosphate) formation by adenylate cyclase. This activation occurs via glucagon receptors independently of the β -adrenergic receptors that are blocked by the β -blockers. In this manner, glucagon functions like a β_1 -agonist. Its benefit in patients with CCB overdose is probably no greater than that noted with standard pressors/inotropes, such as norepinephrine, since the effects of CCBs occur downstream of the adenylate cyclase cascade. An initial dose of 3 to 5 mg IV given slowly over 1 to 2 minutes can be titrated as needed to a maximum single dose of 10 mg⁷; a maintenance infusion of 2 to 5 mg/h may be used subsequently if there is a beneficial response. An important concern with glucagon is the risk of vomiting, which raises the risk of aspiration, and bradycardia due to increased vagal tone. For this reason, since the β -adrenergic receptor is available in patients with CCB overdose, norepinephrine is preferable in these patients.

What is hyperinsulinemia/euglycemia therapy, and when is it appropriate?

In the setting of severe CCB poisoning in which the above interventions have failed, hyperinsulinemia/euglycemia (HIE) therapy, ie, high-dose insulin with dextrose supplementation, has become the preferred therapeutic intervention. Under normal conditions, myocardial tissues preferentially use free fatty acids as their source of energy. However, myocardial metabolism shifts to a glucose-dependent process under stressed conditions (eg, cardiovascular collapse).⁸ For this reason (and likely for other reasons), HIE enhances inotropy in the setting of both CCB and β -blocker poisoning. Although there are no randomized controlled clinical trials of HIE therapy, animal studies and human case reports suggest it is effective in restoring the hemodynamic status of patients with severe nondihydropyridine (verapamil) toxicity.⁹ However, evidence of clinical benefit in the setting of dihydropyridine toxicity is more limited. This seems understandable since with dihydro-

pyridine poisoning the main toxicologic effect occurs in the peripheral vasculature instead of the myocardium. It should be noted that there is generally a delay in the onset of action of HIE therapy of approximately 15 to 60 minutes.¹⁰

An initial insulin bolus of 1 to 2 units/kg IV is immediately followed by continuous infusion of 0.5 to 1 unit/kg/h. The continuous infusion can be increased by 1 unit/kg/h every 15 to 30 minutes and titrated to achieve the desired hemodynamic response. The upper limit of the continuous infusion has not been clearly defined. The common side effects of HIE are hypoglycemia and hypokalemia. Interestingly, the hypoglycemia is not as profound and difficult to prevent as might be expected, an effect likely related to saturation of peripheral insulin receptors.¹⁰ Regardless, the patient's blood glucose and potassium must be closely monitored.

Case Conclusion

Glucagon and calcium gluconate were administered with no hemodynamic improvement. Due to deterioration of her mental status, the patient was intubated for airway protection. She was started on norepinephrine for persistent hypotension (systolic BP, 85 mm Hg) and, despite the addition of vasopressin, remained hypotensive. HIE therapy, bolus plus infusion, allowed downward titration of the pressor agent. Over the next hour, the patient's BP stabilized to 115/62 mm Hg, and all therapy was discontinued over the next 16 hours. The patient fully recovered without any further complications.

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The patient's presentation was felt to be consistent with clonidine toxicity, as the patient had miosis, respiratory depression, and coma. Gabapentin can cause sedation, and may have contributed to the patients' condition as well. Imipramine, lidocaine, and mefenamic acid may result in seizures with toxicity, and seizure precautions were implemented as well as continuous cardiac monitoring for any QRS prolongation due to imipramine.

Why are pediatric patients more at risk for developing systemic toxicity than adults?

Topical drugs can have effects locally or systemically. When systemically absorbed, it is possible for unwanted and unintended effects to occur. In the pediatric patient, several differences exist that put this group at higher risk of toxicity than adults.

Size. The smaller the child is, the larger the surface area relative to body weight ratio. As a human grows in volume, so does the surface area but at a much slower rate. Adults have a relatively small skin surface area to weight ratio, while infants have relatively large surface area in proportion to size and weight.³ Since absorption depends on the amount of surface area exposed to a topical drug, a child will absorb a higher dose per kg than an adult.¹

Integrity of the epidermis. If the epidermal barrier is diseased or damaged, percutaneous absorption is increased greatly.¹ Furthermore, percutaneous penetration can also be affected by skin hydration, temperature, and occlusive bandages or clothing.³ Integrity of the epidermis is certainly a factor for both adults and children.

Maturity of the epidermis. Preterm infants may have a poorly developed stratum corneum, particularly those with gestational ages less than 28 weeks. Topically applied agents can be readily absorbed in these patients, with potential for dangerous consequences. Term infants and children have barrier properties similar to an adult. Preterm infants have rapid maturation of their stratum corneum, and will develop a full protective barrier within 2-3 weeks of age.¹

What are compounding pharmacies?

Pharmaceutical compounding is the combining, mixing, or altering of ingredients to create a customized medication for an individual patient in response to a licensed practitioner's prescription.⁴ Within the past decade, compounding in general has increased substantially in the United States, with an estimated 3000 pharmacies involved.⁵ The US Food and Drug Administration (FDA) has stated that compounding is both ethical and legal as long as a licensed practitioner has prescribed it (the compounded medication) for a specific patient.⁴

Although the FDA has oversight capabilities, most regulatory oversight and inspection of compounding pharmacies falls to state boards and varies from state to state.⁴

Case Conclusion

Once in the PICU, our patient did well with supportive care, with vital signs returning to normal over the following 12 hours. He was extubated the following morning without problems.

Blood taken at the time of ED presentation returned with a serum clonidine level of 9.2 ng/ml (reference range 0.5-4.5 ng/ml) and a norketamine level of 41 ng/ml (reporting limit >20 ng/ml). Other drug levels were not done due to minimal amount of ED blood available. These drug levels, in conjunction with the clinical scenario, confirms toxicity from dermal drug absorption.

Conclusion

Dermal absorption of drugs leading to toxicity in children is well-known, and has been seen in cases of dermal drugs containing salicylates, diphenhydramine, nicotine, and fentanyl.⁶ Our patient had toxicity from a topical pain medication compounded with several potent drugs known to cause CNS depression.

There has been an increase in the use of this method of drug delivery system for management of chronic painful conditions. The popularity and attractiveness of such preparations may be the perception that they are somehow safer and more natural than taking pills. This perception, coupled with the fact that these preparations are often not dispensed in child-proof containers, can lead to increased inadvertent exposures in the pediatric population.

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UPSTATE

MEDICAL UNIVERSITY

Upstate NY Poison Center

750 East Adams Street

Syracuse, NY 13210