# PEDIATRIC PHARMACOTHERAPY

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## A Review of Medications for Pediatric Cardiopulmonary Resuscitation

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Current standards for medication administration during pediatric cardiopulmonary resuscitation are based on the 2005 consensus recommendations from the International Liaison Committee on Resuscitation (ILCOR).[1] ILCOR was founded in 1992 to provide a forum for collaboration among worldwide resuscitation organizations. The current member organizations include the American Heart Association (AHA), the European Resuscitation Council, the Heart and Stroke Foundation of Canada, the Australian and New Zealand Committee on Resuscitation, the Resuscitation Councils of Southern Africa, the Inter-American Heart Foundation, and the Resuscitation Council of Asia. The 2005 ILCOR consensus recommendations were based on reviews of more than 22,000 published studies by 281 experts in resuscitation throughout the world. The next set of ILCOR consensus recommendations will be published in October 2010. Worksheets addressing the questions being evaluated for the upcoming consensus recommendations are available on the ILCOR website at www.ilcor.org.

The AHA Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care put the ILCOR recommendations into a concise document to be used as a teaching tool and guide for practitioners.[2] The material is also incorporated into their Pediatric Advanced Life Support (PALS) course. This issue of *Pediatric Pharmacotherapy* will review some of the more commonly used resuscitation medications, focusing on information from the 2005 ILCOR recommendations, and discuss other recent publications related to pediatric emergency preparedness.

### Intraosseous Medication Administration

One of the changes made in the 2005 ILCOR recommendations was the greater emphasis on intraosseous (IO) access as an alternative route for medication administration when intravenous (IV) access cannot be readily obtained.[1,2] The growing familiarity with placing IO catheters and the availability of tools designed to facilitate rapid placement have substantially increased the use of this route over the past decade. Several studies of both children and adults have shown IO administration to be a safe and effective delivery method for fluids and medications during cardiopulmonary resuscitation.[3,4] Endotracheal medication administration, because of erratic absorption and the lack of established dosing recommendations, is no longer preferred.[1,2]

### Epinephrine

Epinephrine is the most frequently used medication during pediatric cardiopulmonary resuscitation. It is the first drug used in children with severe hypotension, bradycardia, asystole, or pulseless arrest. In the face of decreased perfusion, epinephrine is used to produce alpha-adrenergic vasoconstriction which increases systemic vascular resistance. This results in increased aortic diastolic pressure, improving coronary and cerebral perfusion.[1-3,5,6] An epinephrine dose of 0.01 mg/kg, equivalent to 0.1 mL/kg of a 1:10,000 solution, is recommended for resuscitation (Table). Doses may be repeated every 3-5 minutes. High-dose epinephrine is no longer recommended following the publication of a randomized controlled double blinded study comparing outcomes after standard-dose versus high-dose epinephrine administration demonstrated no benefit and potentially decreased 24 hour survival associated with high-dose epinephrine use.[7]

Epinephrine infusions of 0.1-1 mcg/kg/min are frequently used in patients with prolonged hypotension. Adverse effects from epinephrine include dose-related tachycardia, hypertension, and excessive vasoconstriction. Whenever possible, epinephrine infusions should be administered through central IV access. Extravasation of epinephrine at a peripheral IV site may produce significant tissue ischemia. All health care providers should be familiar with the two strengths of epinephrine: a 1:10,000 (0.1 mg/mL) syringe or vial typically used for

resuscitation and a 1:1000 (1 mg/mL) vial used for IM or subcutaneous administration in treating asthma or hypersensitivity reactions and in the preparation of epinephrine infusions.[1-3,5,6]

In a retrospective study published in the March issue of *Pediatrics*, obese children were found to have a lower rate of survival after in-hospital cardiopulmonary arrest.[8] Of note, the study also reported a significant difference in the number of epinephrine doses given between the obese children and those who were normal or underweight. Forty-three percent of the obese children required more than two doses, compared to 29% of the other children ($p<0.001$). The reasons for the difference were not clear. The authors point out that, in spite of the larger number of doses given, standard weight-based dosing may actually produce excessive serum concentrations of high water-soluble drugs such as epinephrine and lead to a greater risk for toxicity. The choice of ideal versus actual body weight for dosing resuscitation medications in obese children will be addressed in the upcoming 2010 ILCOR consensus recommendations.

**Table. Pediatric Resuscitation Medications[2]**

| **Medication** | **Dose** |
|---|---|
| Adenosine | 0.1 mg/kg IV/IO (max 6 mg); repeat at 0.2 mg/kg (max 12 mg) |
| Amiodarone | 5 mg/kg IV/IO (max 15 mg/kg or 300 mg) |
| Atropine | 0.02 mg/kg IV/IO (min 0.1 mg, max 0.5 mg for a child, 1 mg for an adolescent > 12 yrs) |
| Calcium chloride | 20 mg/kg IV/IO slowly |
| Dopamine | 2-20 mcg/kg/min infusion |
| Epinephrine | 0.01 mg/kg IV/IO (max 1 mg)<br>0.1-1 mcg/kg/min infusion |
| Dextrose | 0.5-1 g/kg IV/IO (5-10 mL/kg 10% dextrose or 2-4 mL/kg 25% dextrose) |
| Lidocaine | 1 mg/kg IV/IO (max 100 mg); 20-50 mcg/kg/min infusion |
| Naloxone | < 5 yrs or ≤ 20 kg: 0.1 mg/kg IV/IO<br>≥ 5 yrs or > 20 kg: 2 mg IV/IO - for full reversal only; reduce dose for partial reversal - |
| Sodium bicarbonate | 1 mEq/kg IV/IO slowly |

Atropine

Bradycardia associated with increased vagal tone (such as that produced by intubation) or AV block may be treated with atropine, a parasympatholytic that reduces vagal tone and increases atrial pacemaker firing and conduction through the atrioventricular (AV) node. Atropine is also indicated as first-line therapy for bradycardia related to cholinergic drug toxicity. Epinephrine remains the primary drug of choice for all other causes of bradycardia. The dose of atropine for pediatric resuscitation is 0.02 mg/kg. It should be administered rapidly and may be repeated after 5 minutes. Doses less than 0.1 mg may produce paradoxical bradycardia. Weight-based dosing charts or computer-generated code drug dosing information should be evaluated to ensure that 0.1 mg is the lowest dose limit.[1-3,5,6]

Calcium chloride

The administration of calcium during pediatric cardiopulmonary resuscitation remains controversial. It is most likely to be of benefit in patients with hypocalcemia, including infants who have recently undergone cardiac surgery. Infants have a greater reliance on calcium for contractility and normalizing serum calcium concentrations can produce an inotropic effect. Calcium is also used in patients with hypermagnesemia, hyperkalemia, or calcium channel blocker overdose. Calcium chloride is the preferred salt form during resuscitation, as it dissociates more rapidly in the blood than calcium gluconate. Calcium chloride (20 mg/kg) should be administered via central IV access. Extravasation of calcium, particularly calcium chloride, can result in significant tissue injury. Slow administration is recommended to avoid bradycardia or asystole.[1-3,5,6]

Sodium bicarbonate

After ventilatory and circulatory support has been established, sodium bicarbonate may be administered in patients with severe metabolic acidosis associated with prolonged arrest or hyperkalemia. If administered prior to adequate ventilatory support, carbon dioxide produced by its buffering actions will not be excreted, leading to paradoxical CSF and intracellular acidosis. Sodium bicarbonate is given at a dose of 1 mEq/kg using a 1 mEq/mL (8.4%) concentration in children and a more diluted 0.5 mEq/mL (4.2%) solution in infants. If the 0.5 mEq/mL solution is unavailable, the 1 mEq/mL solution may be diluted 1:1 with sterile water. Sodium bicarbonate is very hyperosmolar (2,000 mOsm/L) and should be administered at a rate no more than 10 mEq/min to avoid cerebral hemorrhage. Extravasation may produce severe tissue injury.[1-3,5,6]

Dextrose

Hypoglycemia during cardiopulmonary arrest is typically treated with an IV bolus of a dextrose-containing solution. While 50% dextrose is used

during resuscitation in older children and adults, this hypertonic solution may produce thrombosis, hyperglycemia, or intracranial hemorrhage in infants. Current recommendations are to use 10% dextrose or, if unavailable, to dilute 50% dextrose 1:1 with sterile water to provide a 25% solution.[1-3,5,6]

Dopamine

Dopamine is an alternative to epinephrine for patients with shock or hypotension. It provides agonist activity at dopaminergic, beta- and alpha-adrenergic receptor sites. For alpha-adrenergic vasoconstriction during resuscitation, dopamine is typically administered at a rate of 15-20 mcg/kg/min. The availability of premixed dopamine solutions with extended stability at room temperature allows it to be stocked in code carts, clinics, or offices, facilitating rapid initiation of an infusion. Premixed dopamine is available in 0.8 mg/mL (stocked on UVA code carts), 1.6 mg/mL, and 3.2 mg/mL concentrations. Like epinephrine, dopamine should be administered through central IV access to minimize the risk for extravasation-related tissue injury.[1-3,5,6]

Adenosine

Adenosine produces a temporary block of AV node conduction and is used as an alternative to cardioversion for the management of supraventricular tachycardia (SVT). The recommended initial dose is 0.1 mg/kg. In patients who fail to convert to normal sinus rhythm, the dose may be increased to 0.2 mg/kg. Because of its short elimination half-life (< 10 seconds), central IV access is preferred to ensure adequate drug delivery, but the most proximal peripheral IV or IO access to the heart is acceptable. Each dose should be followed with a rapid 5-10 mL saline flush. Adenosine may produce flushing, chest pain or rarely, heart block. It may trigger bronchospasm in asthmatics. Theophylline or aminophylline antagonize the effects of adenosine.[1-3,5,6]

Amiodarone

A class III antiarrhythmic, amiodarone slows AV conduction, prolongs the AV refractory period, and slows ventricular conduction. It is recommended for the treatment of SVT unresponsive to adenosine and pulseless arrest with ventricular tachycardia or ventricular fibrillation unresponsive to defibrillation and epinephrine. Amiodarone may be given rapidly during cardiac arrest, using a dose of 5 mg/kg, up to a maximum of 300 mg. It may be repeated up to a total daily dose of 15 mg/kg. In patients with a pulse, amiodarone should be given more slowly to reduce the risk for hypotension secondary to vasodilation and myocardial depressant effects. Other adverse effects from amiodarone given during resuscitation include bradycardia, heart block, and torsades de pointes.[1-3,5,6]

Lidocaine

Although not commonly used in pediatric emergencies, lidocaine may play a role in the management of patients with ventricular arrhythmias who do not respond to amiodarone. It may be administered by 1 mg/kg bolus doses given every 5-10 minutes or as an infusion of 20-50 mcg/kg/min. Patients continuing on therapy after resuscitation should be monitored for myocardial depression, muscle twitching, disorientation and altered mental status, or seizures. Serum lidocaine concentrations should be maintained in the range of 1.5-5 mcg/mL to minimize toxicity.[1-3,5,6]

Vasopressin

Vasopressin has not yet been added to the recommendations for management of pediatric pulseless arrest, but it may be considered as an alternative agent in patients who have failed to respond to at least two doses of epinephrine.[1,2] A dose of 0.4 units/kg has been used in small number of case reports. In a review of 1,293 pediatric patients with in-hospital pulseless arrest reported to the AHA national registry between 1999 and 2004, only 5% received vasopressin.[9] Over 98% of the children had already received epinephrine and 76% were being treated in an intensive care unit. The duration of arrest was significantly longer in the vasopressin group, suggesting that most clinicians used it during prolonged arrests in patients unresponsive to standard therapy. Vasopressin was associated with a lower rate of return to spontaneous circulation, but there was no difference in survival at 24 hours or at discharge.

Other Issues in Pediatric Resuscitation

*Office Preparedness*

Studies suggest that pediatric emergencies are not uncommon in the primary care setting. It has been estimated that the average pediatric office experiences one or two emergencies per month. In 2007, the American Academy of Pediatrics published a policy statement on emergency preparedness for office-based practices.[10] In addition to providing recommendations for training office personnel, the document provides lists of equipment and medications that should be available. Essential medications include oxygen, albuterol for inhalation, and epinephrine 1:1000. In addition, maintaining a supply of epinephrine 1:10,000 is strongly suggested, as well as activated charcoal, antibiotics, anticonvulsants, atropine, corticosteroids, 25% dextrose,

diphenhydramine, IV fluids, naloxone, and sodium bicarbonate.

*Training*

The most important resource for successful pediatric cardiopulmonary resuscitation is the availability of skilled health care providers. Education on the selection and dosing of resuscitation medications should be reinforced throughout residency. In a study published in the April issue of *Anesthesiology*, 18 of the 19 residents participating in a simulated pediatric resuscitation correctly called for administration of epinephrine, but only 33% gave the correct dose.[11] Two residents would have given the adult dose to the 1-year-old, 10 kg patient, seven would have under-dosed the patient, and the remaining residents stated during the scenario that they did not know the dose. The correct dose of calcium was stated by only 19% of the residents, while the correct doses of sodium bicarbonate and insulin were stated by 17% and 7% of the residents, respectively.

A number of studies have demonstrated the benefit of a combined program of information-based education (in the classroom setting or via computer-based learning) and skilled-based practice in training residents to perform cardiopulmonary resuscitation.[10] The pediatric mock code program at the University of Virginia Children's Hospital has provided a successful training program for several years, using real-time scenarios in actual clinic, inpatient, and intensive care unit settings to allow for interdisciplinary practice of resuscitation skills. Another suggestion for maintaining readiness is the use of a scavenger hunt to ensure that staff and trainees can locate resuscitation equipment, medications, and dosing references.[10]

Summary

This brief review focused on several key medications used in pediatric cardiopulmonary resuscitation, as well as new information on training and preparation for emergencies. For additional information, health care providers should consult the documents published by ILCOR and the AHA. University of Virginia faculty and staff may contact the Life Support Learning Center through their website at http://www.healthsystem.virginia.edu/internet/lslc/ for information on training classes or to review resuscitation policies.

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**Formulary Update**

The following actions were taken by the Pharmacy and Therapeutics Committee at their meeting on 6/25/10:

1. Melatonin was added to the Formulary for the restoration of circadian rhythm in patients with sleep disorders.
2. The restriction on pegfilgrastim (Neulasta®) was updated to reflect current institutional practice.
3. The restriction on Ferumoxytol (Feraheme™) was amended to include use by Nephrology in outpatient clinics for non-dialysis-dependent patients and home dialysis patients.


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