

PEDIATRIC PHARMACOTHERAPY

A Monthly Newsletter for Health Care Professionals from the
Children's Medical Center at the University of Virginia

Volume 7 Number 12

December 2001

Amiodarone Use in Children **Marcia L. Buck, Pharm.D., FCCP**

Amiodarone, a Class III antiarrhythmic, has been used in pediatric patients for nearly two decades, first in Europe then in the United States.¹⁻³ Based on this experience, and that in adults, amiodarone has become one of the most frequently used antiarrhythmics in children and recently was added to the guidelines for pediatric advanced life support.⁴

Mechanisms of action

Although known primarily as a Class III antiarrhythmic, amiodarone has characteristics of all four Vaughan Williams classes. The predominant effects of amiodarone are prolongation of myocardial cell action potential duration and recovery, as well as noncompetitive alpha- and beta-adrenergic inhibition. These effects make it useful in the management of both atrial and ventricular tachyarrhythmias. After intravenous (IV) administration, amiodarone also reduces systemic vascular resistance and may produce a mild negative inotropic effect.¹⁻³

Clinical use in children

Oral amiodarone has been shown in numerous studies to be an effective antiarrhythmic for children, with a success rate (full or partial response) ranging from 80 to 100%.^{1,4-6} While rarely a first-line agent because of its adverse effect profile, amiodarone is often used in patients with arrhythmias refractory to other therapies. In 1980, Coumel and Fidelle published their use of oral amiodarone in 135 children over 8 years.⁴ Many of the patients had arrhythmias associated with previous cardiac surgery. Responses were rated as good in 60% of the children, average in 33%, and poor in 7%. The mean onset of effect, 4 days, was more rapid than that typically seen in adults. Overall, the drug appeared to be well tolerated. The authors

concluded that amiodarone could play an important role in the management of refractory arrhythmias in children.

A number of other investigators have achieved similar results using amiodarone in infants and children. In 1983, Shahar and coworkers treated 10 children with Wolff-Parkinson-White syndrome.⁵ They used a dosing regimen that would become standard for most institutions, an oral loading dose of 10 to 15 mg/kg/day for 4 to 14 days followed by a maintenance dose of 5 mg/kg/day. All children in the series experienced at least a partial response to therapy.

In a study published earlier this year in the *American Heart Journal*, Etheridge and colleagues evaluated the efficacy and safety of amiodarone in 50 infants (average age 1 month) with supraventricular tachycardia.⁶ After loading with either oral or IV amiodarone, therapy was continued with oral doses of 5 to 10 mg/kg/day. Twenty-five of the infants had complete resolution without recurrence. The remaining patients required the addition of propranolol. At discharge, all patients were asymptomatic; 90% were in sinus rhythm. The only significant adverse effects noted were in two patients who experienced hypotension with the IV loading dose.

Intravenous amiodarone has also been studied in a number of settings, often in the management of arrhythmias occurring after repair of congenital heart defects. In 1993, Perry and coworkers evaluated the efficacy of IV amiodarone in 10 children between the ages of 18 months to 26 years.⁷ Seven of the 10 had ventricular tachycardia. One patient had atrial tachycardia, one junctional, and one mixed arrhythmia. After

an initial 5 mg/kg load, given as 1 mg/kg aliquots administered over 5 to 10 minutes, investigators were allowed to give up to an additional 5 mg/kg before starting an infusion of 10 mg/kg/day. The infusion was continued until resolution and/or oral therapy could be given. Half continued on oral amiodarone. Therapy was successful in eight patients; six had complete resolution of their arrhythmia.

The same regimen was used by Perry and colleagues in a larger multicenter trial published in the *Journal of the American College of Cardiology* in 1996.⁸ Forty children were enrolled. The average loading dose was 6.3 mg/kg. Half of the patients received an infusion of 10-15 mg/kg/day. Mean duration was 2.5 days. Resolution of the arrhythmia and improved hemodynamic function occurred in 32 (80%) of the children. Amiodarone was well tolerated, with four cases of transient hypotension and one case of bradycardia. Based on the results of these two studies, the authors concluded that IV amiodarone is a safe and effective treatment for children with critical tachyarrhythmias.

Several other investigators have reported similar findings. Figa and colleagues administered IV amiodarone to 30 infants and children as a 5 mg/kg load infused over 1 hour, followed by an infusion starting at 5 mcg/kg/min.⁹ Eighteen of the patients had arrhythmias associated with prior cardiac surgery. Therapy was considered successful in 94% of the patients, with a mean effective maintenance dose of 9.5 mcg/kg/min (13.7 mg/kg/day). Treatment duration ranged from 1 to 30 days, with a median of 5 days. Bradycardia occurred in three patients receiving amiodarone alone, while other rhythm disturbances occurred in another five patients receiving concurrent propafenone.

Based on the efficacy of IV amiodarone in resolving pediatric arrhythmias in the postoperative setting and a similar change in adult resuscitation guidelines, the guidelines for pediatric advanced life support (PALS) were changed last year. Amiodarone replaced bretylium as the drug of choice for ventricular fibrillation or pulseless ventricular tachycardia unresponsive to defibrillation.¹⁰ Additional research is needed, however, to establish the efficacy of amiodarone in pediatric resuscitation.

Pharmacokinetics

Following oral administration, amiodarone is slowly and erratically absorbed, with an average bioavailability of 50%. Food increases the rate and extent of absorption; patients should be

advised to take their dose at a consistent time in relation to meals. Maximum serum concentrations occur 3 to 7 hours after an oral dose. Amiodarone is widely distributed and highly protein bound. Accumulation of drug occurs in highly perfused and lipophilic tissues. Amiodarone is metabolized primarily to desethylamiodarone through the cytochrome P450 enzyme CYP3A4. The pharmacologic activity of this metabolite is not known. Amiodarone has a biphasic elimination, with a terminal half-life averaging 53 days in adults. A case report of amiodarone pharmacokinetics in a 28 day old infant revealed an estimated terminal half-life of 14.5 days, reflecting a more rapid metabolism.¹¹ The major route of elimination is hepatic excretion into bile; renal excretion is negligible. As a result, no dosage adjustment is recommended in patients with renal impairment. Neither amiodarone nor its primary metabolite are cleared by dialysis.¹⁻³

Drug interactions

Amiodarone is associated with a number of clinically significant drug interactions, often resulting from its inhibition of CYP2C9, CYP2D6, and CYP3A4. (Table). One of the most important interactions in children is with digoxin, since these two drugs are often used in combination. Patients already receiving digoxin should have the digoxin dose reduced by 50% when amiodarone is initiated. Digoxin concentrations should be monitored closely during loading and the initiation of maintenance amiodarone therapy.²

Table. Amiodarone drug interactions

Drug	Result
Anticoagulants	↑ prothrombin time
Beta blockers	Additive beta blockade
Calcium channel blockers	↑ risk of AV block
Cholestyramine	↓ amiodarone concentration
Cimetidine	↑ amiodarone concentration
Cisapride	QT prolongation
Cyclosporine	↑ cyclosporine concentration
Dextromethorphan	↑ dextromethorphan conc.
Digoxin	↑ digoxin concentration by as much as 70%
Disopyramide	QT prolongation
Fentanyl	Hypotension, bradycardia
Flecainide	↑ flecainide concentration
Phenytoin	↑ phenytoin conc.; ↓ amiodar. conc.
Lidocaine	Rare reports of bradycardia, seizures
Methotrexate	↑ methotrexate conc.
Procainamide	↑ procainamide or NAPA concentrations
Quinidine	↑ quinidine concentration
Quinolones	↑ risk of arrhythmias
Theophylline	↑ theophylline conc.
Rifamycins	↓ amiodarone conc.

Ritonavir	↑ amiodarone conc.
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Adverse effects

Approximately 75% of patients given amiodarone experience an adverse effect, and 7-20% of patients discontinue therapy as a result. The most frequently observed adverse effects with oral amiodarone use in adults include: nausea and vomiting (10-33%), photosensitivity (10%), constipation, anorexia, rash, fatigue, tremor, ataxia, dizziness, and elevated liver function tests (4-9%), coagulation disorders, arrhythmias, congestive heart failure (CHF), thyroid function changes, blue discoloration of the skin, vasculitis, and epididymitis (1-3%). Corneal microdeposits occur in nearly all patients after amiodarone use, but cause visual disturbances in only 10%.^{2,3}

For comparison, in their review of 135 children, Coumel and Fidelle observed four cases of photosensitivity, four cases of nightmares (possibly as a precursor of hyperthyroidism in two patients), three cases of corneal deposits, one case of hypothyroidism, and one child with skin discoloration.⁴ In a long-term follow-up study of 95 children who had received amiodarone for a minimum of 1.5 years, the most commonly reported adverse effects were corneal deposits (12%), abnormal thyroid function tests (6%), elevation of liver function tests or rash (3%), peripheral neuropathy (2%), hypertension or vomiting (1%).¹²

After IV administration, the most commonly reported adverse effects are hypotension (15%), arrhythmias, cardiogenic shock, CHF, and elevated liver function tests (2-5%). Approximately 9% of adults receiving IV amiodarone in clinical trials had therapy discontinued because of adverse effects.^{2,3}

Amiodarone has also been linked to the development of pulmonary inflammation or fibrosis in up to 10% of patients. This reaction has been reported after both oral and IV use. In rare cases, the reaction has progressed to fatal interstitial/alveolar pneumonitis. While this reaction has been reported less frequently in children than adults, there are published accounts in all age groups, including infants.^{13,14} Based on these reports, it is recommended that pulmonary function tests and a chest x-ray be obtained prior to starting therapy and every 3 to 6 months during treatment.

Other rare, but serious, adverse effects associated with amiodarone include optic neuropathy and hepatotoxicity.¹⁵ The development of optic

neuropathy may result in vision loss progressing to permanent blindness. Regular ophthalmic examinations are recommended for the duration of therapy, as this adverse effect may occur at any time. Likewise, monitoring of liver function tests is recommended every 6 months during treatment. Dosage reduction or discontinuation should be considered in any patients with liver function tests greater than three times normal. While more common with oral therapy, two cases of fatal hepatocellular necrosis have been reported following IV use.²

The effects of amiodarone on thyroid function, while well known, are of particular concern in children.^{16,17} Amiodarone inhibits peripheral conversion of T₄ to T₃ and provides a large amount of inorganic iodine (37% iodine by weight). In most patients, initiation of amiodarone therapy causes a period of relative hypothyroidism, followed by adjustment to normal levels or long-term hyperthyroidism. Thyroid function studies should be routinely monitored in all children during therapy. Dose reduction is often adequate to achieve a euthyroid state. Accelerated bone maturation has been reported in some children with elevated T₄ and reverse T₃ levels; however, a long-term follow-up study of children receiving amiodarone for periods over 1 year revealed no apparent effect on growth velocity.¹² Because of these inconsistent findings, careful documentation of growth is also recommended.

Special concerns in neonates

With the increased use of amiodarone in the neonatal population, there has been renewed concern over the potentially toxic effects of long-term infusions. In May, a letter was sent by Wyeth, the manufacturer of Cordarone I.V.®, to health care professionals describing changes in the product information.¹⁸ These changes highlight the risk of amiodarone causing the leaching of plasticizers from PVC containers and the risk of benzyl alcohol accumulation in neonates.

The injectable preparation of amiodarone is known to leach out plasticizers, such as di(2-ethylhexyl)phthalate (DEHP), from polyvinyl chloride (PVC) tubing and bags. In order to minimize leaching, Wyeth recommends that a maximum concentration of 6 mg/ml and an infusion flow rate of at least 0.5 mg/min be used. With these limits, the amount of DEHP exposure is expected to remain under the proposed maximum tolerable intake of 0.6 to 0.8 mg/kg/day.¹⁹ In addition, it is recommended that infusions lasting longer than 2 hours be

prepared in non-PVC containers.^{2,3} In neonates, the use of hard plastic syringes (rather than bags) and non-PVC tubing may help to minimize DEHP exposure.

The injectable preparation also contains 20.2 mg/ml benzyl alcohol as a preservative. Accumulation of benzyl alcohol has been associated with neonatal "gaspings syndrome," a form of sudden cardiopulmonary collapse.^{3,18} While this does not preclude use in the neonatal population, the potential for accumulation of benzyl alcohol should be carefully evaluated when administering amiodarone by the IV route.

Dosing recommendations

Oral amiodarone is typically given as a loading dose of 10 to 15 mg/kg/day, in a single dose or divided into two doses, for 4 to 14 days. After the loading phase, an oral maintenance dose of 5 mg/kg/day is given once daily for several weeks or until symptoms are controlled. At that time, the dose may be reduced to the lowest effective amount, usually 2.5 mg/kg/day.

For IV administration, a loading dose of 5 mg/kg is recommended. This may be administered as a rapid IV push for cardiac resuscitation, but is more commonly administered over an hour in less critically ill patients. The alternative method used by Perry and colleagues, giving the loading dose in 1 mg/kg aliquots, may be preferred in neonatal patients to minimize leaching of DHEP.³ Following the loading dose, a continuous infusion of 5 to 15 mcg/kg/min may be administered, titrated to patient response.

Availability

Amiodarone is available in 200 and 400 mg tablets as well as a 50 mg/ml injection.² An extemporaneous formulation for making a 5 mg/ml suspension with commercially-available vehicles (Ora Sweet[®] and Ora Plus[®]) has been published by Nahata and colleagues.²⁰ The formulation is stable for three months when refrigerated or 6 weeks at room temperature.

Summary

Amiodarone appears to be a highly effective antiarrhythmic in the pediatric population, particularly following cardiac surgery. While its use in these patients is fairly well established, its role in pediatric resuscitation has yet to be evaluated. Close monitoring is required in all settings, because of its potential for drug interactions and significant adverse effects.

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Formulary Update

The Pharmacy and Therapeutics Committee did not meet during November.

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