Is It Time to Tell the Emperor He Has No Clothes?
Intravenous Amiodarone for Supraventricular Arrhythmias in Children

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In this issue of the Journal, Chang et al present a thought-provoking, single-center retrospective analysis of 37 patients receiving either procainamide or IV amiodarone for refractory supraventricular arrhythmias (SVA), excluding junctional ectopic tachycardia (JET). They compare the relative efficacy of the drugs, finding procainamide to be fully successful in 50% of cases, whereas amiodarone was only successful for 15%, a statistically significant difference. Adverse effects were similar between the drugs. They conclude that procainamide may be a more effective treatment option and more importantly challenge the “perceived superiority and safety of amiodarone.”

The findings are indeed intriguing, but before drawing too strong a conclusion, it is critical to review a few important limitations of the study. The retrospective nature of the study along with small group sizes and diverse clinical situations led to considerable differences between the patients treated with amiodarone and those treated with procainamide. Those treated with amiodarone were more likely to have congenital heart disease and to have a postoperative arrhythmia. The mechanisms of the tachycardias differed as well, with the procainamide group having more patients with ectopic atrial tachycardia. Thus, the inferiority of amiodarone may reflect a patient population with intrinsically more difficult-to-treat arrhythmias. Further, the initial loading and maintenance doses of amiodarone (median, 2.5 mg/kg and ~7 mg/kg/d, respectively) were considerably lower than the doses reported to be effective in previous retrospective studies and a prospective randomized trial, in which loading doses are typically 5 mg/kg and maintenance 10 mg/kg/d. However, the doses of procainamide used (median, 10 mg/kg load and 20 μg/kg/min maintenance) were comparable to those reported in the literature for acute management of tachyarrhythmias. This difference was probably a reflection of the authors’ observation that an arrhythmia specialist was more likely to be present during administration of the procainamide than for the amiodarone. These limitations are not insignificant and do limit the conclusions that can be drawn from the data; however, when combined with the results of a previous prospective randomized trial, this study does bring into question the seemingly extensive use of intravenous amiodarone as the “King (or Emperor) of Antiarrhythmics” for acute management of refractory SVA.

Amiodarone was developed from khellin, a derivative of the khella plant used as folk medicine for renal colic in Egypt. Khellin was found to relax the ureters and the coronary arteries. Hence, amiodarone was initially introduced in the 1960s as an antianginal drug. Recognition of amiodarone’s prolongation of refractoriness in concert with the understanding of reentrant arrhythmias prompted the development of the Vaughn Williams Class III antiarrhythmic group in 1970; however, the drug is now known to exhibit effects from all 4 Vaughn Williams classes. Used acutely, amiodarone effects are different than with chronic use, exhibiting less Class III activity. These characteristics are due in part to the extensive tissue binding and large volume of distribution, necessitating a prolonged loading regimen when initiating it as maintenance therapy.

Since its introduction, there have been numerous controlled and uncontrolled studies demonstrating efficacy of intravenous amiodarone, in adults particularly, for life-threatening ventricular arrhythmias (VA) and atrial fibrillation. However, until 2005, there was only a handful of small uncontrolled studies in the pediatric population, with most of the patients having JET and a wide variety of other SVAs and VAs. Most have reported high efficacy and low side effects, again most consistently for JET. In 2005, the results of a “large” (n=61) randomized, double-blind, dose-response study (1, 5, and 10 mg/kg) were published, demonstrating that there was a significant difference in time to success for the 3 dose groups, including SVA, JET, and VA (P=0.028). However, when the 31 JET and 26 SVA patients were analyzed separately, the results were not significant (P=0.10 and P=0.29, respectively) (Figure). These results were remarkable because the retrospective data supporting amiodarone’s effectiveness was thought to be so compelling that a placebo-controlled trial was considered unethical by the investigators, particularly for JET. Yet, the randomized controlled data demonstrated that all groups improved regardless of dose, with the low dose of 1 mg/kg considered near placebo.

The most concerning side effect for administration of intravenous amiodarone is hypotension. In addition to an intrinsic vasorelaxant effect, acute hypotension occurs from histamine release triggered by the solvent polysorbate 80 used in the common intravenous amiodarone formulation. The hypotensive effect is dependent on the rate of delivery and may be decreased by using an alternative formulation of amiodarone without polysorbate 80. In the pediatric...
A randomized trial referred to above, dose-related adverse events were common, including hypotension (36%), vomiting (20%), bradycardia (20%), AV block (15%), and nausea (10%). In the highest dose group of 10 mg/kg, hypotension was reported in 45% of subjects. Generally, the side effects can be managed expectantly by decreasing the dose rate or administering fluid; however, in the absence of arrhythmia conversion, the hypotension can be profound and unremitting even after administration is ceased. Amiodarone is rarely proarrhythmic with either acute or chronic administration.

Procainamide owes its origins to the Erythroxylum coca plant—better known for its more popular product, cocaine. Procaine was developed from cocaine in the early 20th century as a local anesthetic with less stimulant effects. Subsequently, it was discovered to affect the epicardial electrogram and prevent extrasystoles during canine heart revascularization experiments, leading to the development of the analogue procainamide in 1951. Subsequent research demonstrated that procainamide has Class IA antiarrhythmic properties, and its active metabolite, n-acetyl procainamide (NAPA), has Class III antiarrhythmic effects but no sodium channel-blocking properties.

Procainamide has appeared rarely in clinical pediatric studies. In 1985, Benson et al. reported that 12 of 27 pediatric patients with a variety of recurrent paroxysmal SVA and VA had termination with a 15 mg/kg IV dose administered over 15 minutes. Termination occurred at a mean of 12.4 minutes after initiation of the infusion (range, 6 to 15 minutes), and it is reported that there were “no complications from this infusion regimen”; however, no blood pressure data were reported. Two other studies of intravenous administration focused on successful management of postoperative JET with 5 to 15 mg/kg infusions over 15 to 30 minutes, often in concert with mild cooling. Despite the acutely ill population, neither study reported any significant acute drug-related side effects. Hypotension caused by sympathetic ganglion blockade is a well-known acute side effect of intravenous administration; however, rapid renal elimination abbreviates the effect, and in the authors’ experience, the administration rate can be easily titrated to prevent any significant hypotension.

High levels of either procainamide or its metabolite NAPA can be proarrhythmic, but it appears to be uncommon with acute administration. Although no longer manufactured in an oral form, procainamide is compoundable into a solution or suspension, which is 75% to 90% bioavailable. However, a frequent dosing schedule makes administration impractical for most patients.

To summarize, a careful review of the literature provides minimal data to guide the use of either intravenous amiodarone or procainamide for the diverse range of pediatric uses. However, the data reviewed above support the conclusions reached by Chang et al: amiodarone may be less effective and procainamide more effective than many pediatric cardiac intensivists and electrophysiologists believe. The randomized study of amiodarone also indicated a much higher incidence of hypotension than previously recognized, and procainamide appears to be very safe in the pediatric population, both consistent with the study by Chang et al.

One interesting point is that although the Chang et al study, as well as our own, finds that intravenous amiodarone is the more utilized drug in the setting of acute refractory SVAs, this may not be the case universally. A 2006 survey of US and Canadian pediatric cardiologists queried the practitioner’s treatment of a hypothetical infant with adenosine refractory SVT. The practice patterns were differentiated based on whether or not the respondents had specialized electrophysiology training. Interestingly, the most commonly recommended treatment among electrophysiology specialists was procainamide (38% to 45%; dependent on the presence of preexcitation), whereas amiodarone was not even in the top 3 drugs used. Even nonelectrophysiology practitioners would use procainamide second only to digoxin or propranolol, with amiodarone again not in the top 3 drugs used.

Figure. Time to success for subgroups of JET and SVA. No interaction of subgroup and dose was present ($P=0.862$) (with permission, American Heart Association).
The identification by Chang et al of procainamide’s potential as an efficacious treatment for acute refractory SVA is both consistent with the clinical literature and the apparent popularity of its use among pediatric cardiologists for refractory SVT in infants. Further, the lack of efficacy demonstrated for amiodarone is consistent with the only randomized pediatric study in the literature. Together, these observations virtually demand further research on the optimal acute therapy for refractory SVAs in children, including the recently FDA-approved intravenous formulation of sotalol. Finally, the data provide an important opportunity for many of us to reconsider the use of amiodarone as the “king” of refractory SVA treatments, or more importantly, to find this king a “clothing” of evidence that all can see.

“The Emperor shivered, for he suspected they were right. But he thought, “This procession has got to go on.” So he walked more proudly than ever, as his noblemen held high the train that wasn’t there at all.”

— H.C. Anderson

Disclosures
Dr Saul is a consultant for Bioniche Pharmaceuticals, owner of intravenous sotalol.

References

Key Words: pediatric amiodarone procainamide supraventricular tachycardia editors
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Circ Arrhythm Electrophysiol. 2010;3:115-117
doi: 10.1161/CIRCEP.110.953356

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