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SHORT – AND INTERMEDIATE – TERM EFFICACY OF AMIODARONE IN INFANTS AND CHILDREN WITH CARDIAC ARRHYTHMIA*

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SUMMARY: Çeliker A, Koçak G, Lenk MK, Alehan D, Özme Ş. (Cardiology Unit, Department of Pediatrics, Hacettepe University Faculty of Medicine, Ankara, Turkey). Short-and intermediate-term efficacy of amiodarone in infants and children. Turk J Pediatr 1997; 39: 219-225.

The antiarrhythmic effect of amiodarone was examined in this retrospective study in a group of 20 patients with a mean age of 8.5 ± 6.7 years (range 42 days to 20 years, median 9 years). Five patients with atrial flutter, one patient with atrial fibrillation, two patients with an intermediate rhythm between atrial flutter and atriala fibrillation, four patients with chaotic atrial tachycardia, three patients with atrioventricular reentry tachycardia, two patients with junctional ectopic tachycardia, and three patients with ventricular arrhythmias were treated with amiodarone. The mean duration of therapy was 9.1 ± 12.3 months (range 1 month to 4 years). Before amiodarone treatment, 18 patients had been unresponsive to various antiarrhythmic drugs (range 1-8, median 2). Two patients received amiodarone as an initial therapy. It was administered orally at a dose of 10 mg/kg once per day for 10 days and then decreased to 5 mg/kg once per day. Amiodarone was effective in 16 patients (80%).

Side effects occurred in three patients, including thyroid dysfunction, elevation of liver enzymes, and keratopathy. All side effects disappeared upon cessation of the therapy. We recommend amiodarone for the treatment of childhood arrhythmias, especially for the refractory types. *Key words: amiodarone, childhood, arrhythmia.*

Amiodarone is known to be effective for the control of various cardiac arrhythmias in adults[1-3]. Recently, successful use of the drug in the treatment of childhood arrhythmias refractory to conventional agents has been reported[2, 4, 5]. Side effects of amiodarone that occur during long-term administration have limited use of the drug in childhood. The purpose of this report was to investigate the efficacy and side effects of amiodarone in different types of arrhythmias in children.

Material and Methods

The study population consisted of 20 patients (7 female and 13 male, mean age 8.5 ± 6.7 years, range 42 days to 20 years, median 9 years). Seventeen patients (85%) had different types of supraventricular tachycardia (SVT), while three patients (15%) had ventricular arrhythmias (Table I). Rhythm was assessed by 12-lead electrocardiogram (ECG) and 24-hour continuous ambulatory electrocardiogram (cardioscan) in all.

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Table I: Clinical Characteristics of Patients

Case No.	Age	Sex	Arrhythmia	Heart Disease	Cardiac Surgery	Previous Drugs
1	11	M	AFL	TGA, PS	+	Dig, Quin, Propa
2	14	F	AFL	Restrictive CMP	–	Dig
3	14	M	AFL	Dilated CMP	–	Dig, V
4	18 months	M	AFL	–	–	Dig, Dilt
5	16	M	AFL	TGA	+	Dig, Propa
6	20	F	AFIB	MS, MI, TI	+	Quin
7	18	F	AFL + AFIB	ASD	+	Dig, Prop, Fle, Propa, V
8	15	M	AFL + AFIB	Single ventricle, PS	+	–
9	5 months	M	CAT	–	–	Dig, Propa, S
10	6 months	F	CAT	ASD	–	Dig, S
11	42 days	M	CAT	–	–	Dig, S
12	3 months	F	CAT	–	–	–
13	7	M	AVRT	Dilated CMP	–	Dig, Fle, Propa
14	5	F	AVRT	–	–	Dig, V
15	3.5 months	M	AVRT	Single ventricle	–	Dig, S, Propa
16	4	M	JET	Dilated CMP	–	Dig, Prop, Pind, Propa, Fle, Proc, Quin, V
17	6	M	JET	AS, AI	+	Dig, Propa
18	12	M	PVC	MI, MVP	–	Propa, S
19	11	M	PVC	TOF	+	Dig, S, Propa, Mex
20	13	F	VT	Dilated CMP	–	Dig, Propa, Epd

No: number, M: male, F: female, AFL: atrial flutter, AFIB: atrial fibrilation, CAT: chaotic atrial tachycardia, AVRT: atrioventricular reentry tachycardia, JET: junctional ectopic tachycardia, PVC: premature ventricular contractions, VT: ventricular tachycardia, TGA: transposition of great arteries, PS: pulmonary stenosis, CMP: cardiomyopathy, MS: mitral stenosis, MI: mitral insufficiency, TI: tricuspid insufficiency, ASD: atrial septal defect, AS: aortic stenosis, AI: aortic insufficiency, MVP: mitral valve prolapse, TOF: tetralogy of Fallot, +: surgery performed, –: surgery not performed, Dig: digoxin, Quin: quinidine, Propa: propafenone, V: verapamil, Dilt: diltiazem, Prop: propranolol, Fle: flecainide, S: sotalol, Pind: pindolol, Proc: procainamide, Mex: mexiletine, Epd:epdantoin.

Ten patients (50%) had congenital structural heart disease, and seven of them had undergone palliative or corrective heart surgery. Five patients (25%) had acquired heart disease, with restrictive cardiomyopathy (CMP) in one patient and dilated CMP in four patients. Three patients developed dilated CMP secondary to incessant tachyarrhythmias. Before amiodarone treatment, 18 patients had been unresponsive to various antiarrhythmic drugs (range 1-8, median 2) and seven patients had previously required one or more synchronized direct-current electrocardioversions. Two patients received amiodarone as an initial therapy.

Amiodarone was given orally at a loading dose of 10 mg/kg/day for 10 days, followed by a maintennace dose of 5 mg/kg/day. Digitalis was used in 11 patients concomitantly. Twelve-lead ECG, 24-hour cardioscan and echocardiography were performed in order to demonstrate the efficacy of amiodarone therapy. Ophthalmologic examination was performed, and serum levels of triiodothyronine (T_3), thyroxine (T_4), thyroid-stimulating hormone (TSH), alanine aminotransferase (ALT), and aspartate aminotransferase (AST) were obtained one, three, six and 12 months after initiation of therapy and were repeated every six months thereafter. The drug was discontinued if it was not effective.

Results

Results were considered to be effective when normal sinus rhythm was reestablished and the clinical state improved in patients treated with amiodarone. In patients whose tachycardia rate was reduced but whose arrhythmia was not effectively suppressed, the results were considered to be partially effective. If there was no change in the clinical and electrocardiographic states, the treatment was considered ineffective.

The mean duration of therapy was 9.1 ± 12.3 months (range 1 month to 4 years). Amiodarone was effective in 13 patients (65%), partially effective in three patients (15%), and ineffective in four patients (20%) (Table II). In one patient in whom amiodarone was effective (Case 7), it was discontinued after four years and there was no subsequeut recurrence. The other patients without drug-related side-effects were still on amiodarone therapy as of this writing. Arrhythmia did not recur in any patients for whom amiodarone had been effective.

Table II: Efficacy and Side Effects of Amiodarone

Case Number	Outcome	Follow-up (months)	Side Effects
Atrial tachycardia			
1	+	6	(–)
2	+	1	(+)*
3	–	10	(–)
4	+	3	(–)
5	+	6	(+)**
6	–	2	(–)
7	+	48	(–)
8	–	5	(–)
9	+	8	(–)
10	+	3	(–)
11	+	1	(–)
12	+	1	(–)
AVRT			
13	–	5	(–)
14	+	8	(–)
15	+	13	(–)
JET			
16	+ (P)	36	(–)
17	+	1	(–)
PVC and VT			
18	+ (P)	4	(–)
19	+ (P)	2	(–)
20	+	19	(+)***

AVRT: atrioventricular reentry tachycardia, JET: junctional ectopic tachycardia, PVC: premature ventricular contractions, VT: ventricular tachycardia, +: success, –: failure, (P): partial, (–): side effects did not occur, (+): side effects occurred, *: hepatic dysfunction, **: keratopathy, ***: thyroid dysfunction.

Atrial Tachycardia

The twelve patients with some form of atrial tachycardia were treated with amiodarone for a mean of 9.8 months. The treatment was effective in nine patients (75%). Four of the five patients with atrial flutter responded well to amiodarone, but one patient required discontinuation of the drug on the seventh day of therapy because of side effects. One patient with atrial fibrillation did not respond to amiodarone. Only one of the two patients with an intermediate rhythm between atrial flutter and atrial fibrillation responded to treatment. Therapy with amiodarone was successful in all four children (100%) with chaotic atrial tachycardia (CAT).

Atrioventricular Reentry Tachycardia (AVRT)

In two of the three patients with AVRT the treatment was effective (67%), whereas in one it was ineffective. The patient who was unresponsive to therapy with a permanent form of junctional reciprocating tachycardia died suddenly due to congestive heart failure while he was still on amiodarone therapy (Case 13).

Junctional Ectopic Tachycardia (JET)

The two patients in this group were treated with amiodarone for a mean of 18.5 months. It was considered to be effective in these patients, one of them being partially responsive. He had dilated CMP and was given eight other antiarrhythmic drugs before the initiation of therapy with amiodarone. He had normal cardiac function assessed by echocardiographic study.

Premature Ventricular Contractions (PVC) and Ventricular Tachycardia (VT)

Two patients with PVC were considered to be partially responsive to amiodarone therapy. Twenty-for-hour cardioscan revealed that ectopic beats were not completely suppressed but were reduced in number. Amiodarone was effective in one patient with VT, but it had to be withdrawn because of side effects (Case 20).

Side Effects

During amiodarone therapy, side effects occurred in three (15%) of 20 patients (Table II). A 13-year-old female patient with VT who had dilated CMP developed hyperthyroidism in the 19^{th} month of therapy (Case 20). In a 14-year-old female patient with restrictive CMP and atrial flutter, amiodarone treatment was stopped because of elevated liver enzymes, nausea, vomiting and abdominal pain (Case 2). Amiodarone keratopathy occurred within four months in a 16-year-old male patient with atrial flutter (Case 5). The drug was discontinued due to side effects in three patients in whom it had been effective, and all side effects were reversible after discontinuation.

Discussion

Amiodarone hydrochloride is an iodinated benzofuran derivative which is structurally similar to thyroxine. It was first used in 1967 as an antianginal agent due to its ability to increase coronary blood flow and to decrease peripheral vascular resistance, but was later found to have antiarrhythmic properties[3]. It has class-III antiarrhythmic actions according to the Vaughan Williams classification[1,2]. Amiodarone prolongs the action potential duration and refractory period, but it also has calcium antagonist and β-receptor blocking effects on cardiac tissues. Consequently, the surface ECG may show sinus bradycardia, prolongation of the QT interval and changes in the T and U waves. Approximately 50 percent of the drug is absorbed after an oral dose, and it has a large volume of distribution. Oral loading is necessary to obtain an antiarrhythmic effect. It is generally used in conjunction with digoxin because of its inotropic properties[6].

The side effects of antiarrhythmics and drug resistance are challenging problems in the treatment of arrhythmias in childhood. After the surgical repair of most congenital heart diseases, patients are at risk for sudden death from various arrhythmias. Supraventricular tachycardia is generally considered benign, but in some patients it is incessant and these patients are at risk for the development of cardiomyopathy. Many children with such life-threatening arrhythmias respond to conventional antiarrhythmic drugs, but some do not. Recent data suggest that amiodarone is highly effective in controlling most of the supraventricular as well as ventricular tachyarrhythmias that have failed to respond to various conventional drugs[7]. Several reports have suggested that amiodarone has an efficacy of between 60 and 100 percent on different arrhythmias[2,4,5,8]. The efficacy of amiodarone in our study, including partial effectiveness, was 80 percent, which is similar to the findings of other researchers[8]. We observed complete control in 65 percent of patients, partial control in 15 percent, and failure in 20 percent. In our experience the efficacy of amiodarone in particular arrhythmias was 62.5 percent in atrial flutter and fibrillation, 100 percent in CAT, 66.6 percent in AVRT, and 100 percent in JET and ventricular ectopy. Guccione et al.[8] observed complete control in 80 percent of their 95 patients, partial control in four percent, and failure in 16 percent. In ventricular tachycardia they had an efficacy of 68 percent, in atrial flutter 97 percent, in SVT 75 percent and in JET 50 percent. Many reports[7-9] show a high efficacy of amiodarone in children with Wolff-Parkinson-White syndrome and JET. Therefore, use of amiodarone before surgical therapy for these arrhythmias is recommended.

Amiodarone has various side effects such as cutaneous disorders, photosensitivity, corneal deposits and keratopathy, hyperthyroidism or hypothyroidism because of the presence of iodine compound, elevation in liver enzymes and proarrhythmia[4,5,8,10,11]. The incidence of side effects associated

with amiodarone therapy ranges from 12.5 to 93 percent, and the side effects are usually reversible after drug discontinuation[5, 8, 11]. Clinical thyroid dysfunction and hepatic dysfunction are rarely seen in children. Intravenous amiodarone may cause acute bradycardia, hypotension and cardiovascular collapse[1, 12, 13]. We had a 15 percent incidence of side effects overall after seven days to 19 months of therapy, and we observed no increase in the incidence of side effects with a longer duration of treatment. It is suggested that amiodarone is more rapidly metabolized in young children, because side effects are less frequent in young patients than in adults[2, 4, 8]. In our study, all patients who had side effects were over greater than 10 years in age.

Pharmacological therapy for tachyarrhythmias is often effective but generally palliative and has side effects in long-term use. Transcatheter ablation using radiofrequency energy of arrhythmia foci or accessory pathways has been used, especially for life-threatening or drug-refractory arrhythmias[15, 16]. This treatment method is being used successfully in patients with atrial flutter, ectopic atrial tachycardia, JET, atrioventricular node reentrant tachycardia, and SVT due to accessory pathways, but side effects such as systemic embolization, myocardial damage or perforation, and rhythm disorders are serious limitations[15, 16]. It is also difficult to perform catheter ablation in infants with tachyarrhythmias.

It is known that amiodarone can be used in newborns and also during intrauterine life. The smallest patient that has been given amiodarone was a 23-week-gestation fetus who had hydrops fetalis secondary to tachycardia[5]. The smallest patient in our series was a 42-day-old infant with CAT.

Because of amiodarone's complex pharmacokinetics, the therapeutic and toxic range of serum levels has not yet been defined[2]. There is no known correlation between amiodarone dosage and serum level, or between serum level and toxicity[2, 14]. Therefore, monitoring amiodarone dosage and serum levels is not useful for evaluating amiodarone toxicity. For this reason, it is crucial to follow up the side effects of the drug. Serious side effects of amiodarone are relatively infrequent in children, but follow-up of patients, especially young ones who have rapid brain development and somatic growth, should be done carefully.

In conclusion, amiodarone is a very effective agent for infants and adolescents who have drug-refractory tachycardia, especially in postoperative patients. It should be used with caution because of its side effects.

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