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Long-Term Follow-Up of Amiodarone Therapy in the Young: Continued Efficacy, Unimpaired Growth, Moderate Side Effects

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Long-term follow-up data on young patients receiving amiodarone is lacking, especially in relation to growth and late side effects. The records of 95 young patients (mean age 12.4 years; range 3 weeks to 31.5 years) who received amiodarone were reviewed. Minimal follow-up time for those continuing to take amiodarone was 1.5 years; the mean duration of therapy was 2.3 years (maximal 6.5). The mean maintenance dosage was 7.7 (1.5 to 25) mg/kg body weight per day. Initial success (based on symptoms and 24 h electrocardiogram) was achieved in 23 of 34 patients with ventricular tachycardia, in 32 of 33 with atrial flutter and in 21 of 28 patients with supraventricular tachycardia. However, in 7 of 33 patients with atrial flutter, the arrhythmia returned after 6 months. Patient growth continued in the same percentiles achieved before amiodarone in all but eight patients, improving in six and worsening in two with severe underlying disease.

Proarrhythmia occurred in three patients: one had torsade de pointes that disappeared when amiodarone administration was stopped; two with severe anatomic heart disease died suddenly during the loading period (one with atrial flutter and one with ventricular tachycardia). Side effects occurred in 28 (29%) of the 95 patients: keratopathy (in 11), abnormal thyroid function test (in 6), chemical hepatitis (in 3), rash (in 3), peripheral neuropathy (in 2), hypertension (in 1) and vomiting (in 1). All side effects disappeared when amiodarone was discontinued or the dose was reduced.

It is concluded that 1) amiodarone was an effective drug for these young patients with tachyarrhythmias; 2) growth was unimpaired; and 3) side effects were relatively common but not severe (no pulmonary side effects). Amiodarone is recommended only for young patients with life-threatening arrhythmias that are resistant to conventional drugs.

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Treatment of arrhythmias in selected groups of children and young adults has been shown to lessen symptoms and reduce the incidence of sudden death (1–3). After the atrial switch operation for transposition of the great arteries, 20% of patients have atrial flutter and 21% of those with flutter have been reported to die suddenly (3). Patients who undergo ventriculotomy for repair of congenital heart disease have been found to be at risk for sudden death from ventricular arrhythmias (1). Supraventricular tachycardia is generally benign, but in some patients it is incessant (>90% of day and night). These patients are at risk for the development of cardiomyopathy, sometimes progressing to referral for cardiac transplantation (4,5). Many children with life-threatening arrhythmias respond to conventional antiarrhythmic drugs (6–8), but many do not and have required amiodarone.

Long-term follow-up data on young patients receiving amiodarone is lacking, especially in relation to patient growth and development of late side effects. The long-term beneficial effects and toxicity of amiodarone have been well described in adults (9). Coumel and Fidelle (10) reported on 135 children with a mean follow-up interval of 5 months; the first 39 patients of their series were reported on after a mean follow-up interval of 12 months (11). The 30 patients of Bucknall et al. (12) were followed up for 23 months.

This report reviews our long-term results on efficacy and toxicity of amiodarone in treating patients with resistant and life-threatening arrhythmias. Each patient who is still receiving amiodarone has been followed up for >18 months.

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Methods

Study patients. We reviewed the charts of 95 patients (mean age 12.4 years, range 3 weeks to 31.5 years) who received amiodarone. Of the 95 patients, 22 (23%) were >2 years of age, 33 (35%) were between 2 and 15 years and 40 (42%) between 15 and 31 years. The criteria for inclusion in the study were: 1) children <18 years of age (those >18 years were included only if they had congenital heart disease); 2) All had "life-threatening" arrhythmias. Atrial flutter or ventricular tachycardia were considered "life-threatening" if the patients were symptomatic and the arrhythmia was sustained and required at least one hospital admission for cardioversion. Supraventricular tachycardia was defined as "life-threatening" if it was incessant, (that is, >90% of a 24 h period); 3) The arrhythmia was unresponsive to conventional drugs. Patients received an average of 2.7 drugs before amiodarone therapy was begun. Nonresponse to conventional drugs was assessed by increasing dosage until symptomatic side effects occurred or the serum concentrations were well above the "therapeutic range." 4) Follow-up of at least 1.5 years for the patients still receiving the drug. Every patient started on amiodarone was included regardless of duration of treatment. The mean duration of therapy was 27 months (range 1 day to 6.5 years). Forty-six patients (49%) received amiodarone for >2 years, 34 (36%) for >3 years and 23 (24%) for >4 years.

Amiodarone protocol. All patients were admitted to the hospital for initial loading therapy. All antiarrhythmic drugs except digoxin were discontinued 3 days after beginning amiodarone therapy. Digoxin dose was reduced by half on the third day of amiodarone therapy (13,14). During the entire hospitalization (before and during treatment), cardiac rhythm was monitored continually with 24 h electrocardiograms (ECG). Pretreatment laboratory data included: a 15 lead ECG, chest radiogram, echocardiogram, complete blood count with differential, serum glutanmic pyruvic transaminase (GPT), serum oxaloacetic transaminase (GOT), urinalysis, serum triiodothyronine (T3), thyroxine (T4) and reverse T3. The laboratory tests were performed 1, 3, 6 and 12 months after beginning therapy and were repeated every 6 months thereafter. Ophthalmologic examination, including slit lamp examination, was performed after 6 months; in all patients after this time, the drug was approved and follow-up ophthalmologic examination became voluntary. In a group of 25 selected patients, trough serum concentrations of amiodarone and desethyl-amiodarone were determined by standard methods (15).

Amiodarone was administered orally in a dose of 10 mg/kg per day for 10 days and then decreased to 5 mg/kg once per day. Since the findings reported in 1985 (16) that infant dosage should be proportional to body surface area, we have used a higher maintenance dose of 7.5 mg/kg per day in infants <2 years of age (keeping the dose per square meter approximately constant). The maintenance regimen was continued for at least 1 month of therapy. If the arrhythmia did not return, attempts were made to decrease the dose every 3 to 4 months. When a stable dose was achieved, the patient was placed on the same daily dose for 5 of 7 days. If the arrhythmia recurred or did not respond during initial loading treatment, the long-term dose was increased to 10 mg/kg per day. If the arrhythmia was still present after 3 weeks, the drug was considered to have failed. The dosage was increased up to 25 mg/kg per day in patients in whom the drug was initially effective, but who had recurrence of arrhythmia. If the reverse T3 was >100 ng/dl, attempts to increase the dose were discontinued (17).

The drug was considered to be successful if patients had no symptoms related to the arrhythmia and if the 24 h ECG revealed no episodes of ventricular tachycardia (three or more beats), atrial flutter or supraventricular tachycardia for at least 6 months. A partial success was defined as both a decrease in the rate of atrial flutter, supraventricular tachycardia or ventricular tachycardia and improvement of symptoms of congestive heart failure. This group was included in the analysis because the drug led to clinical improvement. The arrhythmia was said to have "recurred" if the arrhythmia had been absent for at least 6 months and then reappeared with the patient on the same dose that had previously been effective.

Data analysis. Electrocardiographic intervals (heart rate, PR interval, QRS duration, corrected QT interval [$QT/\sqrt{RR}$]) were compared before and during treatment. However, a patient was excluded from this comparison if 1) an ECG with sinus rhythm was not available both before and during treatment, 2) the patient had a pacemaker implanted, or 3) the patient was taking other drugs at the beginning of amiodarone treatment that might have affected ECG intervals.

Each patient's data before treatment were compared with the same data after treatment by the paired *t* test. Group comparisons of numeric data were made by chi-square analysis. Statistical significance was inferred if the probability of a difference occurring by chance was <0.05.

Results

Cardiac arrhythmia and diagnosis (Table 1). The most common cardiac diagnosis was postoperative repair of congenital heart disease in 33 (35%) of the 95 patients. The most common arrhythmias treated were ventricular tachycardia (36%) and atrial flutter (34%). Of the 28 patients (29%) with supraventricular tachycardia, the mechanism determined at electrophysiologic study in 20 patients was: reciprocating tachycardia through a Kent accessory bundle in 11 patients, junctional ectopic tachycardia in 4, atrial ectopic tachycardia in 3 and atrioventricular (AV) node reentry tachycardia in 2.

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Table 3. Follow-Up Data in 95 Patients

Outcome	No. of Patients	Mean Duration of Treatment (yr)*
Success	42 (43%)	3.8 (1.5–6.5)
Initial success with elective suspension	8 (8%)	0.8 (0.5–3.8)
Initial success and nondrug-related death	14 (15%)	1.4 (0.2–4.3)
Partial success	4 (5%)	1.3 (0.4–4.3)
Side effects leading to drug discontinuation	12 (13%)	1.7 (0.2–4.9)
Failure	15 (16%)	0.3 (0.1–0.6)

*Range is shown in parentheses.

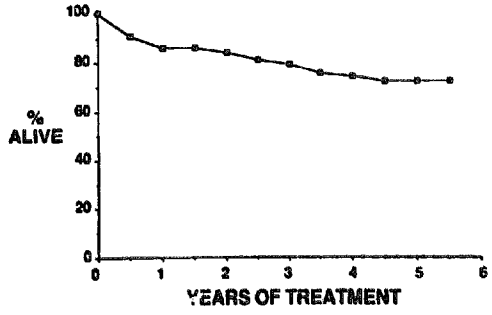
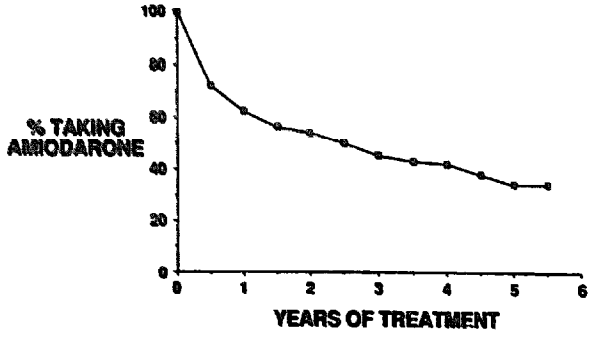


Figure 3. Percent of 95 patients remaining alive by duration of treatment. The majority of the deaths were nonsudden (see text).

patients, the drug was effective and the patients continued to receive amiodarone; mean duration of treatment in this group was 3.8 years (range 1.5 to 6.5). Seven of these 42 patients experienced recurrence of atrial flutter after at least six months of successful treatment with amiodarone (Fig. 2). 2) In eight patients, the drug was successful, but it was stopped because the patient elected to have surgical treatment of the arrhythmia (five patients) or the arrhythmia stopped spontaneously (three infants).

3) Fourteen patients with congenital heart disease in whom the drug was effective had in-hospital nonsudden death due to progressive heart failure at a mean of 17 months after beginning treatment (five after surgical repair, four after surgical palliation and five with pulmonary vascular obstructive disease or surgically noncorrectable anatomy) (Fig. 3). *4) In four patients, the drug was partially effective, and in three of them it was discontinued.* Two infants had junctional ectopic tachycardia; the first underwent successful catheter ablation (18) of the ectopic focus and the other patient died suddenly while asleep after 3 months of amiodarone treatment. Sudden death is common in infants with junctional ectopic tachycardia (19,20) and, therefore, the relation of amiodarone and death is questionable. A 20 month old patient with incessant ventricular tachycardia underwent successful surgical excision of ventricular tumor (21) after 6 months of partially effective therapy with amiodarone. The fourth patient, who is still receiving amiodarone, is a 10 year old girl with atrial ectopic tachycardia due to multiple foci (22); she underwent unsuccessful surgical therapy (23) at 6 years of age. In this patient, amiodarone is now partially effective in reducing the rate of the tachycardia. 5) The drug was discontinued for side effects in 12 patients in whom it had been effective (see the discussion of side effects).

Figure 2. Percent of patients taking amiodarone by duration of treatment. In each time interval, all patients not taking amiodarone were removed (for example, ineffective treatment, elective discontinuation, side effects, death).



6) In 15 patients, the drug failed. Five had incessant ventricular tachycardia caused by a ventricular tumor; four of these had subsequent successful surgical therapy (21), and the fifth died from heart failure 3 months after the arrhythmia had been successfully treated surgically. Two patients had ventricular arrhythmia and severe congestive cardiomyopathy, and both died suddenly after drug discontinuation. Ventricular tachycardia was present in two additional patients, aged 11 and 17 years, both with pulmonary vascular disease; in both, the drug was ineffective. Two patients, aged 6 weeks and 17 years, had supraventricular tachycardia caused by a Kent accessory bundle. One of these patients with severe Ebstein's anomaly died during an intractable episode of supraventricular tachycardia after the drug had been discontinued; the other underwent successful surgical therapy (23). The drug was ineffective in two patients, one with atrial repair of transposition of the great arteries and atrial flutter (the only nonresponder in this group); the other had atrial ectopic tachycardia and underwent subsequent successful surgical therapy (23).

The mean duration of treatment in the unsuccessful group of 15 patients was 3.1 months (range 0.1 to 7). The mean dosage in the nonresponder group was significantly higher than that in the responder group (11.7 ± 6.9 versus 6.9 ± 2.9 mg/kg per day; $p < 0.001$). Reverse T3 measurements were performed in these patients, and were >50 ng/dl in all. The last two patients included in the failure group were the patients who died during the loading period.

Discussion

Amiodarone efficacy. Our results confirm the long-term high efficacy of amiodarone in the management of young patients with life-threatening arrhythmias that are not responsive to conventional drugs. The efficacy of amiodarone in our study is similar to that reported by Coumel and Fidelle (10) in a series of 135 pediatric patients, even though the follow-up period in the present study is longer. Coumel and Fidelle (10) observed complete control of the arrhythmias in 60% of their patients (compared with our 80%), partial control in 33% (compared with our 4%) and failure in 7% (compared with our 16%). In our experience, ventricular tachycardia in patients with ventricular tumor or congestive cardiomyopathy is the only arrhythmia that is relatively resistant to amiodarone in young patients. Ventricular tachycardia related to ventricular tumor in infants is rarely responsive to any medical regimen, and surgery is an established effective and curative therapy (21). The high mortality rate in patients with drug-resistant symptomatic ventricular tachycardia related to cardiomyopathy (24) may prove to be an indication for heart transplantation. Excluding these two groups of patients, the efficacy of amiodarone in treatment of ventricular tachycardia was high (91%).

It has been demonstrated (2) that suppression of atrial flutter reduces the likelihood of sudden death. In our experience, amiodarone was extremely effective in the long-term treatment of resistant atrial flutter. The arrhythmia recurred in 27% of our patients with atrial flutter, but it was slower, well tolerated and did not result in death. Many reports (10,12,25) show a high efficacy of amiodarone in children with Wolff-Parkinson-White syndrome and supraventricular tachycardia. We have no comparable experience because we prefer surgical treatment (23) of Wolff-Parkinson-White syndrome instead of long-term pharmacologic therapy. Our results confirm the efficacy of amiodarone in the treatment of junctional ectopic tachycardia. This arrhythmia is associated with a poor prognosis when it occurs in neonates or infants (19). A recent multicenter study (26) showed that amiodarone was the antiarrhythmic drug with the highest rate of success in the treatment of this arrhythmia. Therefore, we recommend amiodarone treatment before catheter ablative procedures (18) or surgical therapy (23) for junctional ectopic tachycardia.

Proarrhythmia. Torsades de pointes has been reported in several children during amiodarone therapy (27) and was documented in one teenager in our study. The death of two of our patients during the loading period may be explained by the severe heart disease and the terminal condition of these patients. However, it is possible that the drug contributed to their death. Therefore we consider it mandatory to hospitalize all patients for initiation of amiodarone therapy.

All eight patients who required pacemaker implantation were young adults with atrial flutter after atrial repair of complete transposition of the great arteries. Each patient developed severe bradycardia during amiodarone treatment. The American College of Cardiology and the American Heart Association (28) recommend that a pacemaker be implanted in all patients in whom "severe bradycardia resulted from underlying sick sinus syndrome and treatment with an antiarrhythmic drug that suppresses the sinus node." We currently implant a pacemaker before beginning amiodarone therapy in patients who previously had an "atrial switch" procedure performed for transposition of the great arteries.

Side effects. Our results confirm the relative safety of amiodarone in children (10–12), with an overall lower incidence of side effects than in adults. All side effects were reversible after the drug was discontinued or the dosage reduced. Our data suggest that many side effects can be avoided if doses are kept as low as possible. An overall 8% incidence of side effects has been reported by Coumel and Fidelle (10) after a mean duration of therapy of 5 months; patients in the present series have been treated for a mean of 27 months of therapy, with a 29% incidence of side effects. However, our patients developed fewer side effects (5.2%) within the first 6 months of treatment, and we observed no increase in incidence of side effects with longer duration of treatment. In adult patients, however, the incidence of side effects appears to increase with a longer follow-up period (29). *There are also major differences between adults and children concerning the incidence and type of side effects.* Side effects were rare in patients <10 years of age (10–12). In our study, only 4% of the patients <10 years of age had side effects, in contrast to 44% of patients >10 years of age. Pulmonary toxicity has not been reported in children (10–12). Changes in thyroid hormone levels were demonstrated in all studies of adult patients taking amiodarone (29–35). In our series, the incidence of thyroid dysfunction was lower (9%), and no patient developed symptoms. Thyroid test results returned to the normal range in two of six patients after the dosage of amiodarone had been reduced. Behavioral changes, such as aggressiveness and nightmares, have been interpreted to be the precursor of hyperthyroidism (10), but our two patients with these symptoms had normal thyroid tests. The incidence of dose-dependent hepatic abnormalities and their reproducibility in experimental animal models suggest a toxic effect rather than host idiosyncrasy (29). In our experience, the changes were transient and did not progress. In two of our patients, hepatic function test results normalized when the dose was reduced.

The different incidence of side effects in children, adults and elderly patients (occurrence of myxedema is reported in patients >70 years of age [29]) may be related to different pharmacokinetics and pharmacodynamics of amiodarone at different ages (36). Coumel and Fidelle (10) suggested that amiodarone is more rapidly metabolized in young children. Because severe side effects appear to be less frequent in

young patients, if the pharmacodynamics and pharmacokinetics of amiodarone in children were better understood, it might be possible to devise a method for reducing toxicity in adults.

References

1. Garson A, Randall DC, Gillette PC, et al. Prevention of sudden death after repair of tetralogy of Fallot: treatment of ventricular arrhythmias. J Am Coll Cardiol 1985;6:221–7.
2. Garson A, Gillette PC, McVey P, Latson LA, McNamara DG. Sudden death in pediatric cardiovascular patients: relationship to prior dysrhythmias (abstr). J Am Coll Cardiol 1984;3:484.
3. Garson A, Bink-Boelkens M, Hesslein PS, et al. Atrial flutter in the young: a collaborative study of 380 cases. J Am Coll Cardiol 1985;6: 871–8.
4. Gillette PC, Smith RT, Garson A, Mullins CE. Curable cause of cardiomyopathy. JAMA 1985;253:391–2.
5. Packer DG, Bardy GH, Gallagher JJ, Worley SJ, Smith MS, German LD. Tachycardia induced cardiomyopathy: a reversible form of left ventricular dysfunction (abstr). J Am Coll Cardiol 1984;3:521.
6. Moak JP, Smith RT, Garson A. Newer antiarrhythmic drugs in children. Am Heart J 1987;113:179–85.
7. Garson A, Gillette PC. Treatment of chronic ventricular dysrhythmias in children. PACE 1981;4:658–69.
8. Moak JP, Smith RT, Garson A. Mexiletine: an effective antiarrhythmic drug for treatment of ventricular arrhythmias in congenital heart disease. J Am Coll Cardiol 1987;10:824–9.
9. Herre JM, Griffin JC, Sauve MG, Malone P, Scheiman MM. Long term results of amiodarone therapy (abstr). Circulation 1987;76(suppl IV): IV-511.
10. Coumel P, Fidelle J. Amiodarone in the treatment of cardiac arrhythmias in children: one hundred thirty-five cases. Am Heart J 1980;100:1063–9.
11. Garson A, Gillette PC, McVey P, et al. Amiodarone treatment of critical arrhythmias in children and young adults. J Am Coll Cardiol 1984;4:749–55.
12. Bucknall CA, Keeton BR, Curry PVL, Tynan MJ, Sutherland GR, Holt DW. Intravenous and oral amiodarone for arrhythmias in children. Br Heart J 1986;56:278–84.
13. Moysey JO, Jaggarao NSV, Grundy EN, Chamberlain DA. Amiodarone increases plasma digoxin concentrations. Br Med J 1981;282:272–5.
14. Marcus F. Drug interactions with amiodarone. Am Heart J 1983;106: 924–9.
15. Storey GCA, Holt P, Curry PVL. High performance liquid chromatographic measurement of amiodarone and its desethyl metabolite. Ther Drug Monit 1982;4:385–8.
16. Keaton BR, Curry PVL, Holt DW. Efficacy and side effects of amiodarone for resistant arrhythmias in children. In: Proceedings of the Second World Congress of Pediatric Cardiology. New York: Springer-Verlag, 1985:56.
17. Nademanee K, Singh B, Hendrickson A, Reed AW, Melmed S, Hershman J. Pharmacokinetic significance of serum reverse T3 levels during amiodarone treatment: a potential method for monitoring chronic drug therapy. Circulation 1982;66:202–11.
18. Smith RT, Gillette PC, Massumi A, McVey P, Garson A. Transcatheter ablative technique for treatment of the permanent form of junctional reciprocating tachycardia in young patients. J Am Coll Cardiol 1986;8: 385–90.
19. Gillette P. Supraventricular arrhythmias in children. J Am Coll Cardiol 1985;5(suppl B):122B–9B.
20. Garson A, Gillette PC. Junctional ectopic tachycardia in children: electrocardiography, electrophysiology and pharmacological response. Am J Cardiol 1979;44:298–302.
21. Garson A, Smith RT, Moak JP, et al. Incessant ventricular tachycardia in infants: myocardial hamartomas and surgical cure. J Am Coll Cardiol 1987;10:619–26.
22. Garson A, Smith RT, Moak JP, et al. Supraventricular tachycardia due to multiple atrial ectopic foci: a relatively common problem (abstr). J Am Coll Cardiol 1986;7(suppl A):119A.
23. Ott DA, Garson A, Cooley DA, McNamara DG. Definitive operation for refractory cardiac tachyarrhythmias in children. J Thorac Cardiovasc Surg 1985;90:681–9.
24. Griffin MG, Hernandez A, Martin TC. Dilated cardiomyopathy in infants and children. J Am Coll Cardiol 1988;11:139–44.
25. Shahar E, Grand M, Feigl A. Amiodarone in control of sustained tachyarrhythmias in children with Wolff-Parkinson-White syndrome. Pediatrics 1983;72:813–6.
26. Villain E, Garson A. Evolving concepts in the management of congenital junctional ectopic tachycardia: a multicenter study (abstr). J Am Coll Cardiol 1988;11(suppl A):155A.
27. Hesslein PS, Costigan DC, Koren G. Oral amiodarone therapy in childhood: early experience. Pediatr Cardiol 1983;4:313–7.
28. Collins JJ, Desanctis RW. Guidelines for permanent cardiac pacemaker implantation, May 1984. Circulation 1984;70:331A–5A.
29. Harris L, McKenna W, Rowland E, Holt DW, Storey GCA, Krikler DM. Side effects of long-term amiodarone therapy. Circulation 1983;67:45–51.
30. Greene HL, Graham EL, Werner JA, et al. Toxic and therapeutic effects of amiodarone in the treatment of cardiac arrhythmias. J Am Coll Cardiol 1983;2:1114–28.
31. Kaplan LJ, Cappaert WE. Amiodarone keratopathy: correlation to dosage and duration. Arch Ophthalmol 1982;100:601–2.
32. Pickoff AS, Singh S, Flinn CJ, Wolff GS, Gelband H. Use of amiodarone in the therapy of primary ventricular arrhythmias in children. Dev Pharmacol Ther 1983;6:73–82.
33. Melchis S, Lubin E, Laor J, Margaliot M, Strasberg B. Amiodarone induced thyroid gland dysfunction. Am J Cardiol 1987;59:833–5.
34. Albert SG, Alves L, Rose EP. Thyroid dysfunction during chronic amiodarone therapy. J Am Coll Cardiol 1987;9:175–83.
35. Boyd MR, Burkalt LT. In vivo studies on the relationship between target organ alkylation and the pulmonary toxicity of a chemical reactive metabolite of 4-ipomeanol. J Pharmacol Exp Ther 1978;207:687–94.
36. Garson A. Dosing the newer antiarrhythmic drugs in children: consideration in pediatric pharmacology. Am J Cardiol 1986;57:1405–7.