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Digoxin or Flecainide for Prophylaxis of Supraventricular Tachycardia in Infants?

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Objectives. **This study compared the safety and efficacy of digoxin and flecainide in the prophylaxis of supraventricular tachycardia in infants.**

Background. **Recurrence of supraventricular tachycardia in infants is common. Digoxin is the conventional drug of first choice for prophylaxis, but its efficacy has not been tested in a controlled clinical trial, and there is no consensus on the drug of choice when digoxin is ineffective.**

Methods. **We reviewed retrospectively the records of all infants with supraventricular tachycardia due to atrioventricular (AV) reentry admitted to our hospital between January 1986 and December 1993.**

Results. **Thirty-nine infants presented with sustained AV reentrant tachycardia at age 1 to 330 days (median 12). Intravenous flecainide was required to maintain immediate control in six patients who were then treated with oral flecainide. The other 33 patients were treated with oral digoxin. There was no recurrence of tachycardia in 14 (42%) of the 33 patients (95% confidence interval [CI] 25% to 61%). In the other 19 patients (58%) (95% CI 39% to 75%), digoxin was replaced by oral flecainide because of multiple recurrence of tachycardia. Full control was achieved in all 19 of these patients (100%) (95% CI 82% to 100%) and in 5 of the 6 patients treated with both intravenous and oral flecainide. Thus, overall, flecainide was effective in 24 (96%) of 25 patients (95% CI 80% to 100%).**

Conclusions. **Comparison with previous natural history studies suggests that digoxin is ineffective in the prophylaxis of supraventricular tachycardia. Oral flecainide was effective in a small number of infants, with no adverse effects (95% CI 0% to 12%), and may now be preferred as the primary prophylactic agent.**

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Supraventricular tachycardia in early infancy is serious and potentially life-threatening. Once the diagnosis is made, the restoration of sinus rhythm is usually straightforward. Because the risk of spontaneous recurrence of tachycardia is relatively high (1), prophylactic treatment for all patients is usually recommended (2,3). The widely recommended drug of first choice is digoxin, but there is no standardized approach to the treatment of patients in whom digoxin is ineffective (3,4). Over the past 10 years there has been increasing interest in the efficacy and safety of newer antiarrhythmic drugs, particularly those in Vaughan-Williams class IC. This retrospective study was performed to compare the safety and efficacy of digoxin and flecainide in prophylaxis of supraventricular tachycardia in infants.

Methods

The Northern health region of England serves a well defined population of just over 3 million. All pediatric patients with suspected tachycardia from 15 of the 16 districts (combined birth rate 38,500/year) are referred to Freeman Hospital. We reviewed the medical records of all infants at this hospital with a diagnosis of supraventricular tachycardia between January 1986 and December 1993. Patients with an electrocardiographic (ECG) diagnosis of atrial flutter, ectopic atrial tachycardia, His bundle tachycardia (junctional ectopic tachycardia), permanent junctional reentrant tachycardia or chaotic atrial tachycardia were excluded. The diagnosis of orthodromic atrioventricular (AV) reentry was based on a 12-lead ECG and was defined as a tachycardia with a normal QRS complex, no evidence of AV dissociation and a ventriculoarterial interval (RP interval) >70 ms (5). The permanent form of junctional reciprocating tachycardia is also a type of AV reentry and was recognized by a long RP interval, inverted P waves in inferior leads and incessant behavior. Patients with this arrhythmia were excluded. Although no infant had an electrophysiologic study, ECG diagnosis of orthodromic AV reentry is accurate and reliable in this age group. Previous reports (5,6) have demonstrated that if the preceding exclusions are applied, almost all infants with supraventricular tachycardia can be shown to have orthodromic reciprocating tachycardia through an accessory connection.

There was no prospective protocol for the treatment of infant supraventricular tachycardia and the choice of treatment was at the discretion of the admitting pediatric cardiologist. Digoxin was the drug of first choice for prophylaxis in most patients and was administered orally in a dose of 8 to

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10 μg/kg body weight per day. Digoxin therapy was considered ineffective if the patient had a recurrence of sustained tachycardia after 3 days of maintenance therapy with the drug or had multiple or prolonged recurrent episodes of tachycardia requiring treatment during the period of digitalization. Flecainide was used in all patients who had recurrence of sustained tachycardia while receiving maintenance doses of digoxin and was given as the first choice prophylactic agent in the six patients who initially received intravenous flecainide to achieve immediate control of multiple recurrences of tachycardia. The oral preparation of flecainide used was a suspension containing 5 mg/ml (3M Health Care). Plasma flecainide concentrations were measured by using high performance liquid chromatography at The Poisons Unit, New Cross Hospital, London. Digoxin or flecainide treatment was withdrawn electively after 12 months in all patients who had had no recurrence of tachycardia during treatment.

Statistical methods. Ninety-five percent confidence intervals (CI) for results expressed as proportions were taken from Geigy scientific tables (7). Ninety-five percent confidence intervals for adverse events when the numerator is zero were calculated as described by Hanley and Lippman-Hand (8).

Results

Patients. There were 39 cases of infant AV reentrant tachycardia between January 1986 and December 1993 (0.13/1,000 live births). The age at presentation ranged from 1 to 330 days (median 12), and only seven patients were >4 weeks of age. All patients had incessant tachycardia, and six had severe heart failure on presentation. One patient had subaortic stenosis and a ventricular septal defect; the other 38 had no structural cardiac defects. All infants were receiving standard milk formula at the time of initiation of treatment, apart from one infant who was breast fed. Ten patients (25%) had an early recurrence of tachycardia, and intravenous flecainide was used in a dose of 1 to 2 mg/kg for control of multiple recurrences in six.

Efficacy of treatment. Digoxin was used as the primary agent to prevent recurrence of tachycardia in 33 patients. In 14 patients (42%; 95% CI 25% to 61%) there was no recurrence of tachycardia and digoxin treatment was continued for 12 months. In 19 patients (58%; 95% CI 39% to 75%) tachycardia recurred despite an adequate digoxin dose, and digoxin was replaced by flecainide. None of these 19 patients (95% CI 0% to 18%) had a recurrence of tachycardia during treatment with flecainide once a satisfactory dose and plasma concentration had been achieved. The six patients initially treated with intravenous flecainide were started on a regimen of oral flecainide as first line prophylaxis. Five of the six had no recurrence of tachycardia, but control continued to be difficult in one patient who eventually underwent successful radiofrequency ablation at the age of 5 years. Overall, of the 25 patients treated with oral flecainide 24 (96%; 95% CI 80% to 100%) had no recurrence of tachycardia once adequate drug plasma levels had been achieved.

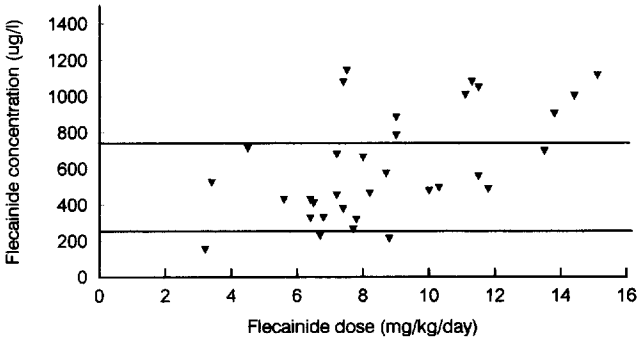

Figure 1. Relation between steady state flecainide plasma concentration (μg/liter) and total oral daily dose (mg/kg per day). **Horizontal lines** at 250 and 750 μg/liter indicate the approximate lower and upper limits of the therapeutic range in children.

Drug dosage. Digoxin was administered in a dose of 8 to 10 μg/kg per day. Plasma concentrations were not measured routinely and the dose was not increased if tachycardia recurred in a patient receiving 10 μg/kg per day. The dose of oral flecainide ranged from 3.2 to 13.5 mg/kg per day and was adjusted in 11 patients because of either high or low plasma levels or inadequate control of supraventricular tachycardia. Flecainide was administered as a twice daily dosage, and plasma concentrations were measured after five doses had been given. Figure 1 shows the relation between the oral dose and the plasma concentration of flecainide and the difficulty of predicting this relation. Doses of 6 to 8 mg/kg per day achieved plasma concentrations of <300 μg/liter in two patients, 300 to 700 μg/liter in nine and >700 μg/liter in two. Doses >8 mg/kg per day resulted in levels of <300 μg/liter in one patient, 300 to 700 μg/liter in seven patients and >700 μg/liter in eight.

Safety. No adverse events were associated with the use of oral digoxin, and there were no cases of proarrhythmia due to flecainide (95% CI 0% to 12%) (7). Although five patients had a flecainide plasma concentration >1,000 μg/liter, they had no associated adverse effects. Two of these five patients had QRS prolongation that resolved after reduction of the dose. Of the 34 patients who have been followed up for >1 year, 5 continue to receive oral flecainide and 2 continue to receive oral digoxin.

Discussion

Supraventricular tachycardia is now widely recognized as a primary cause of heart failure in infants and may cause cardiogenic shock or even death (1,9). Once the diagnosis is made, the immediate priority is restoration of sinus rhythm. The modern therapy for termination of supraventricular tachycardia is safe and effective, and either facial application of ice-cold water or intravenous adenosine is usually recommended (3). Although most infants will experience further

episodes of tachycardia, it is difficult to predict the risk of recurrence in an individual infant. Lundberg (1) reported on 45 infants, with recurrence of tachycardia in 25 (63%) of 40 survivors in the absence of treatment. Benson et al. (4) described criteria for predicting the need for prophylactic treatment, but most authorities (2,3) recommend that all babies should be treated for the 1st 6 or 12 months of life. Digoxin is the conventional first line drug, but it is difficult to assess its efficacy as it has not been subjected to a controlled clinical trial. The reported efficacy of digoxin in suppression of supraventricular tachycardia ranges from 44% to 61% (4,9). Given that approximately 40% of patients have no recurrence of tachycardia without treatment (1), the efficacy of digoxin is not impressive. In our study digoxin was "effective" in only 42%.

There is no consensus on treatment of infants who have recurrence of tachycardia while receiving digoxin. Flecainide has proved effective in patients with accessory connections and AV reentrant tachycardia, and it has been shown to be safe and effective in relatively small numbers of children (10–12), with the exception of postoperative patients with atrial arrhythmias.

Supraventricular tachycardia occurs only when there is a reentry circuit, a precipitating event and an appropriate balance between the electrophysiologic characteristics of the AV node and the accessory connection. Dunnigan et al. (13) showed that supraventricular tachycardia in infants was precipitated either by sinus acceleration or by an atrial premature beat. To prevent tachycardia, a drug must suppress initiating events, block conduction through part of the reentry circuit or alter the relative conduction over components of the circuit to influence the excitable gap. The characteristics of digoxin do not suggest that it is likely to be very effective in preventing orthodromic AV reentry in infants (14). It may suppress atrial premature beats and can prolong AV node conduction, but it has no significant effect on conduction or refractoriness of the accessory connection. In contrast, flecainide blocks conduction through accessory connections (14), and it would be expected to be effective in infants with orthodromic AV reentry, as it is in older children (10–12).

The efficacy of flecainide in our patients contrasts with reports of "medically refractory" tachycardia often cited to justify the use of radiofrequency ablation in infants and small children. However, patients with such "medically refractory" arrhythmia have often been treated only with digoxin and propranolol (15). Franklin et al. (16) recently showed that when a greater range of drugs is used, there are no patients in this age group who do not respond to treatment, and a recent editorial by Kugler (17) counseled against radiofrequency ablation in infants.

The initial oral dose of flecainide recommended in infants is 6 to 8 mg/kg per day (10,18), but in our experience this may result in a plasma concentration as low as 226 μg/liter or as high as 1,140 μg/liter. Little information is available on the pharmacokinetics of flecainide in neonates and young infants, and the reasons for this unpredictable dose/concentration relation are unknown (18,19). The target range in pediatric patients is probably ~300 to 700 μg/liter, and plasma concentrations should be monitored until a therapeutic concentration is achieved with a consistent dosage.

Limitations of the study. Despite the absence of adverse effects in our infant patients treated with flecainide, the results of our study must be interpreted with caution. As demonstrated by Hanley and Lippman-Hand (8) in "If Nothing Goes Wrong, Is Everything All Right?," the zero numerator does not imply absence of risk. We can only be 95% confident that the risk of adverse events is no greater than 12%.

Another limitation of our study is that we did not compare digoxin and flecainide directly in a controlled clinical trial and did not have a placebo group (20). However, comparison with natural history studies suggests that digoxin is relatively ineffective in prophylaxis of supraventricular tachycardia in infants. We have used flecainide as our drug of second choice for 8 years and have shown it to be effective and safe in a small number of infants who did not respond to treatment with digoxin. In our practice flecainide is now the preferred drug for prophylaxis of supraventricular tachycardia in infants.

References

1. Lundberg A. Paroxysmal atrial tachycardia in infancy: long-term follow-up study of 49 subjects. Pediatrics 1982;70:638–42.
2. Ludomirsky A, Garson A Jr. Supraventricular tachycardia. In: Gillette PC, Garson A, Jr, editors. Pediatric Arrhythmias: Electrophysiology and Pacing. Philadelphia: Saunders, 1993:380–426.
3. Till JA, Shinebourne EA. Supraventricular tachycardia: diagnosis and current acute management. Arch Dis Child 1991;66:647–52.
4. Benson DW, Dunnigan A, Beditt DG, Thompson TR, Narayan A, Boros S. Prediction of digoxin treatment failure in infants with supraventricular tachycardia: role of transoesophageal pacing. Pediatrics 1985;75:288–93.
5. Ko JK, Deal BJ, Stasburger JF, Benson DW. Supraventricular tachycardia mechanisms and their age distribution in pediatric patients. Am J Cardiol 1992;69:1028–32.
6. Benson DW, Dunnigan A, Benditt DG, Pritzker MR, Thompson TR. Transoesophageal study of infant supraventricular tachycardia: electrophysiologic characteristics. Am J Cardiol 1983;52:1002–6.
7. Lentner C, editor. Geigy Scientific Tables. Vol 2. 8th ed. Basel, Switzerland: Ciba-Geigy, 1982:89–102.
8. Hanley JA, Lippman-Hand A. If nothing goes wrong, is everything all right? JAMA 1983;249:1743–5.
9. Deal BJ, Keane JF, Gillette PC, Garson A. Wolff-Parkinson-White syndrome and supraventricular tachycardia during infancy: management and follow-up. J Am Coll Cardiol 1985;5:130–5.
10. Perry JC, Garson A. Flecainide acetate for treatment of tachyarrhythmias in children: review of world literature on efficacy, safety and dosing. Am Heart J 1992;124:1614–21.
11. Perry JC, Garson A Jr. Encainide and flecainide in children: separating the wheat from the chaff. J Am Coll Cardiol 1991;18:366–7.
12. Fish FA, Gillette PC, Benson DW. Proarrhythmia, cardiac arrest and death in young patients receiving encainide and flecainide. J Am Coll Cardiol 1991;18:356–65.
13. Dunnigan A, Benditt DG, Benson DW. Modes of onset ("initiating events") for paroxysmal atrial tachycardia in infants and children. Am J Cardiol 1986;57:1280–7.
14. Moak JF. Pharmacology and electrophysiology of antiarrhythmic drugs. In: Gillette PC, Garson A Jr, editors. Paediatric Arrhythmias: Electrophysiology and Pacing. Philadelphia: Saunders, 1990:28–115.
15. Case CL, Gillette PC, Oslozlok PC, Knick BJ, Blair HL. Radiofrequency catheter ablation of incessant, medically resistant supraventricular tachycardia in infants and small children. J Am Coll Cardiol 1992;20:1405–10.

16. Franklin WH, Deal BJ, Strasburger JF, Benson DW. Do infants have medically refractory supraventricular tachycardia [abstract]? J Am Coll Cardiol 1994;23:250A.
17. Kugler JD. Radiofrequency catheter ablation for supraventricular tachycardia. Should it be used in infants and small children? Circulation 1994;90:639–41.
18. Till JA, Shinebourne EA, Rowland E, et al. Paediatric use of flecainide in supraventricular tachycardia: clinical efficacy and pharmokinetics. Br Heart J 1989;62:113–9.
19. Perry JC, McQuinn RL, Smith RT, Gothing C, Fredell P, Garson A. Flecainide acetate for resistant arrhythmias in the young: efficacy and pharmacokinetics. J Am Coll Cardiol 1989;14:185–91.
20. Garson A Jr. Clinical research on children in the 1990s. J Am Coll Cardiol 1992;19:636–7.