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PEDIATRIC CARDIOLOGY

Flecainide Acetate for Resistant Arrhythmias in the Young: Efficacy and Pharmacokinetics

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Drug efficacy and pharmacokinetics were assessed in 63 patients, aged 5 days to 30 years (mean 8 years), who received flecainide acetate for control of resistant arrhythmias. Doses of flecainide ranged from 59 to 225 mg/m^2 body surface area per day (mean 141) in divided doses every 8 to 12 h and serum trough levels ranged from 0.10 to 0.99 μg/ml (mean 0.36).

Flecainide controlled or partially controlled arrhythmia in 53 (84%) of the 63 patients: 7 of 7 patients who had the permanent form of junctional reciprocating tachycardia, 12 of 13 who had an atrial ectopic tachycardia, 10 of 10 who had ventricular tachycardia and 18 of 25 patients who had reentrant supraventricular tachycardia. Five of seven patients who had the latter arrhythmia were unsuccessfully treated with flecainide. They had Wolff-Parkinson-White syndrome and developed asymptomatic, incessant, slower orthodromic reciprocating tachycardia while receiving the drug. Transient blurred vision was reported in three patients and two patients had transient hyperactivity. No significant hemodynamic side effects were seen in any patient.

Twenty-five patients underwent oral pharmacokinetic investigation. Young infants (<1 year of age) had a mean plasma elimination half-life (t 1/2) approximating that (11 to 12 h) found in older children and healthy adults; children aged 1 to 12 years had a shorter mean t 1/2 of 8 h. Dosing schedules based on milligrams per square meter body surface area correlated better with plasma flecainide levels than did dosing based on milligrams per kilogram body weight.

In conclusion, 1) flecainide was effective pediatric therapy for permanent junctional reciprocating tachycardia, atrial ectopic and chaotic atrial tachycardia, ventricular tachycardia and, in most patients, reentrant supraventricular tachycardia; 2) some patients with Wolff-Parkinson-White syndrome developed asymptomatic incessant slow supraventricular tachycardia while receiving flecainide; 3) flecainide resulted in rare side effects and no negative hemodynamic effects in any patient; 4) despite a shorter elimination half-life, every 12 h dosing schedule (with lower flecainide trough levels than usually seen in adults) provided adequate arrhythmia control in 80% of young patients aged 1 to 12 years; and 5) further study of oral flecainide pharmacokinetics is needed for patients <1 year of age.

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Flecainide acetate (Tambocor, 3M/Riker Labs) is a relatively new benzamide derivative that has been classified as a New York Heart Association functional class IC antiarrhythmic agent. It is used for a wide range of tachyarrhythmias in adults and only recently has been investigated for use in pediatric patients (1–3). In adults, flecainide appears to be more effective than quinidine, disopyramide, mexiletine, tocainide and propafenone in suppressing ventricular ectopic activity (4,5), and it has proved effective in the management of reentrant supraventricular tachycardias complicating Wolff-Parkinson-White syndrome (1,6).

Infants and children may manifest entirely different drug therapeutic/toxic ratios from those of adults and they have differences in drug pharmacokinetics and pharmacodynamics secondary to age, body size, protein binding and maturity of systems responsible for drug metabolism and elimination. These factors may then require changes in dosing schedules and calculation of dose based on body surface area rather than body weight (7). Currently, flecainide can be legally prescribed for children, but there are no established guidelines for its use in this group.

The purpose of this study was twofold: 1) to evaluate the

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Table 1. Spectrum of Antiarrhythmic Efficacy of Flecainide Acetate in 63 Patients

	Control			
	Full	Partial	None	Total
SVT				
WPW	10	1	5	16
Concealed WPW	6	1	2	9
PJRT	6	1	0	7
AVNre	2	3	0	5
JET	0	0	1	1
AET	5	2	1	8
CAT	4	1	0	5
Atrial flutter	0	1	1	2
Vent tachycardia	7	3	0	10
Total	40	13	10	63

AET = atrial ectopic tachycardia; AVNre = typical AV node reentrant tachycardia; CAT = chaotic atrial tachycardia; JET = junctional ectopic tachycardia; PJRT = permanent form of junctional reciprocating tachycardia; SVT = supraventricular tachycardia; Vent = ventricular; WPW = Wolff-Parkinson-White syndrome.

efficacy and clinical and laboratory variables of oral dosing of flecainide acetate in the control of supraventricular and ventricular tachyarrhythmias in a large series of children; and 2) to establish the pharmacokinetics of flecainide in these patients to allow delineation of appropriate dosing guidelines.

Methods

Patient data. The study group comprised 63 patients ranging in age from 5 days to 30 years (mean 8 years). Only four patients, aged 19, 26, 26 and 30 years, respectively, were >18 years of age. Of the remaining 59 patients, 13 were ≤6 months, 7 >6 to 12 months, 25 >1 to 12 years and 18 >12 years of age. Patients with refractory tachyarrhythmias were included in the study; the spectrum of arrhythmias is shown in Table 1. With the exception of digoxin in 11 cases, all previous medications were discontinued a minimum of 5 elimination half-lives before administration of flecainide was initiated. No patient had received amiodarone therapy. All patients were admitted to the hospital for initiation of flecainide therapy and either they were discharged after steady state had been reached with control of their arrhythmia or the drug was discontinued because of poor control or proarrhythmia.

All patients had a daily physical examination, vital signs were noted and the following laboratory tests were performed on admission: complete blood count, urinalysis, liver serum enzymes, determination of renal function chemistry values and digoxin level (if applicable). A baseline chest radiograph, electrocardiogram (ECG), 24 h ECG Holter monitor, two-dimensional and M-mode echocardiogram and treadmill test (by modified Bruce protocol in patients aged ≥5 years) were obtained. Patients were monitored by telemetry ECG throughout hospitalization and underwent continuous 24 h Holter monitoring.

Complete pharmacokinetic data were obtained in 26 patients (as described later), and an additional 37 were studied for drug efficacy and had plasma flecainide trough values obtained. All patients (>7 years old) and their parents signed a consent form before administration of flecainide. The protocol and consent forms were approved by the Institutional Review Board of the Baylor College of Medicine.

Initiation pharmacokinetics. Flecainide acetate (supplied by 3M/Riker Laboratories, Inc.) was administered in a single 25 mg/m^2 dose. Plasma flecainide levels were determined at 0, 30 and 60 min, and at 2, 4, 6, 8, 12 and 24 h after this first dose (assay performed by Riker Labs). The concentration of flecainide in plasma and urine was measured by a selective and sensitive high performance liquid chromatographic method (8). The lower limit for quantitation using this assay was 10 ng/ml for plasma and 50 ng/ml for urine. In small infants, the 30 min and 8 h determinations were eliminated to reduce blood drawing. Urine was collected when possible from 0 to 12 h and 12 to 24 h for analysis of urinary flecainide excretion. Twenty-one patients underwent this protocol.

Maintenance flecainide. Twenty-four hours after the first dose pharmacokinetics, maintenance oral therapy was initiated. In the initial phase of the study, the starting dose of flecainide was 50 mg/m^2 per day divided into two doses on a schedule of every 12 h. Because this dose had little or no effect on arrhythmia in the first four patients treated, all subsequent patients were started at 100 mg/m^2 per day divided into two doses on a schedule of every 12 h. Younger patients who could not swallow a tablet were provided with an oral suspension of the intravenous form of flecainide mixed with cherry syrup to a concentration of 10 mg/ml. (Stability of the drug in this suspension was confirmed by Riker Laboratories.)

The drug was considered effective if acute tachycardia was terminated or if a 90% reduction of incessant arrhythmia was seen on 24 h Holter monitor. Partial control was defined by 60% to 90% reduction of incessant tachyarrhythmia on Holter monitor or persistent tachycardia at a rate that was appropriate for age or that did not result in hemodynamic compromise or symptoms. Proarrhythmia was defined as either presence of a new arrhythmia or increasing frequency of the underlying arrhythmia. If arrhythmia control was considered adequate, the patient was discharged on oral flecainide therapy after final serum chemistry values, ECG, echocardiogram and trough flecainide values were obtained. Patients with inadequate control had their dose titrated upward to 150 mg/m^2 per day, then 200 mg/m^2 per day every five doses to an effective dose or until either proarrhythmia occurred or flecainide was deemed unsuccessful. Patients with paroxysmal tachyarrhythmia had the dose increased

until ECG evidence of drug effect (approximately 20% to 30% prolongation of the QRS complex) was seen. In the latter third of the study period, flecainide levels were available with a 4 to 6 h turnaround time and patients with paroxysmal arrhythmias had their final dose based on drug level with long-term efficacy determined over the follow-up period.

The majority of patients were maintained on a 12 h dosing schedule of flecainide. Seven patients were changed to dosing every 8 h (at the same total daily dose as with dosing every 12 h) to manage clinical episodes of breakthrough tachycardia at 10 to 12 h after a flecainide dose.

Withdrawal kinetics. Ten patients receiving long-term oral flecainide therapy had withdrawal pharmacokinetic determinations performed according to the protocol for initiation kinetics. Patients were hospitalized for a 24 h period.

Follow-up. Patients were discharged with an ECG telephone transmitter with standard instructions from our laboratory. Patients from the Houston and Southeast Texas areas were seen in follow-up at the Texas Children's Hospital at 1, 3 and 6 months after discharge or more frequently if needed. Other patients were followed up by their local pediatric cardiologist, who communicated data on serum flecainide levels and continuing assessment of efficacy to Houston. At each follow-up visit, serum flecainide levels were obtained and an ECG, 24 h Holter monitor, echocardiogram and chest radiograph were performed. Optimally, trough flecainide levels were obtained, but in the outpatient setting this was not always possible so notation was made of time after dose.

Pharmacokinetic analysis. The plasma concentration versus time data were fit by nonlinear regression to an open one-compartment model with first-order absorption and first-order elimination with use of the iterative computer program PCNONLIN (Statistical Consultants, Inc.). The data were fit to the following equation:

$$C = \frac{Ka\ FD}{V\ (Ka - K)} (e^{-kt} - e^{-kat}),$$

where C = the plasma concentration, Ka = the apparent first-order absorption rate constant, F = the fraction of the dose absorbed, D = the dose, V = the apparent volume of distribution, K = the first-order elimination rate constant and t = time after dose. The value for F was assumed to be 1, which has been demonstrated for flecainide (9). The area under the curve, total body clearance or plasma clearance (Cl_p), terminal plasma elimination half-life (t 1/2) and the time to maximal concentration (T_{max}) of flecainide in plasma were calculated by standard formulas. The maximal concentration (C_{max}) of flecainide in plasma after a single dose was calculated where $t = T_{max}$. Initial estimates for V, Ka and K were obtained using the computer program PKCALC (10).

A comparison of pharmacokinetic values from children grouped according to age was performed with a one-way analysis of variance followed by *t* tests. A p value of <0.05 was considered significant.

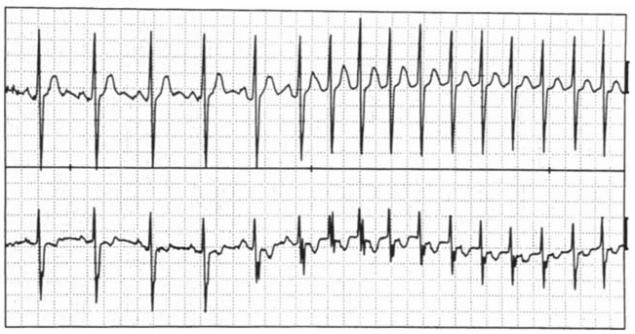

Figure 1. Proarrhythmia after second dose of flecainide at 150 mg/m^2 per day in a patient with intermittent pre-excitation. Supraventricular tachycardia occurs at 158/min (**right**).

Results

Efficacy (Table 1)

Flecainide was effective (control or partial control) in 43 of 53 patients with supraventricular tachyarrhythmias and there were definite differences in efficacy depending on arrhythmia type.

Wolff-Parkinson-White syndrome and "concealed" Wolff-Parkinson-White syndrome. The drug was helpful in 11 of 16 patients with Wolff-Parkinson-White syndrome and supraventricular tachycardia. The majority of these patients had frequent episodes of tachycardia before administration of flecainide; of those with paroxysmal episodes who were maintained on flecainide, the follow-up period ranged from 7 to 14 months. In follow-up, pre-excitation persisted on the surface ECG in 4 of 11 patients but became intermittent in 3 and disappeared in 4 patients.

Five of the 16 patients with Wolff-Parkinson-White syndrome had a "non-life-threatening" proarrhythmic effect (Fig. 1). All five of these patients had had paroxysmal episodes of rapid supraventricular tachycardia before administration of flecainide and had the onset of an incessant slower orthodromic supraventricular tachycardia while receiving flecainide. The incessant tachycardia stopped spontaneously in all with discontinuation of flecainide. Four of the five patients were >5 years of age and one was a newborn. There was no apparent predictive value for efficacy or proarrhythmia in patients with Wolff-Parkinson-White syndrome on the basis of known or presumed accessory connection location, rate of initial tachycardia, flecainide dose per square meter or age.

Nine patients had orthodromic supraventricular tachycardia secondary to a concealed accessory connection. Flecainide controlled or partially controlled the tachyarrhythmia in seven. Two patients whose tachycardia was not

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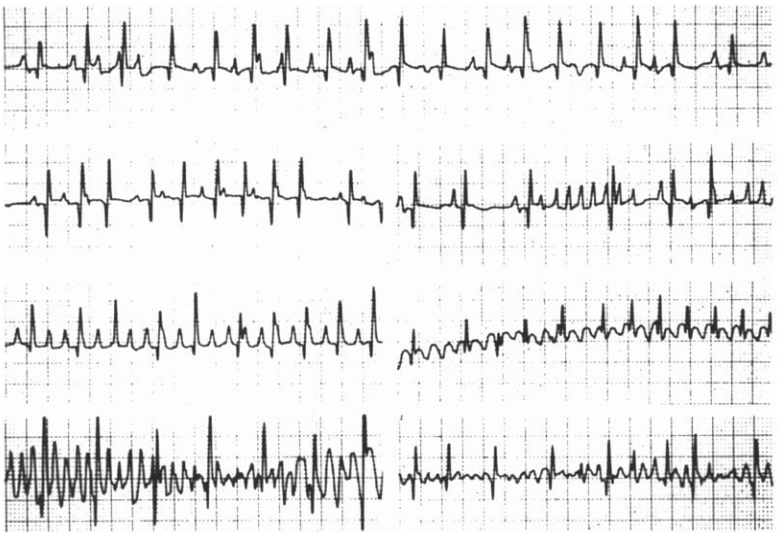


Figure 2. Chaotic atrial tachycardia in a newborn infant. These tracings show elements of ectopic atrial rhythm, atrial fibrillation and atrial flutter (to 580 beats/min) with variable atrioventricular block.

controlled were 6 and 17 years of age and had poor response to flecainide treatment without proarrhythmic effect.

Permanent form of junctional reciprocating tachycardia. Six of the seven patients with the permanent form of junctional reciprocating tachycardia had excellent control of tachycardia, whereas one patient had partial control with long periods of sinus rhythm and slow junctional reciprocating tachycardia. Of five patients with typical AV node reentry supraventricular tachycardia, two had control and three had partial control.

Junctional ectopic tachycardia and atrial flutter. Flecainide was not effective in one patient with junctional ectopic tachycardia who had undergone aortic valve replacement several years previously. It was not effective in a patient with atrial flutter after the Mustard procedure and resulted in fewer but persistent episodes of atrial flutter in an additional patient several years after repair of total anomalous pulmonary venous connection.

Atrial ectopic tachycardia and chaotic atrial tachycardia. In 13 patients with atrial ectopic tachycardia, flecainide administration resulted in control (sinus rhythm) in 9, partial control in 3 and no significant effect in 1. This includes a total of five patients with infantile chaotic atrial tachycardia, a rapid irregular tachycardia with components of rapid atrial flutter and fibrillation and atrial ectopic tachycardia (Fig. 2). Four of these patients had a normal heart and one had cardiomyopathy. This arrhythmia was particularly sensitive to oral flecainide, usually disappearing after the first few doses at 100 mg/m^2 per day. The patient with partial control was a dysmorphic infant with a severe form of hypertrophic cardiomyopathy who died of causes secondary to respiratory failure and sepsis after exploratory thoracotomy for a mediastinal mass. Accurate echocardiographic assessment of the effect of flecainide on ventricular function was not possible in this patient.

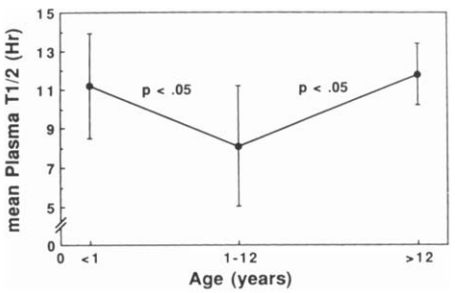
Ventricular tachycardia. There were 10 patients with ventricular tachycardia. Six patients had a normal heart, one had cardiomyopathy, two had postoperative ventricular septal defect and one had complex cyanotic congenital heart disease. One patient, a 1 year old infant, had a typical presentation for a myocardial hamartoma but was not taken to surgery because of successful antiarrhythmic efficacy.

Pharmacokinetic Results

Oral absorption. The mean (±SD) time to peak serum concentration (T_{max}) for all patients was 2.7 ± 1.5 h and the mean maximal plasma concentration (C_{max}) after the single 25 mg/m^2 oral doses was 88 ± 21 ng/ml. Thus, the oral absorption of flecainide in pediatric patients is relatively prompt and is likely to be extensive.

Plasma elimination half-life (t 1/2). The average plasma t 1/2 was 9.6 ± 3.2 h. However, when patients were separated into groups of those aged <1 year, 1 to 12 years and >12 years (Fig. 3), it was shown that the t 1/2 values in the first and last groups were both significantly longer than

Figure 3. Plasma flecainide elimination half-life (t 1/2) versus age. See text for description.



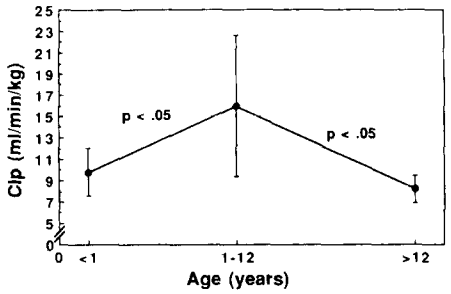


Figure 4. Plasma flecainide clearance (Cl_p) versus age. See text for description.

those in the middle group ($p < 0.05$). Similarly, the patients <1 year or >12 years of age had significantly slower plasma flecainide clearance than did the 1 to 12 year old group (Fig. 4). Seven patients benefited from a change to an every 8 h dosing schedule to prevent occurrence of breakthrough tachycardia before drug administration on the every 12 h regimen. In these patients, the total daily dose was kept constant but divided in an 8 h schedule. Five of these seven patients had incessant arrhythmia and all were young (aged 3 months to 3.5 years). There was no difference between the total flecainide dose of these seven patients (134 ± 35 mg/m^2 per day) and that of the patients on an every 12 h dosing schedule (142 ± 36 mg/m^2 per day). Flecainide elimination half-life, available in two patients aged 1 year and 20 months, was 9.9 and 6.5 h, respectively. The mean volume of distribution for all patients was 9.5 ± 2.6 liter/kg; there were no differences in this value by age group.

In those patients who had complete 24 h urine collections, the percent of a single oral dose excreted in urine as unchanged flecainide ranged from 17% to 47%.

Flecainide serum trough values. For the entire group these ranged from 0.1 to 0.99 μg/ml (mean = 0.36 μg/ml). There were no statistical differences in flecainide trough level among patients with control, partial control or no control of arrhythmia with serum levels of 0.36 ± 0.24, 0.41 ± 0.15 and 0.390 ± 0.023 μg/ml, respectively. There was somewhat better correlation of trough flecainide level with a dosing schedule based on body surface area (mg/m^2 per day) than on body weight (mg/kg per day) (correlation coefficient [r] = 0.63 versus 0.51, respectively). When grouped by age, there were marked disparities in r values for flecainide trough versus dose per square meter. Correlation coefficient values for the 0 to 1 year, 1 to 12 year and >12 year age groups were 0.30, 0.48 and 0.85, respectively.

Serum digoxin levels. Eleven patients also received digoxin during flecainide therapy; seven had empiric decreases in their digoxin dose by 25% before drug initiation. Of the four patients who continued on steady dose, there were no significant changes in serum digoxin concentration. Patients who remained on digoxin were not distinguished by age, arrhythmia type, cardiac size or function.

Other Drug Effects

Electrocardiographic changes. The predominant ECG effects were an average increase in the PR interval by 23 ± 11 ms (a 13% average increase over preflecainide intervals) and a 17 ± 11 ms (24%) average increase in the QRS duration. Increases in the QT interval were secondary to increases in the QRS duration. No patient had excessive increases in ECG measurements that required decreasing the dose of flecainide or discontinuation of therapy.

Proarrhythmia. No life-threatening proarrhythmia occurred in any patient. All five patients in whom flecainide had a proarrhythmic effect had overt Wolff-Parkinson-White conduction in normal sinus rhythm and paroxysmal episodes of orthodromic supraventricular tachycardia. The youngest patient, aged 1 week, had had frequent episodes of tachycardia since birth. Proarrhythmia in every patient consisted of development of an incessant orthodromic supraventricular tachycardia at a rate slower than the tachycardia seen before flecainide therapy was started (before 210/min, after 175/min). In all, proarrhythmia occurred during the initiation phase of flecainide at doses of 90 to 150 mg/m^2 per day and was well tolerated hemodynamically. There was no predilection for age (7 days to 26 years), gender (3 male, 2 female) or site of accessory connection when the variables were compared with those in patients with Wolff-Parkinson-White syndrome who did not have proarrhythmia. No proarrhythmias were seen during long-term therapy in any patient.

Echocardiographic changes. It is not appropriate to assess changes in echocardiographic ventricular size and contractility in patients with abnormal impulse propagation, such as patients with incessant ventricular arrhythmia (abnormal QRS complexes) or pre-excitation. Therefore, we have restricted echocardiographic data reporting to those patients with incessant atrial ectopic tachycardia, infantile chaotic atrial tachycardia and permanent junctional reciprocating tachycardia. As a group, patients with these three arrhythmias had an average increase in left ventricular end-diastolic diameter of 8% and no patient had an increase >8 mm. There was an average decrease in left ventricular shortening fraction of 2% units if two patients with dramatically improved shortening fractions are excluded. One of these was a 13 year old who had atrial ectopic tachycardia and preflecainide left ventricular shortening fraction of 6% to 8%. With therapy and a resumption of sinus rhythm, this patient's shortening fraction improved to 29%. A newborn with chaotic atrial tachycardia had a shortening fraction of 26% that improved to 40% after flecainide. These two patients had the lowest left ventricular shortening fraction of the group before therapy and no patient had a >5% unit reduction after flecainide. No patient included in this report had an increase in left ventricular end-diastolic dimension or decrease in left ventricular shortening fraction greater than those from the groups just mentioned.

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Side effects. Two patients reported that blurred vision occurred approximately 2 h after administration of oral flecainide dose. This symptom resolved spontaneously in one and after a decrease in dose in another. A 15 month old patient was unsteady on her feet, could not grasp a bottle well and was irritable 2.5 h after oral flecainide administration. These symptoms may have reflected blurry vision and resolved after two times a day dosing was changed to three times a day dosing at the same cumulative daily dose. Two patients (aged 18 months and 3 years, respectively) were reportedly hyperactive in the first month of therapy, but these symptoms resolved spontaneously.

A teenage patient, in an apparent suicide attempt, ingested a single dose of 2 g of flecainide (equal to 934 mg/m^2). At 2 to 3 h after ingestion, this patient experienced headache, blurred vision and gastrointestinal distress at a serum flecainide concentration of 2.10 μg/ml. The symptoms resolved within 12 h with usual ingestion therapy (charcoal, magnesium citrate).

Discussion

In this report we have demonstrated the spectrum of antiarrhythmic efficacy of flecainide in young patients and have documented important differences between the oral pharmacokinetics of this drug in children and adults that will affect appropriate dosing.

Efficacy in supraventricular tachycardia. The efficacy of oral flecainide in treating reentrant supraventricular tachycardia involving an accessory connection has been reported in adults (11) and a small series of children (1). Flecainide slows conduction in both the AV node and accessory connections and prolongs the anterograde and retrograde accessory connections refractory periods. Therefore, the drug is appealing for treatment of patients with Wolff-Parkinson-White conduction and supraventricular tachycardia because both "limbs" of the circuit are affected. Seventeen of 25 patients with overt or concealed Wolff-Parkinson-White conduction had excellent control of tachycardia episodes. The development of proarrhythmia as an event specific to patients with overt Wolff-Parkinson-White conduction has not been stressed in previously published reports. It is possible that early in the course of flecainide initiation, conduction in the accessory pathway or AV node, or both, was slowed to a degree whereby the conditions of reentry (albeit at a longer cycle length) were more favorable and "proarrhythmia" occurred. It is also possible that in some patients further increases in flecainide dose beyond this initial range will slow conduction further and thereby eliminate tachycardia. Such increases were not attempted in our series.

Three pediatric arrhythmias deserve special comment: the permanent form of junctional reciprocating tachycardia, atrial ectopic tachycardia and infantile chaotic atrial tachycardia. Each of these arrhythmias tends to be incessant pediatric tachyarrhythmia that increases the risk of developing poor ventricular function and cardiomyopathy (12). Flecainide was particularly effective in treating these arrhythmias (control or partial control in 19 of 20 patients), terminating tachycardia early in the course of initiation therapy (90 to 150 mg/m^2 per day). Equally important, the return to normal sinus rates in these patients brought about gradual improvement in cardiac contractility, and the decreases in function reported in adult patients were not seen (13).

Efficacy in ventricular tachycardia. The efficacy of flecainide in ventricular tachycardia bears some similarity to that reported in adult series (14,15), but important additions particular to pediatric patients exist. Though ventricular tachycardia may prove to involve a different underlying anatomic substrate in children, it appears to be as well controlled by flecainide as are adult ventricular arrhythmias. Ventricular arrhythmias tend to be uncommon in children who had not had intracardiac surgery, but only 2 of 10 patients with ventricular tachycardia in our series had a previous open heart procedure (closure of ventricular septal defect). His-Purkinje conduction can be markedly affected by flecainide, which may prolong the HV interval beyond the normal range in the majority of adult patients (16). We were reluctant, therefore, to use this agent in some of the more common postoperative settings in which pediatric ventricular arrhythmias occur (e.g., postoperative tetralogy of Fallot), because many patients in such settings have baseline HV prolongation. As intracardiac electrophysiologic studies were not part of this protocol, we cannot comment on the effect of flecainide on the HV interval in our patients.

One patient, a 1 year old, had a suspected ventricular tumor (17) causing ventricular tachycardia but responded to flecainide. No other patient in this series had a ventricular tumor. A 14 month old patient (not in this report) referred to us for ventricular tachycardia had been treated with flecainide at another institution unsuccessfully and was found at surgery to have a ventricular tumor as described in earlier patients from our center.

Pharmacokinetics. We emphasize the oral pharmacokinetic data presented in this report because they provide guidelines for pediatric oral dosing of flecainide. Infants <1 year of age tended to have an elimination half-life (t 1/2) for flecainide that was similar (11 to 12 h) to that of children >12 years of age and healthy adults. However, in the age range of 1 to 12 years, t 1/2 was approximately 8 h.

The longer plasma t 1/2 in many of the very young patients may be due to not yet fully developed hepatic and renal clearance mechanisms; flecainide is reported to be cleared extensively from the body via hepatic biotransformation and renal excretion (9,18). Because the plasma t 1/2 values for four of the six patients <1 year of age were determined after multiple dosing, it may be possible that the

longer t 1/2 observed for this group was due to a reduction in the clearance of flecainide with long-term dosing. However, this seems unlikely because the plasma t 1/2 for flecainide in pediatric patients after long-term multiple dosing has been reported to be not different from that observed after single doses (Till JA, personal communication). The longer t 1/2 values observed in the patients >12 years of age may be associated with physiologic changes that commonly occur with the onset of adolescence.

The time to peak serum concentrations (T_{max}) and maximal serum concentrations (C_{max}) are in good agreement with previously reported values for adult patients. The tendency for slower plasma flecainide clearance in the youngest and oldest groups is consistent with the longer plasma t 1/2 observed in those groups. Mean plasma flecainide clearance in these patients was also similar to that previously reported for adult subjects.

The low correlation coefficient for serum trough flecainide level versus dose in patients <1 year of age reflects a wide scatter of values in this group. Pharmacodynamics are probably highly variable in this age range and further delineation of the kinetics of flecainide seems indicated in these young patients.

The paucity of side effects and lack of negative hemodynamic effect in our series is encouraging. It does not appear that empiric reduction in digoxin dose, which has been recommended for adult patients, is warranted in all pediatric patients receiving flecainide. Additionally, a wide therapeutic/toxic ratio may be inferred from the overdose incident, wherein the adolescent ingested nearly 10 times the usual total daily dose without deleterious cardiovascular effect.

Conclusions. 1) Flecainide was effective therapy in pediatric patients with the permanent form of junctional reciprocating tachycardia, atrial ectopic and infantile chaotic atrial tachycardia, selected patients with ventricular tachycardia and most patients with reentrant supraventricular tachycardia. 2) Some patients with Wolff-Parkinson-White syndrome and supraventricular tachycardia developed an asymptomatic, incessant, slower orthodromic tachycardia while receiving flecainide during initiation of therapy and it was not possible to predict this result. 3) Flecainide resulted in rare side effects and no negative hemodynamic effects in these patients. 4) Infants and children aged 1 to 12 years tended to have a shorter flecainide elimination half-life and more rapid plasma clearance than did infants <1 year of age and older children; Dosing 3 times daily may be beneficial in this age group. Further investigation of the pharmacokinetics of flecainide in patients <1 year of age is needed. We recommend, in the pediatric population, in-hospital initiation of flecainide therapy with incremental dosing titrated to response and based on body surface area rather than body weight.

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