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The response of paediatric arrhythmias to intravenous and oral flecainide

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SUMMARY Flecainide acetate was administered intravenously and orally to 12 consecutive children, aged 1–15 years, presenting with arrhythmias that were life threatening or resistant to conventional medical treatment. Three children had arrhythmias related to Wolff-Parkinson-White syndrome, four had concealed accessory pathways, two had His bundle tachycardia, and three had ventricular tachycardia. Of seven patients who were given flecainide intravenously, four returned to sinus rhythm and in a fifth successful rate control of His bundle tachycardia was achieved. All 12 patients were given the drug orally: in nine it was successful in preventing recurrence of arrhythmia, in one satisfactory rate control was achieved, and in two it was withdrawn because it produced more frequent attacks of tachycardia. No other adverse effects occurred.

The efficacy and low toxicity of treatment in this study suggests that flecainide acetate may have an important role in the management of selected paediatric arrhythmias.

Symptomatic and life threatening arrhythmias are fortunately relatively uncommon in paediatric practice. When they do occur their treatment is particularly demanding. Efficacy is obviously important but in infants and children drug toxicity is of special relevance, particularly when long term dosing may be necessary.

When arrhythmias in adults prove refractory to conventional management strategies, new drugs and investigational compounds are often tried. Caution in the institution of such treatment in children is justifiable as treatment may be necessary for many years, long term effects are unknown, and pharmacokinetic responses in children cannot be predicted from experience in adults.

Flecainide acetate, an antiarrhythmic drug with Vaughan Williams class IC actions, has rapidly become established in the management of a wide variety of arrhythmias in adults.[1–3] With the exception of arrhythmogenesis, it has a relatively low toxicity, has stable and reliable kinetics, and its half life of 8–12 hours facilitates dosing twice or three times a day. Experience with the use of flecainide in children is limited[4,5] but these properties suggest a potentially important role in paediatric practice.

This report describes our experience of using intravenous and oral flecainide in 12 children with life threatening arrhythmias or arrhythmias that were difficult to manage with conventional agents.

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Patients and methods

PATIENTS

All 12 children (mean aged 8, range 1–15) presenting between May 1983 and October 1985 with arrhythmias that were potentially dangerous or had failed to respond to at least one conventional antiarrhythmic agent were treated with flecainide (table 1). Only four patients had associated structural heart disease. The mechanism of the arrhythmia was confirmed at electrophysiological study in nine patients and was apparent from the surface electrocardiogram in the other three. Ten patients had received previous drug treatment (six intravenously and eight orally), which had been unsuccessful. Before administering flecainide, five half lives of any previous antiarrhythmic therapy were allowed to elapse to clear that drug from the circulation. In the two patients who had taken amiodarone this was not possible: the drug withdrawal period was three months in patient 8 and three weeks in patient 9.

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Table 1 *Details of patients and previous drug treatment*

Case No	Age (years)	Sex	Weight (kg)	Diagnosis	Rate (beats/min)	Other diagnosis	Failed iv drugs	Failed oral drugs	Follow up (months)
1	9	M	36	CAP*	200	—	—	Dg Pt Pr V Q	39
2	11	F	27	CAP*	195	1°ASD	V	—	33
3	13	F	66	CAP*	190	—	—	Dg Pr	27
4	13	M	40	CAP*	180	—	—	Dg	21
5	13	F	47	WPW*	172	CTGA	Dg	—	31
6	13	F	43	WPW*	200	Ebstein's anomaly	—	V	17
7	7	M	26	WPW*	230	—	Dg V	Dg Q V Ds Fc	12
8	15	M	49	HBT*	160	CTGA	Pr Pc Dg V	Dg Q A	26
9	2	M	13	HBT*	210	—	Dg V	Dg Pr Q A	23
10	1	F	12	VT	220	—	Dg V Ds	Dg Ds Pr	22
11	2	F	11	VT	360	—	—	—	16
12	1	M	9	VT	290	—	—	—	10

iv, intravenous; A, amiodarone; Dg, digoxin; Ds, disopyramide; Fc, flecainide; Pc, procainamide; Pr, propranolol; Pt, practolol; Q, quinidine; V, verapamil; 1°ASD, ostium primum atrial septal defect; CTGA, corrected transposition of the great arteries; CAP, concealed accessory pathway; WPW, Wolff-Parkinson-White syndrome; HBT, His bundle tachycardia; VT, ventricular tachycardia.
*Confirmed at electrophysiology study.

Table 2 *Response to intravenous and oral flecainide*

Intravenous			Oral				
Case No	Dose (mg)	Response	Daily dose (mg)	(mg/kg)	Response	Plasma concentration (μg/l)	(mmol/l)
1	20	→SR	100	3·7	NR	535	1·13
2	—	—	200	3·0	NR		
3	25	→SR	100	2·7	NR		
4	—	—	200	5·0	F		
5	90	Slowed	150	3·5	NR	417	0·88
6	20	→SR	300	6·4	F		
7	30	→SR	250	9·6	NR	463	0·98
8	25	Slowed 210→130	150	11·5	RC	343	0·72
9	100	Slowed 150→120	200	4·1	NR	396	0·84
10	—	—	75	6·3	NR	410	0·86
11	—	—	75	6·8	NR		
12	—	—	200	22·2	NR	492	1·04

→SR, reverted to sinus rhythm; NR, no recurrence; RC, rate controlled; F, failed; —, not given.

FLECAINIDE ADMINISTRATION

Flecainide was given intravenously to seven children during tachycardia that either had occurred spontaneously or was induced at electrophysiological study (table 2). The maximum dose was 2 mg/kg. Thereafter all seven received oral treatment. Oral treatment in all 12 children was started in doses of 3–6 mg/kg/day and increases were guided by the patient's response and, in some cases, by plasma concentrations. The maximum oral dose was 22 mg/kg/day. For the two youngest children, flecainide was made into a syrup or suspension. The other children were given standard tablets; some took them crushed in yoghurt or other palatable food. Twice daily dosing was used where possible and three times daily dosing was advised in four patients taking small doses. All patients were monitored in hospital during the initiation of treatment. They were allowed home when they were seen to tolerate the drug or, in those with His bundle or ventricular tachycardia, when 24 hour electrocardiographic monitoring confirmed suppression of the arrhythmia.

TREATMENT ASSESSMENT

Intravenous treatment was judged to be successful if the arrhythmia was terminated or, in the case of incessant ectopic arrhythmias, if a clinically beneficial reduction in rate was obtained. Any other response was regarded as a failure. Long term treatment was judged to be a success if there was no recurrence of arrhythmia, or if there was no more than an occasional minor episode of tachycardia, or if long term rate control was achieved in incessant arrhythmias. Any other response was regarded as a failure. Trough concentrations of plasma flecainide

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were measured in seven patients. Plasma concentrations were used to adjust dosing only if the arrhythmia persisted. Follow up assessment was by history of recurrence of symptoms, 12 lead electrocardiogram, and 24 hour ambulatory monitoring.

Results

All patients satisfying the inclusion criteria had one of the following arrhythmias: atrioventricular reentry by an accessory pathway, His bundle tachycardia, or ventricular tachycardia. We expected that the response to flecainide would vary depending on the mechanism of the arrhythmia, and the analysis of the clinical results was based on this premise.

CONCEALED ACCESSORY PATHWAY (FOUR PATIENTS)

In all patients the arrhythmias were orthodromic reentry tachycardias with rates of 180–200 impulses/minute. In both patients given intravenous flecainide sinus rhythm was restored promptly and in one this was due to a block in the accessory pathway. Three patients have had no recurrence of arrhythmia since the start of oral treatment. The fourth (patient 4) experienced more frequent episodes of tachycardias on oral flecainide and these could not be controlled by increasing the dose. He is now symptom free on treatment with disopyramide.

WOLFF-PARKINSON-WHITE SYNDROME (THREE PATIENTS)

Intravenous flecainide terminated an orthodromic tachycardia in two patients (in the retrograde limb in both instances) and on return to sinus rhythm there was no evidence of preexcitation. In one of these (patient 5) oral flecainide caused more frequent episodes of tachycardia although there was a persisting anterograde block in the pathway. Symptomatic control could not be achieved and flecainide was discontinued and replaced by disopyramide.

Patient 6 had two accessory pathways. When flecainide was given intravenously during orthodromic tachycardia the cycle length increased and the atrial activation pattern changed, suggesting retrograde block in one of the pathways, although the reentry tachycardia persisted and had to be terminated by programmed stimulation. Despite this response there has been no recurrence of symptoms since the start of oral flecainide.

Patient 7 had already received oral flecainide in a dose of 4 mg/kg/day at his referring hospital and his episodes of tachycardia had become more frequent. Because intravenous flecainide given during electrophysiological study produced bidirectional block in the pathway, he was given a higher oral dose (10 mg/kg/day) and he is now free from symptoms.

HIS BUNDLE TACHYCARDIA (TWO PATIENTS)

Patient 8 had had episodes of ectopic His bundle tachycardia since infancy. Intravenous flecainide slowed the arrhythmia but failed to terminate it. Because all conventional antiarrhythmic drugs had been unsuccessful, oral flecainide was started and there has been no recurrence during 26 months follow up.

In patient 9 the rate of an incessant His bundle tachycardia was reduced from 210 to 130 impulses/minute by intravenous flecainide and satisfactory rate control has been maintained on oral treatment (with a resting heart rate of about 90 beats/minute and a maximum rate of 140 beats/minute on ambulatory monitoring).

VENTRICULAR TACHYCARDIA (THREE PATIENTS)

Two children had paroxysmal uniform ventricular tachycardia (patient 10, rate 220; patient 11, rate 290 beats/minute) and the third (patient 12) had frequent self-terminating episodes of multiform ventricular tachycardia with rates of 320–400 beats/minute lasting for up to several minutes at a time. The clinical history suggested the presence of a tachycardia for nine months, two weeks, and three weeks respectively. Despite the rate of the tachycardias, all three children were haemodynamically stable and oral treatment was started. Flecainide has successfully controlled the arrhythmias in all three, with no recurrences. In patient 12 a progressive increase in dose was monitored with plasma concentrations.

Table 3 *Results for each arrhythmia*

		Intravenous			*Oral*		
Diagnosis	*No*	*No*	*Success*	*Failure*	*No*	*Success*	*Failure*
CAP	4	2	2	—	4	3	1
WPW	3	3	2	1	3	2	1
HBT	2	2	1	1	2	2	—
VT	3	—	—	—	3	3	—
Total:	12	7	5	2	12	10	2

CAP, concealed accessory pathway; WPW, Wolff-Parkinson-White syndrome; HBT, His bundle tachycardia; VT, ventricular tachycardia.

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Daily doses of 60 mg, 100 mg, 150 mg, and 200 mg produced plasma concentrations of 155, 114, 450, and 492 μg/l (0·33, 0·24, 0·95, and 1·04 mmol/l) respectively and suppression of ventricular tachycardia was achieved only on the highest dose.

OVERALL RESULTS (TABLE 3)

Seven patients were given intravenous flecainide during tachycardia. In four sinus rhythm was restored by 0·4–1·0 mg/kg of the drug. In the other three the arrhythmia persisted although the rate was reduced; but in only one was this a satisfactory response.

All 12 patients received oral flecainide and in 10 treatment has been successful. In two patients with accessory pathways oral flecainide was withdrawn because it caused more frequent symptoms; although in both cases intravenous flecainide had produced complete block in the pathway.

All patients who received intravenous flecainide were subsequently given the drug orally. Successful intravenous treatment predicted continuing clinical benefit on oral treatment in four of five patients. In two patients (6 and 8), despite a poor response when the drug was given intravenously, oral flecainide has proved successful in preventing recurrence of the arrhythmia.

UNWANTED EFFECTS

With the exception of the exacerbation of arrhythmia in the two patients described above, no unwanted effects were observed or reported during intravenous treatment or during 276 patient-months of follow up.

Plasma concentrations

Results were obtained in seven patients (table 2) and on doses of 2·7–22·2 mg/kg/day they ranged from 343 to 535 μg/l (0·72–1·13 mmol/l) which is within the lower end of the therapeutic range in adults. No abnormalities of haematological and biochemical indices were noted.

Discussion

Controlled randomised clinical trials of antiarrhythmic drugs are scientifically important, but such study designs are not applicable to all clinical situations. Rare arrhythmias (that preclude the enrolment of adequate numbers of patients in a study), serious life threatening arrhythmias (raising ethical objections), medically refractory arrhythmias (introducing selection bias because of previously tested agents), and arrhythmias in children (demanding exceptional short and long term safety) are perhaps the most clinically important arrhythmias but are those least suitable for controlled antiarrhythmic drug studies. In this open study, flecainide acetate was given to paediatric patients who had manifest serious and/or medically refractory arrhythmias. Flecainide was chosen because its electrophysiological actions have been well examined[6] and because it is important in the management of arrhythmias in adults, including ventricular tachycardia[2] and the arrhythmias associated with the preexcitation syndrome.[3]

In 10 of 12 patients an excellent therapeutic response was obtained either by complete suppression of the arrhythmia or by control of ventricular rate. In eight of these 10 patients other antiarrhythmic drugs had been ineffective or poorly tolerated, including amiodarone in two children.

Arrhythmogenesis occurred in two patients with tachycardias caused by accessory pathways. Occasional arrhythmogenesis has been reported before and might be predicted by the drug's electrophysiological effects. Slowed conduction may increase the excitable gap of reentrant arrhythmias enhancing tachycardia although slowing its rate.

The pharmacokinetics of flecainide in children are not established. Plasma flecainide concentrations were not investigated systematically in this study but results in seven patients were at the lower end of the adult therapeutic range.[7] Adult patients are rarely given more than 4–5 mg/kg/day, whereas half of our patients required more than 5 mg/kg/day. Even allowing for differences in body surface area these doses are higher than those used in adults; this feature accords with paediatric use of other antiarrhythmic drugs.

The place of flecainide in the treatment of paediatric arrhythmias will be determined by further experience and long term follow up. Nevertheless, this demonstration of the drug's efficacy, safety, and relative freedom from unwanted effects suggests that it will be important in the management of selected paediatric arrhythmias and may prove an attractive alternative to more toxic antiarrhythmic drugs.[8 9]

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References

1 Hellestrand KJ, Nathan AW, Bexton RS, Spurrell RAJ, Camm AJ. Cardiac electrophysiologic effects of flecainide acetate for paroxysmal reentrant junctional tachycardias. *Am J Cardiol* 1983;**51**:770–6.

2 Anderson JL, Stewart JR, Perry BA, *et al*. Oral flecainide acetate for the treatment of ventricular arrhythmias. *N Engl J Med* 1981;**305**:473–7.

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3 Neuss H. Long term use of flecainide in patients with supraventricular tachycardia. *Drugs* 1985;**29**(suppl 4):21–5.
4 Pfefferkorn J, Hilgenberg F. Erste Erfahrungen mit Flecainid im Kindesalter. *Drug Evaluation and Development* 1984;**8**:167–73.
5 Ward DE, Jones S, Shinebourne EA. Use of flecainide acetate for refractory junctional tachycardia in children with the Wolff-Parkinson-White syndrome. *Am J Cardiol* 1986;**57**:787–90.
6 Estes NAM, Garan H, Ruskin JN. Electrophysiologic properties of flecainide acetate. *Am J Cardiol* 1984;**53**:26B–9B.
7 Conard GJ, Ober RE. Metabolism of flecainide. *Am J Cardiol* 1984;**53**:41B–51B.
8 Garson A Jr, Gillette PC, McVey P, *et al*. Amiodarone treatment of critical arrhythmias in children and young adults. *J Am Coll Cardiol* 1984;**4**:749–55.
9 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.

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