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Acute electrophysiological effects of flecainide acetate on cardiac conduction and refractoriness in man

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SUMMARY The electrophysiological effects of flecainide acetate (2 mg/kg as an intravenous infusion over five minutes) were assessed in 47 patients undergoing electrophysiological study. Seven patients had normal electrophysiology, 16 had a direct accessory atrioventricular pathway, 12 had dual atrioventricular nodal (AH) pathways, five had paroxysmal ventricular tachycardia, six had conduction system disease, and one patient had a left atrial tachycardia.

No significant change occurred in sinus cycle length. The PA interval, AH interval, and HV interval were all significantly prolonged. The QRS complex duration increased significantly. The QT interval showed slight prolongation due entirely to the increase in QRS duration.

Refractoriness of the atrial and ventricular myocardium was slightly prolonged, but was significant only at ventricular level. No significant change occurred in refractoriness of the normal atrioventricular node. Pronounced prolongation of retrograde "fast" AH pathway refractoriness was observed in those patients with dual AH pathways. Anterograde and retrograde accessory pathway refractoriness were both greatly increased.

These electrophysiological properties strongly suggest that flecainide will be useful in the management of a wide variety of cardiac arrhythmias. It should be administered, however, with caution to patients with pre-existing conduction system disease. Because repolarisation is not delayed flecainide is unlikely to induce ventricular arrhythmias related to prolongation of the QT interval.

Flecainide acetate‡ (N-(2-piperidylmethyl)-2,5-bis (2,2,2-trifluoroethoxy) benzamide acetate) belongs to a unique series of trifluoroethoxybenzamides[1 2] which have proven antiarrhythmic activity against a variety of experimentally induced arrhythmias.[3–5]

Human pharmacokinetic studies have shown that flecainide is almost completely absorbed after oral administration, undergoes minimal hepatic biotransformation, and has a long plasma elimination half-life ranging from 11 to 22 hours,[6 7] properties that are highly desirable for the long term use of antiarrhythmic agents.

This study was undertaken to investigate the acute electrophysiological effects of intravenous flecainide on cardiac conduction and refractoriness in man.

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Patients and methods

Forty-seven patients, 27 male and 20 female, whose ages ranged from 16 to 80 (mean 42) years, underwent routine electrophysiological study for the investigation of either symptoms suggesting or documentary evidence of recurrent arrhythmias or cardiac conduction disturbances. The majority of patients with episodes of documented tachycardia had been previously treated with a variety of antiarrhythmic agents. The clinical data are summarised in Table 1.

Seven patients, in whom arrhythmias could not be provoked, were found to have normal cardiac electrophysiology. Sixteen patients had an accessory atrioventricular pathway with atrioventricular reentrant (orthodromic) tachycardia which could be provoked. In eight of these patients accessory pathway conduction was bidirectional with ventricular pre-excitation (Wolff-Parkinson-White syndrome) while the other eight had conduction in the retrograde ventriculoatrial direction alone (that is electrophysiologically concealed). Twelve patients had dual AH conduction pathways with inducible intra

Table 1 *Patient data*

No of patients	*Age range*	*(mean)*	*Sex*	*Electrophysiological diagnosis*
7	16–60	(43)	5M, 2F	Normal
16	22–73	(41)	10M, 6F	WPW overt 8 concealed 8
12	23–55	(38)	5M, 7F	Dual AH pathways
5	16–36	(27)	2M, 3F	Ventricular tachycardia
6	40–80	(63)	4M, 2F	Conduction delay/block
1	43		M	Left atrial tachycardia

atrioventricular nodal re-entrant tachycardia. Five patients had recurrent paroxysmal ventricular tachycardia and one patient had an intermittent automatic left atrial tachycardia. Six patients underwent electrophysiological study to investigate conduction disturbances involving the sinus node (two patients), atrioventricular node (one patient), or more distal conduction system (three patients).

ELECTROPHYSIOLOGICAL STUDY

All patients were studied in the non-sedated, post-absorptive state after written informed consent was obtained. All antiarrhythmic drugs were discontinued at least three drug elimination half-lives before the electrophysiological study.

Under local anaesthesia (1% lignocaine) and fluoroscopic guidance four or five electrode wires were introduced into the heart. A hexapolar electrode was inserted via the left subclavian vein and positioned with its tip at the right ventricular apex. The two distal poles were used for right ventricular pacing and the four proximal poles were selected to obtain the best possible bipolar recording from the lateral wall of the high right atrium. Where appropriate a quadripolar electrode wire was introduced via the same subclavian vein and positioned in the coronary sinus for recording and stimulation. In the majority of patients these two electrode wires were left in situ at the completion of the acute electrophysiological assessment in order to perform follow-up electrophysiological studies.[8] Two bipolar electrode wires were introduced via a femoral vein. One electrode wire was advanced into the high right atrium for pacing and recording, and the other electrode wire was positioned against the septal leaflet of the tricuspid valve to record His potentials. This "His bundle" electrode wire was adjusted to record distinct low right atrial, His bundle, and right ventricular electrograms.[9] Intracardiac signals were filtered between 50 and 500 Hz and recorded on a 16-channel Siemens-Elema* Mingograf inkjet recorder simultaneously with surface electrocardiographic leads I, aVF, V1, and V6. Paper speeds of 100 and 250 mm/s were used. Intracardiac stimulation was achieved with a Devices† type 4279 "programmable" stimulator using pulse amplitudes at twice diastolic threshold[9] and pulse durations between 1·5 and 2·5 ms. Conduction intervals were studied during sinus rhythm and during constant rate atrial pacing slightly above sinus rate. Anterograde and retrograde conduction characteristics and refractoriness of the heart were determined by the introduction of an extrastimulus after regular atrial or ventricular pacing at a cycle length of 600 ms in most instances.[9 10]

Incremental atrial pacing from the high right atrium was performed until atrioventricular Wenckebach periodicity occurred or a minimum pacing cycle length of 200 ms was achieved. Incremental ventricular pacing from the right ventricular apex was performed until retrograde ventriculoatrial Wenckebach periodicity occurred or a minimum pacing cycle length of 240 ms was attained. For comparison, characteristics of conduction and refractoriness were measured at identical paced rates and driven cycle lengths before and after flecainide. All intervals were measured to the nearest 5 ms.

FLECAINIDE ADMINISTRATION

After baseline electrophysiological evaluation, flecainide in a dose of 2 mg/kg body weight was administered intravenously over five minutes. Fifteen to 30 minutes after administration of the drug electrophysiological evaluation was made, during which a blood sample was taken for serum flecainide estimation using a sensitive and specific spectrofluorimetric technique described previously.[11]

DEFINITION OF TERMS

Right intra-atrial conduction time (the PA interval) was measured from the onset of earliest atrial activation, on any channel, to the intrinsicoid deflection of the low right atrial electrogram recorded on the His bundle electrode wire.[12–14] Atrioventricular nodal conduction time (the AH interval) was measured from the intrinsicoid deflection of the low right atrial electrogram to the onset of the His bundle deflection.[12–14] His-Purkinje conduction time (the HV interval) was measured from the onset of the His bundle deflection to the earliest onset of ventricular activation.[12–14]

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Intraventricular conduction was measured as the QRS duration from the earliest onset of ventricular activation to the latest J point of the QRS complex in any surface electrocardiographic lead. The QT interval was measured from the earliest onset of ventricular activation to the point at which the latest T wave returned to the isoelectric line. The JT interval during identical rate atrial pacing was used as an index of ventricular repolarisation and was measured from the J point to the point at which the latest T wave returned to the isoelectric line, that is JT=QT—QRS.

Atrioventricular Wenckebach cycle length was defined as the longest atrial cycle length at which anterograde Wenckebach periodicity occurred during incremental atrial pacing.[12-14] Ventriculoatrial Wenckebach cycle length was defined as the longest ventricular cycle length at which retrograde Wenckebach periodicity occurred during incremental ventricular pacing.[9]

Effective refractory period of the atrium was defined as the longest coupling interval of an atrial premature stimulus which failed to cause atrial depolarisation. Effective refractory period of the atrioventricular node was defined as the longest coupling interval of an atrial premature stimulus which failed to cause His bundle depolarisation. Ventricular effective refractory period was defined as the longest coupling interval of a ventricular premature stimulus which failed to cause ventricular depolarisation.[9]

An atrioventricular accessory pathway was defined as a direct atrioventricular connection which bypassed normal atrioventricular nodal and His-Purkinje conduction.[15] Anterograde effective refractory period of an accessory pathway was defined as the longest coupling interval of an atrial premature beat at which block occurred in the accessory pathway with normalisation of the atrial to ventricular activation sequence or at which the atrial premature stimulus failed to conduct to the ventricles. Retrograde effective refractory period of an accessory pathway was defined as the longest coupling interval of a ventricular premature beat at which block occurred in the accessory pathway with normalisation of the retrograde ventricular to atrial activation sequence or at which the ventricular premature stimulus failed to conduct to the atria.

An atrioventricular nodal "fast" pathway was defined as a path which showed the electrophysiological properties of fast, non-decremental conduction and a relatively long refractory period.[16-18] Anterograde effective refractory period of an atrioventricular nodal "fast" pathway was defined as the longest coupling interval of an atrial premature beat at which block in the "fast" pathway occurred with a sudden increase and normalisation of the AH conduction time or at which the atrial extrastimulus failed to conduct to the His bundle and ventricles.[17 18] Retrograde effective refractory period of an atrioventricular nodal "fast" pathway was defined as the longest coupling interval of a ventricular premature beat at which a sudden increase in the retrograde V to A conduction time occurred or at which the ventricular extrastimulus failed to conduct to the atria.

An atrioventricular nodal "slow" pathway was defined as a path demonstrating the electrophysiological properties of slow, decremental conduction with a relatively short effective refractory period.[16-18] Anterograde effective refractory period of an atrioventricular nodal "slow" pathway was defined as the longest coupling interval of an atrial premature beat at which the atrial extrastimulus failed to conduct to the His bundle,[17 18] when anterograde conduction block had previously occurred in the "fast" pathway at longer atrial extrastimulus coupling intervals. Retrograde effective refractory period of an atrioventricular nodal "slow" pathway was defined as the longest coupling interval of a ventricular premature beat at which the ventricular extrastimulus failed to conduct to the atria when retrograde conduction block had previously occurred in the "fast" pathway at longer ventricular extrastimulus coupling intervals.

Accessory pathway and dual AH pathway refractory periods were measured from the same intracavitary positions as close to the pathway as possible before and after drug administration.

STATISTICS

Statistical data were analysed using Student's t test for paired data.

Results

Comparative electrophysiological data are summarised in Tables 2 and 3. All measurements are written as the mean value ± one standard deviation from the mean.

CONDUCTION (TABLE 2)

Flecainide produced a small insignificant decrease in sinus cycle lengths from 745±198 to 734±180 ms. The PA interval prolonged significantly from 41±13 to 50±13 ms; $p<0.001$. AH conduction times during sinus rhythm, excluding two patients with overt ventricular pre-excitation which obscured the His potential and the patient with left atrial tachycardia, prolonged from 67±21 to 81±33 ms; $p<0.001$. Similar AH prolongation occurred during constant rate atrial pacing slightly faster than sinus rates (84±33 to 101±39 ms; $p<0.001$). Flecainide produced complete AH block in one patient with intermittent Wenckebach second degree AV block present before drug administration.

Table 2 *Conduction intervals*

Interval	*No.*	*Control (ms) (mean±SD)*	*Flecainide (ms) (mean±SD)*	*Statistical significance (p)*
Sinus cycle length	47	745±198	734±180	NS
PA	43	41±13	50±13	<0·001
AH (SR)	43	67±21	81±33	<0·001
AH (AP)	43	84±33	101±39	<0·001
HV	39	44±9	61±12	<0·001
QRS	47	96±21	118±30	<0·001
QT (SR)	39	368±43	382±44	<0·02
QT (AP)	39	342±25	349±30	<0·01
QTc	39	427±34	446±40	<0·001
JT	39	246±27	232±33	<0·001
WCL (AV)	19	371±153	410±178	<0·05
WCL (VA)	19	355±91	496±72	<0·001

PA, right intra-atrial conduction time; AH (SR), AV nodal conduction time in sinus rhythm; AH (AP), AV nodal conduction time during atrial pacing; HV, H to V conduction time; QRS, QRS duration; QT (SR), QT interval during sinus rhythm; QT (AP), QT interval during atrial pacing; QTc, the corrected QT interval; JT, the JT interval during atrial pacing (QT–QRS); WCL (AV), anterograde Wenckebach periodicity of the AV node; WCL (VA), retrograde Wenckebach periodicity of the AV node.

His-Purkinje conduction times measured in the 39 patients without overt ventricular pre-excitation prolonged considerably from 44±9 to 61±12 ms; p<0·001 (Fig. 1). After flecainide administration the HV interval prolonged in 37 patients and remained unchanged in two patients. Maximum HV prolongation in any patient was 40 ms. The increment in the HV interval expressed as a percentage of the control HV interval ranged from 0 to 100%, with a mean of 42%. Seventy per cent of patients developed abnormal HV prolongation of greater than 55 ms.[9] One patient with a previously documented episode of complete atrioventricular block, a normal control HV interval, and right bundle-branch block with left anterior hemiblock on his surface electrocardiogram developed complete HV block during flecainide administration. Maximum HV prolongation occurred an average of five minutes after the start of flecainide administration.

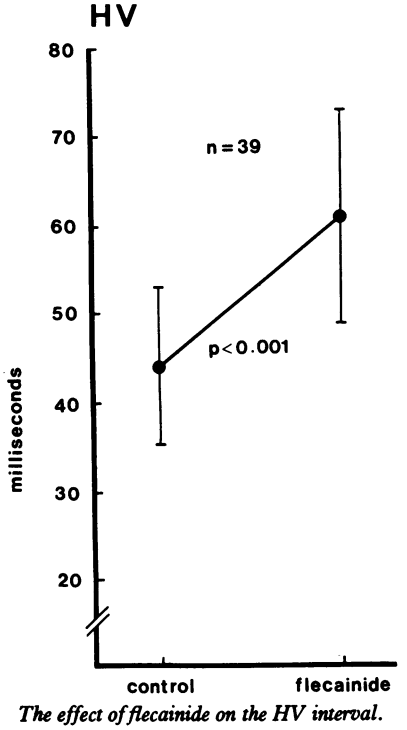

Fig. 1 *The effect of flecainide on the HV interval.*

QRS durations, measured during sinus rhythm in 39 patients and during reciprocating tachycardia in the eight patients with overt ventricular pre-excitation, increased conspicuously from 96±21 to 118±30 ms; p<0·001 (Fig. 2). QRS durations increased in 44 patients and remained unchanged in three patients. The maximum QRS prolongation was 75 ms in a patient who developed complete right bundle-branch block after flecainide administration. The increment in QRS duration expressed as a percentage of the control QRS duration ranged from 0 to 79%, with a mean of 23%.

QT intervals were compared in the 39 patients without ventricular pre-excitation. The QT intervals during sinus rhythm (368±43 to 382±44 ms; p<0·02), constant rate atrial pacing (342±25 to 349±30 ms; p<0·01), and the corrected QT interval derived from Bazett's formula (Q–Tc=Q–T measured/ (R–R interval in s)$^{0.5}$) showed slight significant lengthening (427±34 to 446±40 ms; p<0·001). The JT interval shortened slightly from 246±27 to 232±33 ms; p<0·001. Fig. 3 illustrates the typical effect on conduction produced by flecainide.

Flecainide produced complete anterograde accessory pathway block in two patients and complete retrograde block in seven patients, all of whom initially had retrograde accessory pathway conduction only. Retrograde accessory pathway conduction time in the nine patients still capable of retrograde conduction

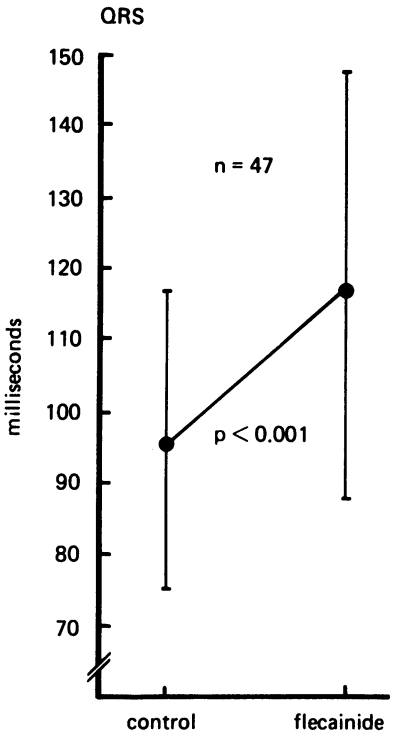

Fig. 2 *The effect of flecainide on QRS duration.*

after flecainide prolonged from 166±51 to 213±60 ms; p<0·01.

WENCKEBACH PERIODICITY (TABLE 2)

Wenckebach periodicity was compared in the 19 patients with normal atrioventricular conduction. The anterograde atrioventricular Wenckebach cycle length prolonged from 371±153 to 410±178 ms; p<0·05, and the retrograde ventriculoatrial Wenckebach cycle length prolonged from 355±91 to 496±72 ms; p<0·001. Two patients developed transient complete atrioventricular block as previously described. Eight patients, however, developed transient complete ventriculoatrial retrograde block after flecainide administration.

REFRACTORINESS (TABLE 3)

(i) *Atrium*

Mean right atrial effective refractory periods increased slightly but did not achieve statistical significance (213±32 to 219±28 ms).

(ii) *Atrioventricular node*

Of the 26 patients with "normal" atrioventricular nodal conduction, excluding the eight patients with overt ventricular pre-excitation, the 12 patients with dual AH pathways, and the patient with intermittent atrioventricular nodal Wenckebach block, assessment of atrioventricular nodal effective refractory period was limited by atrial refractoriness in 16. No significant change in atrioventricular nodal effective refractory period occurred in the remaining 10 patients (314±66 to 287±21 ms)

(iii) *Ventricle*

Right ventricular effective refractory periods prolonged slightly from 220±22 to 229±23 ms; p<0·01.

(iv) *Accessory pathways*

Anterograde atrioventricular accessory pathway refractoriness prolonged significantly from 262±47 to 361±138 ms (p<0·05). Complete anterograde accessory pathway block occurred in two patients. In contrast, atrial effective refractory periods in these eight patients changed insignificantly from 185±22 to 189±25 ms. Retrograde ventriculoatrial accessory pathway refractoriness prolonged more conspicuously

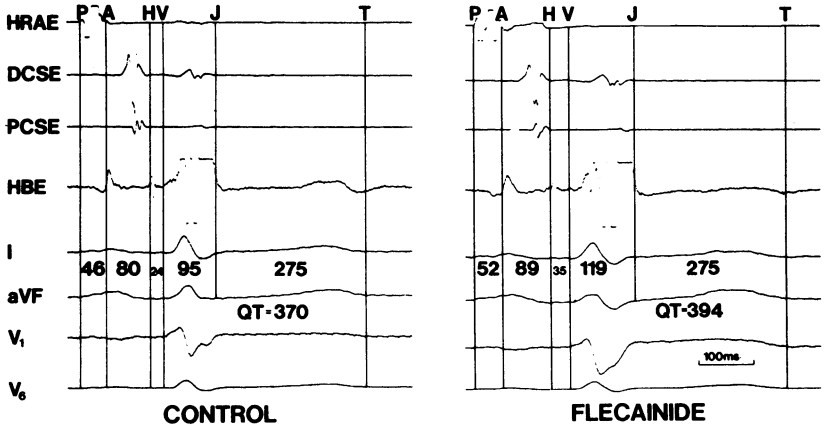

Fig. 3 *Electrocardiographic recordings during sinus rhythm, recorded at 250 mm/s, before (left) and after (right) the administration of flecainide.*

Table 3 *Refractory periods*

Refractory period	*No.*	*Control (ms) (mean±SD)*	*Flecainide (ms) (mean±SD)*	*Statistical significance (p)*
A ERP	47	213±32	219±28	NS
AVN ERP	10	314±66	287±21	NS
V ERP	47	220±22	229±23	<0·01
AHfast (AV)	12	342±59	364±59	NS
AHfast (VA)	11	315±99	450±144	<0·01
AHslow (AV)	6	277±40	293±37	NS
AHslow (VA)	1	280	300	
AP (AV)	8	262±47	361±138	<0·05
AP (VA)	13	300±49	453±169	<0·01

A ERP, atrial effective refractory period; AVN ERP, AV nodal effective refractory period; V ERP, ventricular effective refractory period; AHfast (AV), anterograde refractoriness of "fast" AH pathway; AHfast (VA), retrograde refractoriness of "fast" AH pathway; AHslow (AV), anterograde refractoriness of "slow" AH pathway; AHslow (VA), retrograde refractoriness of "slow" AH pathway; AP (AV), anterograde refractoriness of accessory pathway; AP (VA), retrograde refractoriness of accessory pathway.

from 300±49 to 453±169 ms ($p<0·01$). Complete retrograde accessory pathway block occurred in seven patients, all of whom had concealed conduction. Ventricular effective refractory periods in these 16 patients changed slightly from 215±22 to 227±24 ms ($p<0·01$).

(v) *Dual AH pathways*

Anterograde atrioventricular "fast" pathway refractoriness was not significantly affected (342±59 to 364±59 ms). One patient developed complete block in the anterograde "fast" pathway. Retrograde ventriculoatrial "fast" pathway refractoriness prolonged considerably from 315±99 to 450±144 ms ($p<0·01$). Five out of 12 "fast" pathways showed complete retrograde block after flecainide administration.

No significant changes in refractoriness of the atrioventricular nodal "slow" pathways were observed in either the anterograde or retrograde direction. The majority of "slow" pathway values were, however, limited by atrial refractoriness.

SERUM LEVELS OF FLECAINIDE

Blood for flecainide levels, collected 15 to 30 minutes after drug administration, disclosed serum flecainide levels ranging from 85 to 785 (mean 335) ng/ml. Serum levels of flecainide did not correlate with acute changes observed in conduction intervals or refractory periods.

SIDE EFFECTS

One patient experienced a significant arrhythmia after flecainide administration. This patient, with ventricular pre-excitation, developed ventricular flutter during ventricular extrastimulation after but not before flecainide had been given. Complete AH block occurred in one patient with prior Wenckebach second degree atrioventricular block, and one patient with underlying bifascicular block (right bundle branch block and left anterior hemiblock) developed complete HV block during drug administration. Because of slow ventricular escape rhythms both of these patients required ventricular pacing for periods of 20 to 30 minutes until atrioventricular conduction returned. Minor side effects that occurred only during drug administration included oral paraesthesiae in over 90% of patients and transient drowsiness and dizziness in a small minority. Several patients complained of slight local pain at the site of injection.

Discussion

After initial reports describing the synthesis and antiarrhythmic potential of a series of N-(aminoalkyl) trifluoroethoxybenzamides, one of these compounds, flecainide acetate (R818), has been studied extensively using animal models.[1,2] Its antiarrhythmic potency in dogs, pigs, and mice compared very favourably with reference compounds quinidine, procainamide, and lignocaine when used both parenterally and orally against a variety of experimentally induced supraventricular and ventricular arrhythmias.[3-5]

An evaluation of the intracellular electrophysiological effects of flecainide using isolated rabbit atria showed slowing of conduction velocity and a striking reduction in the maximum rate of depolarisation of the action potential. The effect of flecainide on repolarisation was to produce an alteration in the shape of the action potential without prolonging its duration. Flecainide reduced the spontaneous frequency of sinus node discharge and had a small negative inotropic effect on isolated rabbit atrial muscle.[19]

All of the properties manifested by flecainide are typical of Vaughan Williams Class 1 agents[20] and imply that this drug restricts the fast inward movement of sodium ions.[19]

Initial electrophysiological evaluation in man showed a distinct depressant influence on His-Purkinje and intraventricular conduction, a lesser effect on atrioventricular nodal conduction, and insignificant changes in atrial and ventricular refrac-

toriness. Significant depression of accessory pathway conduction and refractoriness was reported in several patients with the Wolff-Parkinson-White syndrome.[21]

Further human electrophysiological studies combining right ventricular monophasic action potential recordings with programmed ventricular stimulation using larger intravenous doses of flecainide showed significant prolongation of the ventricular effective refractory period concomitant with prolongation of ventricular repolarisation.[22]

The electrophysiological results of the present series show that flecainide significantly depresses conduction within working myocardium and throughout the specialised conduction system. Right atrial conduction was significantly delayed. Ventricular conduction measured by the QRS duration was severely depressed as described by Orning[21] and Olsson and Edvardsson[22] in their initial studies. Atrioventricular nodal conduction times, independent of any rate-related changes in the AH interval, were prolonged by flecainide. The most pronounced effect appeared to be on His-Purkinje conduction where the HV interval prolonged beyond the normal range[9] in 70% of patients after flecainide administration and transient complete HV block occurred in one patient. These changes in cardiac conduction caused by flecainide could be reliably produced in the His-Purkinje system and ventricle but were less predictable in atrial myocardium or the atrioventricular node. Seipel *et al.*[23] also reported similar and dose dependent changes in cardiac conduction when intravenous doses of 2 mg/kg were used.

Slight lengthening of both atrial and ventricular effective refractory periods occurred in the present study group, but only the ventricular refractoriness increased significantly. These findings correlate closely with the findings of Olsson and Edvardsson[22] and indicate that flecainide does have a significant depressant effect on ventricular muscle refractoriness, especially at higher doses. In any one patient, however, a change in atrial refractoriness did not predict a similar change in ventricular refractoriness.

The small increments in QT interval during sinus rhythm, corrected for rate using Bazett's formula, and during constant rate atrial overdrive pacing resulted from QRS widening and not from prolongation of ventricular repolarisation. This is consistent with similar results obtained by Campbell Cowan and Vaughan Williams in their in vitro model.[19] These electrophysiological findings are, however, at variance with the monophasic action potential studies reported by Olsson and Edvardsson where a significant delay of right ventricular repolarisation measured by the monophasic action potentials was observed in their group of nine patients.

The concept of the JT interval was introduced as another index of ventricular repolarisation in order to exclude errors resulting from drug-induced prolongation of ventricular depolarisation. The JT interval did not prolong after flecainide administration which suggests that this drug, unlike quinidine (a Vaughan Williams class 1a drug) or lignocaine (a Vaughan Williams class 1b drug), does not materially affect ventricular repolarisation.

The electrophysiological properties of flecainide do not fall strictly within the modified criteria used to define Vaughan Williams class 1a and class 1b agents.[24] D C Harrison (1981, personal communication) has proposed that a further subgroup, class 1c, should be used to define such drugs including encainide[25] and lorcainide,[26] both of which manifest many electrophysiological similarities to flecainide.

Touboul *et al.*[27] have recently suggested a classification of antiarrhythmic agents according to their electrophysiological characteristics defined by standard electrophysiological assessment. According to this proposed classification flecainide manifests class 3 antiarrhythmic activity, which comprises drugs showing a wide electrophysiological spectrum. In addition to atrioventricular nodal depression they prolong HV conduction times (aprindine[28 29]) or His-Purkinje refractoriness (amiodarone[29 30]). These class 3 drugs may also lengthen refractoriness of accessory pathways and atrial myocardium.

A most profound effect on accessory atrioventricular pathways and "fast" nodal pathways was produced by flecainide. After intravenous administration of the drug complete anterograde block occurred in two out of eight overt accessory atrioventricular pathways and complete retrograde block occurred in seven of 16 accessory atrioventricular pathways. Of the six remaining overt accessory pathways, anterograde refractoriness increased in all cases. Of the nine accessory pathways still capable of retrograde conduction after flecainide administration, refractoriness increased in four patients and in two cases accessory pathway refractoriness slightly shortened. In three cases assessment of accessory pathways refractoriness was limited by ventricular refractoriness.

In the 16 patients with accessory atrioventricular pathways it is of interest that flecainide has such a significant depressant effect on accessory pathway refractoriness compared with the changes in atrial or ventricular myocardial refractoriness in the same patients. These findings suggest that bypass tracts possess electrophysiological characteristics quite distinct from those of atrial or ventricular muscle.

In the 12 patients with dual AH pathways flecainide acetate selectively affected "fast" atrioventricular nodal pathway refractoriness, specifically retrograde refractoriness of this "fast" pathway. Complete

retrograde block occurred in five of 12 "fast" pathways. Of the remaining seven patients, "fast" pathretrograde refractoriness was considerably increased in five, unchanged in one, and shortened in the remaining case. Complete anterograde block occurred in only one "fast" pathway. No significant change, however, in anterograde "fast" pathway refractoriness was observed overall. No statistically significant changes in anterograde or retrograde refractoriness of the "slow" pathways were seen though two patients developed complete retrograde ventriculoatrial block of both "fast" and "slow" pathways within the atrioventricular node. The dramatic selective effect of flecainide on "fast" atrioventricular nodal pathway retrograde refractoriness supports the hypothesis of Gomes *et al.*[31 32] and Platt *et al.*[33] that the "fast" atrioventricular nodal pathway possesses quite different electrophysiological characteristics from that of the "slow" or normal atrioventricular nodal pathway.

The electrophysiological effects manifested by flecainide on cardiac conduction, refractoriness, and in particular its effects on accessory pathway and "fast" atrioventricular nodal pathway refractoriness imply that it will be very useful in the management of tachycardias where such conduction and refractoriness are crucial to their continuation, that is atrioventricular nodal and atrioventricular re-entrant tachycardias. Potential problems resulting from conduction failure, however, must be considered particularly in patients with underlying atrioventricular or intraventricular conduction disturbances, or in patients receiving drugs which are known to depress atrioventricular nodal[34 35] or His-Purkinje conduction.[26 28 36]

In conclusion, flecainide acetate clearly manifests the desirable properties of potent depressant effects on cardiac conduction and refractoriness with minimal side effects, suggesting that it may prove a valuable addition to the therapeutic armamentarium in the acute management of a wide variety of cardiac arrhythmias.

References

1 Banitt EH, Coyne WE, Schmid JR, Mendel A. Antiarrhythmics. N-(aminoalkylene) trifluoroethoxybenzamides and N-(aminoalkylene) trifluoroethoxynaphthamides. *J Med Chem* 1975; **18**: 1130–4.

2 Banitt EH, Bronn WR, Coyne WE, Schmid JR. Antiarrhythmics. 2. Synthesis and antiarrhythmic activity of N-(piperidylalkyl) trifluoroethoxynaphthamides. *J Med Chem* 1977; **20**: 821–6.

3 Schmid JR, Seebeck BD, Henrie CL, Banitt EH, Kvam DC. Some antiarrhythmic actions of a new compound, R818, in dogs and mice (abstract). *Fed Proc* 1975; **34**: 775.

4 Verdouw PD, Deckers JW, Conard GJ. Antiarrhythmic and hemodynamic actions of flecainide acetate (R-818) in the ischemic porcine heart. *J Cardiovasc Pharmacol* 1979; **1**: 473–86.

5 Hodess AB, Follansbee WP, Spear JF, Moore EN. Electrophysiological effects of a new antiarrhythmic agent, flecainide, on the intact canine heart. *J Cardiovasc Pharmacol* 1979; **1**: 427–39.

6 Conard GJ, Carlson GL, Frost JW, Ober RE. Human plasma pharmacokinetics of flecainide acetate (R818), a new antiarrhythmic, following single oral and intravenous doses (abstract). *Clin Pharmacol Ther* 1979; **25**: 218.

7 Conard GJ, Carlson GL, Frost JW, Ober RE, Leon AS, Hunninghake DB. Human plasma elimination kinetics of R-818, a new antiarrhythmic. Abstract, 21st National Meeting APhA Academy of Pharmaceutical Sciences, Orlando, 1976; 106.

8 Bexton RS, Hellestrand KJ, Nathan AW, Spurrell RAJ, Camm AJ. A comparison of the antiarrhythmic effects on AV junctional reentrant tachycardia of oral and intravenous flecainide acetate. *Eur Heart J* (in press).

9 Josephson ME, Seides SF. *Clinical cardiac electrophysiology. Techniques and interpretations*. Philadelphia: Lea & Febiger, 1979.

10 Damato AN, Lau SH, Patton RD, Steiner C, Berkowitz WD. A study of atrioventricular conduction in man using premature atrial stimulation and His bundle recordings. *Circulation* 1969; **40**: 61–70.

11 Muhiddin KA, Johnston A. Spectrofluorimetric assay and buccal absorption of flecainide (R818). *Br J Clin Pharmacol* 1981; **12**: 283P.

12 Narula OS, Cohen LS, Samet P, Lister JW, Scherlag B, Hildner FJ. Localization of A-V conduction defects in man by recording of the His bundle electrogram. *Am J Cardiol* 1970; **25**: 228–37.

13 Castellanos A Jr, Castillo CA, Agha AS. Contribution of His bundle recordings to the understanding of clinical arrhythmias. *Am J Cardiol* 1971; **28**: 499–508.

14 Rosen KM. Evaluation of cardiac conduction in the cardiac catheterization laboratory. *Am J Cardiol* 1972; **30**: 701–3.

15 Anderson RH, Becker AE, Brechenmacher C, Davies MJ, Rossi L. Ventricular pre-excitation—a proposed nomenclature for its substrates. *Eur J Cardiol* 1975; **3**: 27–36.

16 Moe GK, Preston JB, Burlington H. Physiologic evidence for a dual A-V transmission system. *Circ Res* 1956; **4**: 357–75.

17 Denes P, Wu D, Dhingra RC, Chuquimia R, Rosen KM. Demonstration of dual A-V nodal pathways in patients with paroxysmal supraventricular tachycardias. *Circulation* 1973; **48**: 549–55.

18 Rosen KM, Mehta A, Miller RA. Demonstration of dual atrioventricular nodal pathways in man. *Am J Cardiol* 1974; **33**: 291–4.

19 Campbell Cowan J, Vaughan Williams EM. Quantitative characterisation of a new antiarrhythmic drug, flecainide (R818). *Eur J Pharmacol* 1981; **73**: 333–42.

20 Vaughan Williams EM. The classification of antiarrhythmic drugs. In: Sandoe E, Flensted-Jensen E, Olesen KH, eds. *Symposium on cardiac arrhythmias*. Sodertalje, Sweden: A B Astra, 1970.

21 Orning OM. Electrophysiologic effects of flecainide acetate in arrhythmias. Unpublished observations. On file, Loughborough: Riker Laboratories.
22 Olsson BS, Edvardsson N. Acute effects of flecainide upon intraventricular conduction and repolarisation in man. *Am Heart J* 1981; **102**: 864–71.
23 Seipel L, Abendroth RR, Breithardt G. Electrophysiologische Effekte des neven Antiarrhythmikums Flecainide (R818) beim Menschen. *Z Kardiol* 1981; **70**: 524–9.
24 Singh BN, Hauswirth O. Comparative mechanisms of action of antiarrhythmic drugs. *Am Heart J* 1974; **87**: 367–82.
25 Sami M, Mason JW, Peters F, Harrison DC. Clinical electrophysiologic effects of encainide, a newly developed antiarrhythmic agent. *Am J Cardiol* 1979; **44**: 526–32.
26 Bär FW, Farré J, Ross D, Vanagt EJ, Gorgels AP, Waellens HJJ. Electrophysiological effects of lorcainide, a new antiarrhythmic drug. Observations in patients with and without pre-excitation. *Br Heart J* 1981; **45**: 292–8.
27 Touboul P, Attalah G, Gressard A, Michelon G, Chatelain MT, Delahaye JP. Effets electrophysiologiques des agents antiarrhythmiques chez l'homme. *Arch Mal Coeur* 1979; **72**: 72–81.
28 Reid PR, Varghese PJ. Electropharmacology of aprindine HCl (abstract). *Circulation* 1974; **50**: III–200.
29 Zipes DP, Troup PJ. New antiarrhythmic agents. Amiodarone, Aprindine, Disopyramide, Ethmozin, Mexiletine, Tocainide, Verapamil. *Am J Cardiol* 1978; **41**: 1005–24.
30 Marcus FI, Fontaine GH, Frank R, Grosgogeat Y. Clinical pharmacology and therapeutic applications of the antiarrhythmic agent, amiodarone. *Am Heart J* 1981; **101**: 480–93.
31 Gomes JAC, Dhatt MS, Damato AN, Akhtar M, Holder CA. Incidence, determinants and significance of fixed retrograde conduction in the region of the atrioventricular node. *Am J Cardiol* 1979; **44**: 1089–98.
32 Gomes JAC, Dhatt MS, Rubenson DS, Damato AN. Electrophysiologic evidence for selective retrograde utilization of a specialized conducting system in atrioventricular nodal reentrant tachycardia. *Am J Cardiol* 1979; **43**: 687–98.
33 Platt M, Peter T, Mandel W. New evidence for intranodal tracts. Effect of verapamil in paroxysmal supraventricular tachycardia (abstract). VIII European Congress of Cardiology, Paris, France.
34 Chapelle M, Benaim R, Lejwi G. Effects of beta-blocking agents on atrio-ventricular and intraventricular conduction in man. *Acta Cardiol (Brux)* 1973; **28**: 238–54.
35 Rosen MR, Wit AL, Hoffman BF. Electrophysiology and pharmacology of cardiac arrhythmias. VI. Cardiac effects of verapamil. *Am Heart J* 1975; **89**: 665–73.
36 Alboni P, Malacarne C, Pedroni P. Effeti elettrofisiologici dell'ajmalina sul sistema di conduzione nell'uomo. *G Ital Cardiol* 1978; **8**: 752–63.

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