Conversion of supraventricular arrhythmias to sinus rhythm using flecainide

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We evaluated the efficacy of flecainide acetate (given intravenously to a maximal dose of 2 mg kg^{-1} and then orally in a dose of 100 mg b.d. or 100 mg t.d.s.) in the conversion to sinus rhythm of 50 patients exhibiting supraventricular arrhythmias (39 with atrial fibrillation, 6 with atrial flutter, 4 with supraventricular tachycardia and one with supraventricular tachycardia in association with the Wolff–Parkinson–White syndrome). Conversion was achieved in 36 patients (72%) (29 cases with atrial fibrillation, 4 cases with supraventricular tachycardia, 2 cases with atrial flutter and one case with Wolff–Parkinson–White syndrome), over a mean period of 7·4 ± 9 h.

The patients in which conversion was achieved had arrhythmias which had been in existence for a shorter time (5·3 ± 9·8 days) than those in which conversion was not achieved (16·7 ± 26·2 days) (P < 0·01).

The mean dosage of flecainide used to achieve conversion was 2·5 ± 2·36 mg kg^{-1}. Flecainide appears to be an effective agent for the conversion to sinus rhythm of atrial fibrillation and supraventricular tachycardias. Its efficacy in cases of atrial flutter has not yet been demonstrated.

Flecainide acetate, a group 1 anti-arrhythmic agent[1–4], has been in clinical use for a short while. Its efficacy in the treatment of ventricular arrhythmias[5–8] and of re-entrant junctional tachycardias[9] has been clearly demonstrated. There are few studies which have evaluated the efficacy of flecainide acetate in the treatment of supraventricular arrhythmias[10]. We therefore undertook a prospective study of the efficacy of flecainide in converting supraventricular arrhythmias of recent origin (less than 3 months) to sinus rhythm.

Patients and methods

PATIENTS

Fifty consecutive patients hospitalized in the University Hospital of Lausanne (CHUV), were included in this study. Thirty-nine exhibited atrial fibrillation, 6 atrial flutter, 4 supraventricular tachycardia (SV) and one with SV in association with the Wolff–Parkinson–White syndrome. The

arrhythmia was dated on the basis of the appearance of symptoms which could be related to an arrhythmia subsequently confirmed by an ECG. Ten patients exhibiting electrolyte imbalance or endocrinological disorders or cardiac decompensation, pregnancy, unstable angina, conduction disorders or a poor general state of health were excluded from the study. All antiarrhythmic drugs were discontinued at least 3 times the half-life of the drug prior to the study. Cardiotonics and diuretics were permitted providing they had been started at least 7 days before the beginning of the study. The clinical characteristics of each patient are summarized in Table 1. There were 31 men and 19 women with a mean age of 64 years (ranging from 38 to 93 years). In 21 of these patients we identified the absence of underlying organic heart disease. There were 8 cases of valvular heart disease, 3 cases of congestive cardiomyopathy, 4 cases of mitral valve prolapse, 7 cases of ischaemic heart disease, 3 cases of hypertensive heart disease and one case each of hypertensive heart disease associated with ischaemic heart disease, obstructive cardiomyopathy, pericarditis associated with ischaemic heart disease and pericarditis. Thirty-four patients were digitalized and 9 had received a different anti-arrhythmic agent

without success before the start of the study (Table 2). One female patient (with obstructive cardiomyopathy) had been receiving beta blockers for some months.

PROTOCOL

The protocol was accepted by the Ethical Committee of the CHUV and all patients gave their assent orally to being included in the study. Before the start of the treatment, a 12-lead ECG was recorded. A monitoring electrocardiogram was recorded. Flecainide was administered at the rate of 50 mg diluted in 50 cc of glucose 5% and infused over 10 min. If the sinus rhythm had not been restored by 15 min after the end of the infusion, a second infusion of 50 mg of flecainide was given up to an initial dose (by the intravenous route) not exceeding 2 mg kg^{-1}. The arterial pressure was measured every 2 min during the intravenous treatment. Oral treatment with 100 mg b.d. or 100 mg t.d.s. was instituted thereafter (patients weighing less than 70 kg received 200 mg day^{-1} and those whose weight exceeded 70 kg received 300 mg day^{-1}). Each day, after treatment began, the patient was questioned in order to establish the onset of any side-effects and an ECG was recorded. Arterial pressure was measured 3 times a day. If an increase in the QRS complex (>0.10 s), A–V block, or abnormal lengthening of the QT interval became apparent (QTc >430 ms) or if severe side-effects were noticed the treatment was discontinued immediately. The serum concentration of flecainide was measured in 17 cases at the time the conversion to sinus rhythm occurred. The concentration was measured again 7 h after conversion. In those cases which did not respond to treatment, the serum concentration was determined 7 h after the final oral dose. If sinus rhythm was not restored 48 h after treatment was begun, the study was discontinued and the patient was treated conventionally by means of electrical cardioversion or with traditional anti-arrhythmic drugs.

STATISTICS

The statistical evaluation comparing the various parameters was conducted using the Student t test.

BLOOD SAMPLING

Blood samples were taken by means of venous puncture then centrifuged and the serum was frozen immediately. The serum concentration of flecainide was measured by means of gas-liquid chromatography. Reference samples were examined systematically at the same time as the plasma samples.

A reference curve was drawn up and used to determine the flecainide concentrations. The sensitivity limit of the method is 10 ng ml^{-1}.

Results

Conversion to sinus rhythm was achieved in 36 patients (72%) (29 cases of atrial fibrillation, 4 cases of SV tachycardia, 2 cases of atrial flutter and one case of Wolff–Parkinson–White syndrome). In 19 cases, the restoration of sinus rhythm occurred after the first or after the second injection (Table 1). Nine patients had received an alternative anti-arrhythmic treatment before their inclusion in the study (Table 2). Of the 14 patients not converted, 4 were converted by electrical cardioversion. In the 6 remaining patients the rhythm disorder persisted either after the failure of drug treatment (4 cases) or after failure of electrical cardioversion (2 cases), (Table 2).

DURATION OF THE ARRHYTHMIA

The duration of the rhythm disorder was 5.3 ± 9.8 days in the group of patients converted, and 16.7 ± 26.2 days in the group not converted ($P < 0.01$). One should note that 11 patients (79%) in the group not converted had arrhythmias which had persisted for more than 1 day. There were 15 (42%) such patients in the group converted. In 7 cases (50%) of those not converted, the arrhythmia had lasted for 1 week or more: in the group converted, there were only 6 cases (17%). In all the cases of flutter, the arrhythmia had lasted for less than 7 days.

HEART MEASUREMENTS

The mean cardiothoracic index on a standard chest radiograph was 0.53 ± 0.08 in the group not converted, and 0.48 ± 0.07 in the group converted ($P < 0.05$). The size of the left atrium was not measured in all cases, but in fact only patients in whom an echocardiogram was essential underwent this examination. Nevertheless, the size of the left atrium was 40 ± 11 mm in the group converted, and 46 ± 11 mm in the group not converted (difference not statistically significant).

AETIOLOGY OF THE ARRHYTHMIA

There was no predominant cardiac pathology in either of the two groups. However, we established

Table 1   Data for patients converted and not converted

Patient	Age (years)	Sex	Diagnosis (cardiac) (disease)	Arrhythmia	Diameter of left atrium (mm)	Duration of arrhythmia (days)	Cumulative dose (mg kg^{-1})*	Side-effects	Time before conversion	Cardiac index
Patients converted										
1	54	F	none	flutter	—	1	1·9	—	15 min	0·55
2	72	F	peric.	AF	34	1	7·5	sino-atrial block	16 h	0·51
3	60	M	none	AF	32	1	4·2	—	14 h	0·43
4	38	M	MVP	SVT	30	1	0·7	—	5 min	0·45
5	66	F	IHD	AF	—	1	0·85	—	5 min	0·47
6	78	F	IHD, HHD	AF	—	?	9·5	—	24 h	0·56
7	61	M	none	flutter	—	4	2·7	—	16 h	0·39
8	36	M	none	W–P–W	32	2	0·68	—	2 min	0·46
11	75	M	none	AF	—	1	1·16	—	5 min	0·44
13	80	M	VHD	AF	—	1	1·11	—	25 h	0·47
15	85	M	none	AF	—	1	5·3	—	14 h	0·51
16	72	M	none	AF	43	1	2·5	hyperthermia	3 h	0·48
17	84	F	none	SVT	—	1	0·77	LBBB	5 min	0·53
18	93	F	HHD	AF	—	1	3·6	RBBB	12 h	0·52
19	58	M	IHD	AF	44	21	0·59	—	5 min	0·51
20	68	M	MVP	AF	33	1	2·6	—	6 h	0·51
22	55	F	VHD	AF	68	2	1·72	nausea	10 min	0·78
24	65	F	VHD	SVT	56	3	4·6	optical dis.	24 h	0·50
27	67	M	none	AF	—	1	1·52	—	10 min	0·48
28	92	F	HHD	AF	—	12	3·1	—	16 h	0·50
30	37	M	none	AF	—	1	0·7	—	5 min	0·44
31	62	F	none	AF	—	45	3·51	—	7 h	0·46
32	64	M	IHD	AF	—	1	0·63	—	5 min	0·48
33	57	M	IHD	AF	—	1	0·85	—	5 min	0·41
35	75	F	none	AF	—	4	3·33	—	26 h	0·50
36	38	M	none	AF	—	1	0·79	—	5 min	0·45
38	55	M	none	AF	47	28	3·85	—	24 h	0·35
39	55	M	none	SVT	—	1	0·80	—	30 min	0·48
40	56	F	HHD	AF	42	1	0·63	bradycardia	5 min	0·56
42	62	M	peric. IHD	AF	36	10	9·0	—	19 h	0·50
43	58	M	none	AF	—	?	4·44	—	6 h	0·46
44	52	M	MVP	AF	43	20	0·46	—	7 min	0·45
46	51	M	none	AF	—	1	0·63	—	5 min	0·41
47	74	F	none	AF	28	?	4·7	—	12 h	0·47
48	72	F	CCM	AF	—	3	1·33	—	15 min	0·56
50	68	M	IHD	AF	36	1	1·11	—	15 min	0·44

Mean values	63·7 ± 14				40 ± 11	5·34 ± 9·8	2·59 ± 2·36	7·4 ± 9·2 h	0·48 ± 0·07
Patients not converted									
9	77	M	none	AF	38	10	7·5	none	0·43
10	56	M	VHD	AF	60	10	7·3	none	0·52
12	62	F	VHD	AF	54	21	8·3	none	0·55
14	78	M	none	flutter	—	1	9·4	none	0·42
21	82	F	IHD	AF	30	5	8·6	none	0·64
23	62	F	OHCM	AF	36	2	5·7	none	0·69
25	54	F	VHD	AF	62	21	10·5	none	0·62
26	57	F	VHD	flutter	32	3	9·3	none	0·54
29	53	M	CCM	AF	42	90	7·9	none	0·51
34	68	M	IHD	AF	51	3	10·9	nausea	0·49
37	49	M	CCM	AF	50	7	8·6	nausea	0·55
41	55	M	MVP	AF	57	60	7·8	none	0·42
45	78	M	none	flutter	—	1	10·3	none	0·55
49	65	M	VHD	flutter	—	1	3·5	none	0·52
Mean values	64 ± 11				46 ± 11	16·7 ± 26·2	8·26 ± 1·96		0·53 ± 0·08

*Cumulative dose before reduction for 'patients converted' and total cumulative dose for 'patients not converted'.

Abbreviations: AF — atrial fibrillation, VHD — valvular heart disease, IHD — ischemic heart disease, HHD — hypertensive heart disease, CI — cardiothoracic index, CCM — congestive cardiomyopathy, OHCM — obstructive hypertrophic cardiomyopathy, MVP — mitral valve prolapse, LBBB — left bundle branch block, RBBB — right bundle branch block, SVT — supraventricular tachycardia.

Table 2   Other treatment prescribed to try to achieve cardioversion

Patient	Treatment tried before the study and results		Treatment tried after failure of flecainide and results	
30	disopyramide	negative	responded to flecainide	
43	quinidine	negative		
44	quinidine	negative		
48	disopyramide, verapamil	negative		
9	quinidine, verapamil, disopyramide	negative	amiodarone	positive
10	quinidine	negative	electrical cardioversion	positive
12	quinidine	negative	electrical cardioversion	positive
14	none		disopyramide	positive
21	quinidine	negative	none	
23	verapamil	negative	disopyramide	negative
			amiodarone	positive
25	none		amiodarone	negative
26	none		amiodarone	negative
			electrical cardioversion	positive
29	none		amiodarone, quinidine	negative
			electrical cardioversion	negative
34	none		amiodarone, procainamide, quinidine	negative
			electrical cardioversion	positive
37	none		amiodarone, quinidine	negative
			electrical cardioversion	negative
41	none		amiodarone, quinidine	negative
			sotalol + lignocaine	positive
45	none		quinidine, amiodarone	negative
49	none		beta-blocker	negative

that in the group of patients not converted only 3 patients (21%) did not exhibit organic heart disease. In the group of patients converted there were 18 patients without organic heart disease, i.e. 50%. There was no difference between the two groups as regards the age of patients

OTHER TREATMENT

No patient received any other anti-arrhythmic drug for the duration of the study. Twelve patients (85%) were digitalized in the group of those not converted, and 22 patients (61%) received digitalis in the group of converted patients. One female patient was under treatment with a beta blocker for obstructive cardiomyopathy. Moreover, she did not respond to the treatment.

DOSE AND DOSAGE OF FLECAINIDE

The cumulative doses of flecainide before conversion were $2 \cdot 59 \pm 2 \cdot 36$ mg kg^{-1} in the group of patients converted, and $8 \cdot 26 \pm 1 \cdot 96$ mg kg^{-1} in the group of those not converted. The concentration of flecainide at the time of conversion was 402 ± 427 ng ml^{-1}. Seven hours after conversion this concentration was $363 \cdot 6 \pm 195$ ng ml^{-1}. In the group of patients not converted 7 hours after the

last oral dose, the mean concentration was $386 \cdot 8 \pm 205$ ng ml^{-1} (difference not significant).

SIDE-EFFECTS

Side-effects attributable with certainty to the drug were observed in 9 patients (Table 1). One patient exhibited hyperthermia with no apparent cause on the day after treatment was initiated. Although it was impossible to attribute this with any certitude to flecainide, the treatment was terminated.

The drug had to be discontinued in 5 patients (10%): in 2 cases due to the occurrence of bundle branch block, in 2 cases due to the occurrence of a 2nd-degree sino-atrial block type II, and in one case of hyperthermia already referred to. In the 4 remaining patients, the side-effects disappeared after 2 days of treatment. We agree that it is advisable not to administer flecainide to patients exhibiting conduction disorders. Apart from conduction disorders, the side-effects are not very frequent and only necessitate termination of treatment in exceptional cases.

Discussion

EFFICACY

Our results show that flecainide is an effective

drug for the conversion of supraventricular arrhythmias to sinus rhythm, in particular for atrial fibrillation with a success rate of 75% and for junctional tachycardias with a success rate of 100%. The rate of conversion achieved for atrial fibrillation and SV tachycardia is higher than with other anti-arrhythmic drugs[11−15] used singly. An excellent association described by Stern[20] is that combining beta blockers with quinidine. Treatment with beta blockers is, however, not always possible in patients who are in the majority of cases elderly, and in addition, the side-effects of quinidine are quite frequent and sometimes inconvenient, and quite often necessitate termination of treatment.[15,26].

In these studies, moreover, the duration of the atrial fibrillation is not always reported, whilst in our study it was short, and it has been shown that the duration of the atrial fibrillation[18] is one of the principal factors in achieving conversion to and maintenance of sinus rhythm. Kayden *et al.* and Fenster *et al.*[16,17] have also recorded that for fibrillation which has persisted for more than 15 days the conversion rate was notably lower than for that which had lasted less than 15 days. Our results are in agreement with this, although there was no statistically significant difference. We converted 79% of fibrillations which had appeared less than 15 days before and only 64% of those which had appeared more than 15 days before. In addition, our group of patients undoubtedly includes some in whom the rhythm disorder would have been paroxysmal and which would have reverted spontaneously. In particular, atrial fibrillation is paroxysmal in 9 to 35% of those free from organic heart disease. Only 1/3 of these patients will develop persistent atrial fibrillation[19]. It is, however, impossible to predict with certainty which patient will develop transitory arrhythmia. With regard to SV tachycardia, although the number of cases is small, the efficacy of flecainide is noteworthy because all the patients were converted. This is in agreement with Hellestrand *et al.*[9]. In the case of atrial flutter, although the number of cases is again small, efficacy does not appear to be as good because the success rate is only 33%, and the duration of the arrhythmia does not appear to play any part. Studies involving a larger number of patients are necessary to determine whether flecainide is ineffective in converting atrial flutter or whether the low success rate is attributable to the small number of cases. One should also note that of the 14 patients who did not

respond to treatment, only 4 were converted by other anti-arrhythmic drugs and in the converted group that 4 patients had received a different anti-arrhythmic agent without success, before being converted with flecainide.

A crucial problem in our study was to estimate the relative proportion of spontaneous conversion and conversion by flecainide. In the 19 patients who were converted within 3 h, conversion could be attributed to flecainide. In the 17 remaining patients it is impossible to tell whether conversion was spontaneous or not. For the 10 patients in whom arrhythmia was present for more than one day it is highly probable that the drug was efficacious. In the 7 other patients, the delay before conversion is long compared to the duration of the arrhythmia: we cannot therefore prove that the conversion was not spontaneous, particularly in patient number 24, who presented with SVT, an arrhythmia which is usually quickly converted by drugs.

AETIOLOGY

There was no type of heart disease represented more frequently in the group of patients who responded to treatment than in that which did not. One significant difference is that patients without organic heart disease are clearly more numerous in the group converted. It is known that atrial fibrillation is more difficult to convert and recurs with greater ease if organic heart disease is present[21]. We might comment that the patients converted had a cardiothoracic index significantly lower than the patients not converted. Sandøe *et al.*[22] earlier described how patients with a heart volume of less than 500 ml m^{-2} were more likely to be converted than those with a volume greater than 700 ml m^{-2}.

Although not all of the patients had an echocardiogram, we nevertheless studied the size of the left atrium, which was smaller in the group of patients converted than in the group not converted. This difference is not, however, statistically significant. Fenster *et al.*[16], Halpern *et al.* and Henry *et al.*[23,24] have similarly shown that the size of the left atrium is one of the important factors in determining the possibility of converting atrial fibrillation to sinus rhythm and maintaining it.

PLASMA CONCENTRATIONS

The mean serum concentrations which we observed were within the normal range of those usually recognized for ventricular arrhythmias, namely from 200 to 1000 ng ml^{-1}[25] and the

concentration in patients not converted were even higher than those of patients converted. Thus it is unlikely that the patients not converted received insufficient flecainide. The doses we used therefore seem to be quite adequate. The doses, calculated cumulatively and averaged by bodyweight in kg, were 2.59 ± 2.36 mg kg^{-1}. The mean time required, 7.4 ± 9 h, shows that the conversion is usually quite rapidly achieved. No case was converted after 26 h, and this makes us think that if the arrhythmia persists after 1 day of treatment, it is pointless persisting in attempting to convert it using flecainide.

Conclusion

We conclude that flecainide is a fast-acting drug for the conversion to sinus rhythm of patients exhibiting SV tachycardia or atrial fibrillation of recent onset. Its efficacy is especially good if there is no underlying heart disease, if the arrhythmia has only been in existence a short time, if the cardiothoracic index is normal and if the size of the left atrium is normal. This treatment is particularly useful in people who cannot undergo electrical cardioversion or for whom quinidine is contraindicated. Its efficacy in cases of flutter has yet to be evaluated.

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