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Effect of quinidine on maintaining sinus rhythm after conversion of atrial fibrillation or flutter
A multicentre study from Stockholm

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In a controlled study comprising 176 patients, quinidine in the form of Kinidin Durules was found to reduce significantly the recurrence of atrial fibrillation during a 1-year follow-up period after successful electric shock conversion. After one year, 51 per cent (52/101) of the patients in the quinidine group, and 28 per cent (21/75) in the control group remained in sinus rhythm ($P < 0.001$). No less than 43 per cent of the patients converted to sinus rhythm during treatment with maintenance doses of quinidine sulphate before intended DC conversion. Gastrointestinal side-effects were not uncommon, and caused interruption of quinidine treatment in some cases.

The introduction of electric shock conversion to sinus rhythm, little more than a decade ago (Lown, Amarasingham, and Neuman, 1962), provided an effective method of treating various arrhythmias. In the majority of countries, electric conversion has replaced quinidine conversion of atrial fibrillation since the former is more effective and less hazardous.

The outstanding problem is how to prevent recurrence of fibrillation after conversion. Among various drugs which have been used for this purpose, quinidine has gained the widest acceptance. The value of quinidine is, however, a subject of controversy. Korsgren *et al.* (1965), Rossi and Lown (1967), and Cramér (1968) found quinidine to be effective while, for example, Oram and Davies (1964), Halmos (1966), Hall and Wood (1968), Gunning *et al.* (1970), and Waris, Kreus, and Salokannel (1971) decided it was not. Some authors also consider that the risks of quinidine treatment are so great that it is doubtful whether quinidine should be used prophylactically to prevent a recurrence of arrhythmia after conversion (Oram and Davies, 1964; Radford and Evans, 1968; Åberg, 1969).

With the exception of two investigations published since the beginning of the present study (Härtel *et al.*, 1970; Hillestad *et al.*, 1971), the majority of previous investigations have comprised a limited number of patients, have lacked suitable control groups, and have involved the use of rapidly disintegrating quinidine tablets. Pharmacokinetic studies suggest that in order to maintain adequate and constant concentrations of quinidine in the blood, quinidine should be administered in the form of sustained release tablets (Cramér, Varnauskas, and Werkö, 1963; Török *et al.*, 1970).

In view of this background, a controlled investigation was started in 1969 to 1970 in order to establish the value of quinidine for the maintenance of sinus rhythm after conversion of atrial fibrillation. In order also to investigate whether treatment with quinidine influences the result of DC conversion, the patients were randomly allocated to a quinidine group or an untreated control group before conversion.

By performing the investigation in the form of a multicentre study, with several Stockholm hospitals participating, it was possible to obtain a sufficiently large number of patients within a reasonable period of time.

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Subjects and methods

The material comprises consecutive patients admitted to hospital for conversion of chronic atrial fibrillation or flutter. The primary criteria for exclusion of patients from the study were the following:

1) Paroxysmal atrial fibrillation.

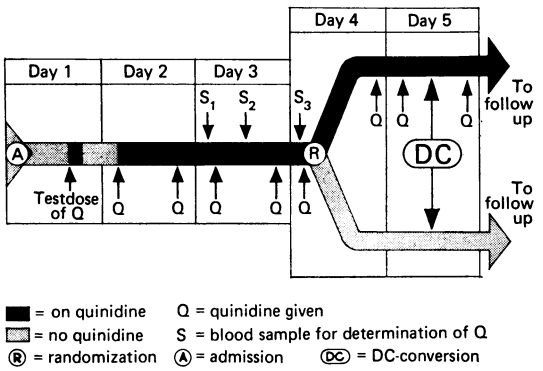

FIG. 1 *Inpatient routine.*

2) Known duration of atrial fibrillation of more than 36 months.
3) Relative heart volume > 700 ml/m² body surface area.
4) Previous history of intolerance to quinidine.

Altogether 211 patients participated in the study, of whom 198 had atrial fibrillation and 13 had atrial flutter. One hundred and forty-four (68%) were men and 67 women. The mean age was 58 years (range 24 to 78 years).

The patients were admitted to hospital and followed the schedule shown in Fig. 1. On the first day, a test dose of 0.2 g quinidine sulphate was given. On days 2 and 3, and in the morning of day 4, maintenance doses of quinidine were given in the form of Kinidin Durules,[1] 3 tablets b.i.d. to patients less than 80 kg, and 4 tablets b.i.d. to those 80 kg or over. Irrespective of whether conversion to sinus rhythm occurred with the maintenance dose of quinidine, the patients were randomly allocated on day 4 to a group receiving continued quinidine treatment and an untreated control group. Patients who did not convert to sinus rhythm on the maintenance dose of quinidine were subjected to DC conversion on day 5. Patients in the control group had then been without quinidine for approximately 30 hours. Digitalis therapy was generally interrupted at least two days before DC conversion.

Blood samples for determination of quinidine were drawn on the morning of days 3 and 4 before the morning dose of quinidine was taken, and also four hours after the morning dose on day 3. The serum determinations were performed at two of the hospitals. The same method (Udenfriend, 1962; modified after Hamfelt and Malers, 1963) was used, and control with double samples showed good agreement between the two laboratories.

Conversion was performed with a synchronized DC defibrillator and the energy increased as required, generally stepwise from 100 up to 300 joules. The patients were given a light anaesthetic.

The indications for anticoagulant treatment varied between the hospitals, and anticoagulants were given for at least three weeks before admission to hospital in 40 per cent of the patients.

The patients underwent follow-up outpatient examinations with electrocardiographic control after 1, 3, 6, and 12 months if sinus rhythm persisted or until recurrence of atrial fibrillation was recorded at the check-up. In the event of side-effects being so severe that the patient had to discontinue treatment with quinidine or reduce the dose by more than 0.4 g per day, the patient dropped out of the study. A thorough history concerning side-effects was also taken at these visits. The fate of the few patients not coming to the outpatient clinics for check-ups was investigated by contact with appropriate parish office, where in Sweden a register of births, deaths, and other personal data is kept.

Within the framework of the large investigation a small crossover study on patients in the control group who suffered recurrence of fibrillation during the follow-up period was also performed. These patients were readmitted to hospital, converted once again, and now placed on prophylactic quinidine therapy. The patients were submitted to control examinations after 1, 3, 6, and 12 months.

Results

1) Initial quinidine treatment in hospital

During initial treatment with quinidine in hospital 91 patients (43%) converted to sinus rhythm. One of these patients died suddenly.[1] In a further 8 patients quinidine treatment was discontinued because of syncope (1 patient), ventricular ectopic beats with bigeminy (1 patient), and diarrhoea (6 patients). Of these 6 patients, 4 also had pyrexia.

Two patients suffered early recurrence of atrial fibrillation during their stay in hospital, and were, therefore, excluded from the study.

Eighty patients in sinus rhythm proceeded to the follow-up outpatient phase of the study.

[1] Hässle; containing 0.25 g quinidine bisulphate – equivalent to 0.2 g quinidine sulphate.

[1] A 70-year-old woman, with a history of hospital treatment of chest pain one year previously, was on diuretics and methyldopa because of hypertension. After a fortnight's history of pyrexia and myalgia, for which she had been given tetracycline, she was admitted to hospital because of central chest pain. On admission she was in cardiac failure, and the rhythm was atrial fibrillation with rapid ventricular rate (120/min). The blood pressure was 180/100 mmHg (23.9/13.3 kPa). A chest *x*-ray revealed a few scattered opacities and slight cardiac enlargement. The electrocardiogram confirmed the arrhythmia and showed left anterior hemiblock. Enzyme series excluded acute myocardial infarction and the patient made a rapid recovery. The diagnosis was a viral infection, and conversion of her atrial fibrillation was decided upon. Two weeks after admission, quinidine therapy (see above) was started and on the following day she was in sinus rhythm and digitalis therapy was instituted. The patient was found dead in her bed the following morning.

Necropsy revealed moderate subendocardial fibrosis and only minimal signs of coronary artery disease. There were no signs of recent myocardial infarction or myocarditis.

TABLE 1 *Quinidine serum concentrations during inpatient routine*

		Quinidine concentration (mg/l)			
		Sample 1	*Sample 2*	*Sample 3*	*No.*
Patients in sinus rhythm after initial quinidine	Mean	2.91	3.92	3.28	57
	SEM	0.2	0.2	0.2	
Patients still in atrial fibrillation after initial quinidine	Mean	2.85	3.83	3.19	72
	SEM	0.1	0.2	0.2	

Before starting maintenance treatment with quinidine, the patients received a test dose of 0.2 g quinidine on day 1. No patient showed any signs of intolerance to this dose. The value of giving a small test dose of quinidine may, therefore, be debated.

No differences in serum concentrations of quinidine were found between patients who converted to sinus rhythm and those in whom atrial fibrillation persisted after initial quinidine treatment (Table 1).

2) DC conversion

Atrial arrhythmia persisted in 120 patients after initial quinidine treatment. Three of these patients were excluded because of diarrhoea probably related to the drug given. Conversion was attempted in the remaining 117 patients.

Sinus rhythm was restored in 99 patients (85%) while atrial arrhythmia persisted in 18 patients, who were therefore excluded from the study. In the group who converted to sinus rhythm, 3 patients were excluded because of the presence of arrhythmias considered to be contraindications to continued treatment with quinidine. Two of these had periods of atrioventricular block, in one case combined with nodal rhythm; the other developed a transient bundle-branch block.

Thus, 96 patients with sinus rhythm proceeded to the follow-up outpatient phase of the study.

No difference was found between the group treated with quinidine and the untreated group, as regards the energy required for conversion or the occurrence of benign arrhythmias at the time of conversion.

3) Outpatient follow-up

One hundred and seventy-six patients participated in the follow-up phase: 101 of these had been randomly allocated to treatment with quinidine, and 75 to the untreated control group. There were 13 patients with atrial flutter, 9 in the quinidine group. Other clinical data concerning these two groups are presented in Tables 2 to 5.

TABLE 2 *Clinical data for 176 patients participating in follow-up phase*

	Quinidine group	*Control group*
No. of patients	101	75
Men/women	78/23	47/28
Mean age (yr)	58	56
Relative heart volume (ml/m^2), mean values	527	546

TABLE 3 *Diagnoses of patients participating in follow-up phase*

	Quinidine group	*Control group*
Mitral valve disease	10	15
Mitral valve disease operation	9	13
Aortic valve disease	2	1
Other valve disease	3	1
Myocardial infarction	2	3
Ischaemic heart disease	34	18
Hypertension	9	6
Thyrotoxic disease	8	2
Alcohol cardiomyopathy	10	4
Myocarditis (verified or suspected)	9	3
Unknown or uncertain	5	9
Total	101	75

TABLE 4 *Functional groups (NYHA)* before conversion*

	Quinidine group		*Control group*	
	No.	%	*No.*	%
Group 1	32	32	21	28
2	63	62	44	59
3	6	6	9	12
4	—	—	1	1
Total	101	100	75	100

* New York Heart Association.

TABLE 5 *Duration of atrial arrhythmia before conversion*

	Quinidine group		*Control group*	
	No.	%	*No.*	%
< 1 mth	24	24	19	25
1–3 mth	35	34	24	32
4–6 mth	21	21	12	16
7–12 mth	10	10	14	19
> 12 mth	11	11	6	8
Total	101	100	75	100

The mean age in the quinidine group was 58 ± 8.5 years (range 24 to 78 years) and in the control group 56 ± 10.0 years (range 29 to 74 years). The quinidine group comprised 78 men and 23 women, and the control group 47 men and 28 women. Thus, the proportion of women was higher in the control group than in the quinidine group.

Mitral valve disease was more common in the control group than in the quinidine group. In the quinidine group, 7 had mitral regurgitation, 3 mitral stenosis, and 9 had undergone successful valvotomy. In the control group 7 patients had mitral regurgitation, 8 had mitral stenosis, 12 had undergone succesful valvotomy and in one, a mitral valve prosthesis had been inserted. There were relatively few patients with thyroid disease, alcoholic cardiomyopathy, and myocarditis in both groups but there were slightly more in the quinidine group.

The distribution with respect to functional groups (Table 4) was largely similar in the quinidine and control groups. Nor was there any great difference between the groups as regards the duration of atrial arrhythmia before conversion (Table 5). The same proportion of patients had been treated with digitalis or diuretics in the two groups. The relative heart volume in the quinidine group was 527 ± 86 (range 320–690) ml/m^2, and in the control group 546 ± 94 (range 330–690) ml/m^2.

Of the patients in the quinidine group, 24 per cent had previously been treated with DC conversion compared to 19 per cent in the control group.

Fig. 2 shows the number of patients in the quinidine and control groups, respectively, who remained in sinus rhythm after 1, 3, 6, and 12 months. At the 12-month examination there was a significant difference in favour of quinidine (Table 6). The difference still persists if patients who suffered a recurrence of atrial arrhythmia or who were excluded from the study during the follow-up period because of side-effects are added to the quinidine group.

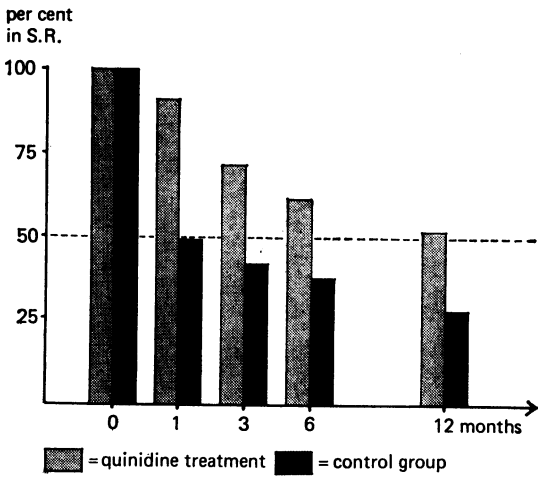

FIG. 2 *Percentage of patients still in sinus rhythm after 1, 3, 6, and 12 months.*

4) Complications during follow-up period

Two patients in the control group died during the follow-up period, 4 and 5 months, respectively, after discharge from hospital in sinus rhythm. The causes of death were myocardial infarction and cerebral vascular lesions, respectively. Three patients dropped out during the follow-up but all were alive more than 12 months after discharge from hospital.

Five patients in the quinidine group died during the follow-up period. None of these deaths was ascribed to quinidine (Table 7). Six patients in the quinidine group dropped out during the follow-up period but all were alive more than 12 months after discharge from hospital. A further 3 patients in the

TABLE 6 *Number of patients in sinus rhythm and atrial fibrillation after 12 months in quinidine and control group, respectively*

	Sinus rhythm	*Atrial fibrillation*
Quinidine group	52	23
Control group	21	49
	P < 0.001	
Quinidine group	52	35*
Control group	21	49
	P < 0.001	

* Includes patients excluded because of side-effects.

TABLE 7 *Reasons for exclusion during follow-up phase in quinidine group*

Deceased (5 patients)	Myocardial infarction
	Hepatic coma
	Renal cancer
	Reticular cell sarcoma
	Pneumonia
Unwanted effects (12 patients)	Diarrhoea (9)
	Allergic reaction
	Vertigo
	Ventricular ectopic beats
Lost during follow-up (6 patients)	All patients alive more than 12 months after study
Other reasons (3 patients)	Psychiatric disease
	Phenytoin treatment
	Dose reduction without medical reasons

quinidine group were excluded during the follow-up period for other reasons: one patient was given phenytoin, in one the dose of quinidine was reduced without medical indication, and one patient developed a psychiatric condition.

5) Other side-effects during follow-up period

Twelve patients (12%) in the quinidine group interrupted treatment because of side-effects, usually diarrhoea. Side-effects were most frequent during the initial phase of the follow-up period. The quinidine dose was reduced by 0.4 g per day or less in 46 (46%) patients. Twenty-one of these reported diarrhoea, but in no less than 25 patients, the dose was reduced without medical indication.

6) Crossover study

Of the 49 patients in the control group who suffered recurrence of atrial arrhythmia during the follow-up period, 33 were discharged from hospital on quinidine after renewed conversion. Five of these were excluded from the study before the first examination, one month after discharge. Two patients were excluded because of diarrhoea, one because of fever and urticaria, and one because of tinnitus: these symptoms were considered to be caused by treatment with quinidine. One patient was excluded from the study because of a reduction of the dose of quinidine by more than 0.4 g without medical indication.

On examination after one month, 22 remained in sinus rhythm. Atrial arrhythmia had recurred in 6. After three months, atrial arrhythmia had recurred in 1 further patient. There was no recurrence of arrhythmia between three and six months. One year after discharge from hospital, 17 of the 33 patients in the control group who had been treated with quinidine remained in sinus rhythm (Fig. 3).

Discussion

Free randomization was employed in this study. This resulted in the quinidine group being larger than the control group.

Several factors have been suggested as being of importance with regard to maintenance of sinus rhythm after conversion of atrial flutter or fibrillation, namely duration of the arrhythmia, as shown for example by Bierkelund and Orning (1968) and Szekely *et al.* (1970b), the degree of myocardial injury assessed by heart volume and functional group, and the aetiology of the arrhythmia, as shown, for example, by Waris *et al.* (1971) and Resnekov and McDonald (1971). In the present investigation, the proportion of women was higher in the control group than in the group treated with quinidine; there is, however, no evidence in previous investigations that sex influences maintenance of sinus rhythm after DC conversion. As regards age, duration of arrhythmia, functional group, treatment of heart failure, and heart volume, there were no significant differences between the groups. Mitral valve disease was more common in the control group than in the quinidine group. Radford and Evans (1968) and Gunning *et al.* (1970) consider that this type of patient has a greater tendency to suffer recurrence of fibrillation, both with and without quinidine. In the present investigation, sinus rhythm persisted in only 12.5 per cent after one year in patients with mitral valve disease in the control group, irrespective of whether or not they had been operated upon, while 50 per cent of the patients in the quinidine group with mitral valve lesions remained in sinus rhythm after the same period of time. Quinidine was thus effective in preventing recurrence of fibrillation even in patients with mitral valve

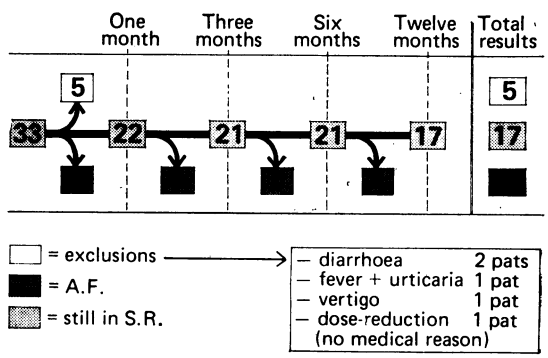

FIG. 3 *Results from crossover study.*

disease, so that the overrepresentation of such patients in the control group did not influence the results of the study as a whole (Table 3). Exclusion of this category of patients does not influence the statistically significant difference between the quinidine and control group.

This investigation thus shows that treatment with quinidine reduces the recurrence of atrial arrhythmia after conversion to sinus rhythm. These results are in agreement with previous studies (Korsgren *et al.*, 1965; Rossi and Lown, 1967; Lown, 1967; Härtel *et al.*, 1970; Byrne-Quinn and Wing, 1970; Hillestad *et al.*, 1971).

In the study by Härtel *et al.* (1970), as in the present investigation, Kinidin Durules were used, though usually in a dose equivalent to 0.8 g quinidine sulphate daily. Hillestad *et al.* (1971) used another long-acting quinidine preparation in a dose of 0.8 to 1.2 g daily, i.e. lower doses than those used in the present study. On the other hand, the dose was reduced by 0.2 to 0.4 g daily during the follow-up year in 46 per cent of the patients in the present study.

Conversion to sinus rhythm occurred in almost half the patients during their stay in hospital with only the maintenance dose of quinidine. Cramér (1968) reported a 62 per cent incidence of conversion in a Swedish series of 237 patients with atrial fibrillation. She gave considerably larger doses of quinidine, however, than the maintenance doses given in the present study. Cramér used quinidine sulphate tablets in doses up to 4.2 g per day, and Kinidin Durules up to 4.8 g per day. Härtel *et al.* (1970) found that 7 of 88 patients converted to sinus rhythm with quinidine tablets alone in a study of similar design to the present one, though using considerably lower doses.

The same mean concentration of quinidine in blood was found in patients who converted to sinus rhythm as in those who remained in atrial fibrillation on maintenance doses of quinidine in the present study. Thus, conversion to sinus rhythm is not explained by higher quinidine concentration in the blood.

Several factors have been discussed by previous authors as being conducive to successful conversion of atrial fibrillation but conclusions vary in different studies. Sandøe *et al.* (1965) stated that a relative cardiac volume below 500 ml/m^2 was favourable compared to a relative cardiac volume exceeding 700 ml/m^2. Patients with relative cardiac volumes exceeding 700 ml/m^2 were excluded from the present study. Cramér (1968) showed that a duration of atrial fibrillation of less than 6 months increased the likelihood of successful conversion. In the present study, patients with a duration of atrial arrhythmia of three years or more were excluded and approximately 75 per cent of the patients had had their arrhythmias for less than 6 months before the attempt at conversion. These criteria for inclusion of the patients in the study, and also possible selection of patients before referral to the participating hospitals for conversion, mean that the material is selected.

The results seem to indicate that the administration of quinidine before electroconversion had no effect on the success rate of conversion. This is in agreement with the results published by Hillestad, Dale, and Storstein (1972) and by Szekely *et al.* (1970a).

One patient treated with maintenance doses of quinidine in the present study died before being discharged from hospital. A not inconsiderable incidence of sudden deaths in patients with atrial fibrillation has been reported even without quinidine treatment (Cramér, 1968; Takkunen *et al.*, 1970). The possibility that quinidine influenced the fatal course in the patient in this material cannot, however, be excluded (see case history). None of the deaths during the follow-up period was sudden, and there is no reason to suspect that quinidine was the cause of these deaths. No patient had syncope or serious arrhythmia during the follow-up period. No deaths were reported in the studies by Härtel *et al.* (1970) or Hillestad *et al.* (1971). Sudden death not infrequently occurred with the use of high doses of quinidine for the purpose of conversion of atrial fibrillation (Cramér, 1968), and can probably also occur when moderate maintenance doses of quinidine are given. However, it seems to be rare, and it is doubtful whether treatment with quinidine is significantly more hazardous than with many other antiarrhythmic agents in widespread use.

In the present study, a slow release form of quinidine was used. Despite administration of only two doses daily, a constant blood concentration of quinidine without high peaks was achieved. This is in agreement with previous reports (Cramér *et al.*, 1963; Török *et al.*, 1970; Békés *et al.*, 1972). This factor appears to be responsible for the good results and for the low incidence of serious side-effects in the present study, as in that of Härtel *et al.* (1970) and Hillestad *et al.* (1971).

A relatively high incidence of gastrointestinal side-effects was reported in this study. All previous authors have reported side-effects of this type, though usually occurring less frequently. Platelets were not determined systematically in the patients during medication with quinidine in this study, but there was no case of bleeding in which thrombocytopenia was the possible cause. Few cases of allergic reactions were noted.

Crossover studies supporting the value of treatment with quinidine for prevention of recurrence of fibrillation after electric cardioversion have been performed by, for example, Resnekov *et al.* (1971). In the present study a nonsystematic crossover experiment was performed with 33 of the 49 patients from the control group in whom atrial fibrillation had recurred (Fig. 3). They were converted to sinus rhythm once more, but this time they left the hospital with prophylactic quinidine treatment. During the first month five were excluded from the study, two because of diarrhoea, one because of fever, one because of vertigo, and one because of a dosage reduction of more than 0.4 g without medical reason. Atrial fibrillation had recurred in six patients, while 22 were still in sinus rhythm. One year after discharge, 17 of the 33 patients in the control group who had been treated with quinidine remained in sinus rhythm.

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