Comparative efficacy of short-acting and long-acting quinidine for maintenance of sinus rhythm after electrical conversion of atrial fibrillation

J. P. Normand, M. Legendre, J. C. Kahn, J. P. Bourdarias, and A. Mathivat

From the Department of Cardiology, Hôpital Ambroise Paré, Université René Descartes (Paris V), France

Forty patients with chronic atrial fibrillation, apparently unrelated to any overt heart disease, were randomly allocated to two groups after restoration of sinus rhythm by direct current shock. The patients in group A were given 4 daily doses of quinidine polygalacturonate, while those in group B were given 2 daily doses of a long-acting quinidine preparation, quinidine arabogalactan sulphate.

The percentage of early relapses (within the first month following DC shock) was not significantly different in the two groups: 44.4 per cent in group A and 35 per cent in group B ($P > 0.50$). On the other hand, there were fewer late relapses with long-acting quinidine. After 18 months of treatment, 27.8 per cent of patients in group A remained in sinus rhythm, compared with 61 per cent in group B ($P < 0.05$).

The average amount of quinidine actually ingested by the patients in group A was smaller than that in group B. However, this could not entirely account for the difference observed in the incidence of relapse since with short-acting quinidine the proportion of patients remaining in sinus rhythm was similar whether the dose was decreased or not. The incidence of gastrointestinal side-effects was the same in the two groups and there were no serious complications that could be attributed to treatment.

It is concluded that long-acting quinidine preparations are more effective than conventional quinidine in preventing late relapses of atrial fibrillation.

While it is usually possible to reverse atrial fibrillation effectively and safely with direct current shock (DC shock) (Lown, 1967), it is more difficult to maintain sinus rhythm. The efficacy of quinidine in the prevention of relapse has been a subject of controversy and, in the opinion of several authors (Oram and Davies, 1964; Killip and Yormak, 1965; Halmos, 1966; Bjerkelund and Orning, 1968; Hall and Wood, 1968; Radford and Evans, 1968; Waris, Kreus, and Salokannel, 1971), this drug does not achieve better results than those observed in the absence of any treatment. However, recent studies by Byrne-Quinn and Wing (1970), Hartel *et al.* (1970), Szekely, Sideris, and Batson (1970), Hillestad *et al.* (1971), and Sodermark *et al.* (1975) have shown the efficacy of long-acting quinidine preparations in preventing relapse. These authors were led to this conclusion by the comparison of two groups of patients, one of which was treated with quinidine and the other with a placebo.

The purpose of this work was to compare the results obtained, after DC shock, by maintenance therapy with either long-acting or short-acting quinidine.

Subjects and methods

The trial was prospectively conducted in a group of 40 patients admitted to hospital with atrial fibrillation, in whom sinus rhythm had been restored with DC shock (Mathivat, Clément, and Marie-Louise, 1963). In all cases, the arrhythmia had been present for at least 15 days.

The group comprised 29 men and 11 women whose ages ranged from 46 to 81 years, with a mean age of 60.7 years. The arrhythmia had been present for periods ranging from 15 days to 5 years, with a mean duration of 6.4 months. Seven patients had previously undergone one or more conversions by DC shock: in these sinus rhythm had persisted for a mean duration of 3.7 years (range: 7 months to 6 years).

In 26 cases, atrial fibrillation was 'lone'; the patients did not have angina, valve disease, high blood pressure,

FIG. 1 Distribution of patients in each group according to age, sex, body weight, blood pressure, cardiothoracic ratio (CTR), and heart failure (HF).

electrocardiographic abnormalities suggestive of coronary heart disease, or significant enlargement of the heart (McCarthy, Varghese, and Barritt, 1969). In the remaining 14 cases, the cardiothoracic ratio was greater than 0.55 (from 0.56 to 0.70) in 12 and the blood pressure was above 160/100 mmHg (21.3/13.3 kPa) in 2. The arrhythmia had resulted in congestive heart failure in 12 cases.

Digitalis therapy had been discontinued at least 8 days before DC shock and no patient had been given quinidine before conversion. The patients were randomly allocated to two groups, A and B. After DC conversion, those in group A were given quinidine polygalacturonate¹ in a

daily dose of 1.1 g (one 0.275 g tablet every 6 hours). The patients of group B received a long-acting quinidine preparation (quinidine arabogalactan sulphate²) in a daily dose of 1.1 g, given in two doses (two 0.275 g capsules every 12 hours). The dosage in both régimes corresponds to 0.660 g quinidine base daily. According to Renais, Scebat, and Lenègre (1971), the blood quinidine levels obtained with the two types of quinidine preparation used in the present work are comparable at equal dosage. With a daily dose equivalent to 0.660 g quinidine base, the mean serum quinidine level is around 3 µg/ml (determination by the method of Brodie and Udenfriend, 1943).

¹Cardioquine (Laboratory Nativelle).

²Longacor (Laboratory Nativelle).

FIG. 2 Distribution of patients according to duration of atrial fibrillation (AF), heart rate (HR), aetiology (lone AF in contrast to other patients), amplitude of f wave, energy of DC shock, and previous cardioversion.

FIG. 3 Maintenance of sinus rhythm in whole series (38 patients).

All patients had daily clinical and electrocardiographic examination during the week following the DC shock. After leaving the hospital, they were examined every 3 months for 18 months or until atrial fibrillation recurred. An electrocardiogram was recorded at each visit. No patient was lost to follow-up.

After randomization, 20 patients were included in group A and 20 in group B. For 2 patients, originally in group A, conventional quinidine was replaced by the long-acting preparation after a 15-day and a 6-month treatment period. The change in treatment was made, independently of the result obtained, by the patient's personal physician who was unaware that the choice of the quinidine preparation had been made by randomization. These two patients were still in sinus rhythm when treatment was changed. These two patients were excluded when the results were analysed.

There was no significant difference between the two groups with respect to: age, sex, weight, systolic and diastolic blood pressure, heart rate before DC shock, cardiothoracic ratio, duration of atrial fibrillation, amplitude of *f* waves on the electrocardiogram, energy of the DC countershock, previous DC conversion, aetiology, and incidence of congestive heart failure (Fig. 1 and 2).

The results were expressed by plotting the percentage of patients remaining in sinus rhythm on the Y axis and the time elapsed since DC shock on the X axis. For a given time interval, the percentage of patients remaining in sinus rhythm was derived from the ratio of the number of patients remaining in sinus rhythm at the end of that time interval to the number of patients for whom the duration of follow-up was at least equal to this interval. In 1 case, the administration of long-acting quinidine was discontinued after 7 months even though sinus rhythm still persisted; this case was taken into account only for the assessment of results up to 6 months. One patient treated with long-acting quinidine

died after 4 months from intercurrent disease (haemorrhage due to alcoholic cirrhosis); he was included only for the estimation of the percentage of patients still in sinus rhythm up to 3 months.

Results

The results are shown in the Table and Fig. 3 for all patients and in the Table and Fig. 4 for groups A and B separately.

Overall, there was a large proportion of early relapses since only 60 per cent of patients remained in sinus rhythm after 1 month of treatment. These relapses took place between the 2nd and 25th days. After the first month the incidence of relapse was lower and the percentage of patients still in sinus rhythm at 18 months was 44 per cent.

56 per cent of patients in group A and 65 per cent of those in group B remained in sinus rhythm after 1 month of treatment. The difference was not significant ($P > 0.50$). On the other hand, the incidence of long-term relapse was lower in the group treated with long-acting quinidine: after 18 months of treatment, 61 per cent of patients in group B remained in sinus rhythm, compared with only 28 per cent in group A ($P < 0.05$).

Tolerance of treatment was comparable in the two groups: 1 patient in group A and 2 in group B complained of gastrointestinal symptoms. In one of the latter, the drug had to be discontinued; this was followed by immediate return of the arrhythmia.

Mean heart rate during the follow-up period was 65 ± 14 beats/minute in group A and 67 ± 9 beats/minute in group B. There was no significant

FIG. 4 Maintenance of sinus rhythm in the two groups of patients.

TABLE Effect of quinidine on maintenance of restored sinus rhythm

Follow-up (mth)	No. of patients	Sinus rhythm						Atrial fibrillation			% sinus rhythm			Standard deviation			
		A+B	A	B	A+B	A	B	A+B	A	B	A+B	A	B	A+B	A	B	P
≥1	38	18	20	23	10	13	15	8	7	60.5	55.6	65.0	7.9	11.7	10.7	>0.50	
≥3	38	18	20	23	10	13	15	8	7	60.5	55.6	65.0	7.9	11.7	10.7	>0.50	
≥6	37	18	19*	21	9	12	16	9	7	56.8	50.0	63.2	8.1	11.8	11.1	>0.40	
≥9	36	18	18†	19	8	11	17	10	7	52.8	44.4	61.1	8.3	11.7	11.5	>0.30	
≥12	36	18	18	18	7	11	18	11	7	50.0	38.9	61.1	8.3	11.5	11.5	>0.10	
≥15	36	18	18	16	5	11	20	13	7	44.4	27.8	61.1	8.3	10.6	11.5	<0.05	
≥18	36	18	18	16	5	11	20	13	7	44.4	27.8	61.1	8.3	10.6	11.5	<0.05	

*1 death at 4 months; †treatment discontinued in 1 patient after 7 months.

A, treatment with short-acting quinidine; B, treatment with long-acting quinidine.

P, significance of difference between A and B (% remaining in sinus rhythm).

difference between the two groups with regard to mean duration of QT interval (409 ± 51 ms in group A and 410 ± 33 ms in group B) or QU interval (614 ± 54 ms in group A and 614 ± 40 ms in group B).

The initial dose was reduced more often in group A (10 cases) than in group B (2 cases) ($P < 0.005$). In group A, the initial dose of 4 tablets of quinidine polygalacturonate daily was reduced to 3 tablets in 6 patients and to 2 tablets in 4 others. In 4 cases, the dose of quinidine had to be reduced because of quinidine toxicity (excessive prolongation of QT interval) demonstrated on the electrocardiogram; in the other cases, reduction of quinidine dose was decided either by the patient or by his personal physician because of the inconvenience of taking a tablet every 6 hours. In group B, quinidine dose was reduced to 2 capsules daily in 2 cases (on the patient's own initiative in 1 case and in order to adjust the dose to the patient's weight (39 kg) in the other).

Irrespective of the type of treatment, the percentage of patients still in sinus rhythm after 18 months was not significantly different whether dosage was decreased or not. Of the 10 patients in group A in whom dosage was reduced, 4 remained in sinus rhythm at 18 months, compared with 1 only of the 8 patients in whom dosage was unchanged, but the difference was not statistically significant ($P > 0.10$). In group B, the 2 patients in whom dosage was decreased remained in sinus rhythm at 18 months.

Discussion

The results of this trial suggest that long-acting quinidine is more effective than short-acting quinidine for the maintenance of sinus rhythm after DC conversion of atrial fibrillation. After 18 months of treatment, sinus rhythm persisted in 61 per cent

of patients taking long-acting quinidine compared with 28 per cent of those on the short-acting drug ($P < 0.05$). This difference is all the more significant as the choice of treatment was determined by randomization, and the two groups were comparable in all important respects (Fig. 1 and 2). In addition, both groups were relatively homogeneous, since atrial fibrillation was unaccompanied by overt heart disease in most cases.

One-third of the patients treated with short-acting quinidine reduced the dose initially prescribed because of difficulties in the practical conduct of treatment. As a result, the average amount of quinidine actually taken was lower in this group than in that treated with long-acting quinidine.

FIG. 5 Number of patients (%) remaining in sinus rhythm after DC conversion. Comparison with the published data in untreated groups.

However, this fact could not entirely account for the difference observed in the incidence of relapse, since with short-acting quinidine the maintenance rate of sinus rhythm was similar whether dosage was decreased or not. We did not determine blood quinidine levels systematically. Byrne-Quinn and Wing (1970) and Hillestad *et al.* (1971) were not able to find a correlation between blood quinidine levels and the incidence of relapse.

In this trial, the duration of maintenance of sinus rhythm obtained with short-acting quinidine was similar to that previously reported in the absence of any treatment (Fig. 5) (Radford and Evans, 1968; Byrne-Quinn and Wing, 1970; Gunning *et al.*, 1970; Szekely *et al.*, 1970; Hillestad *et al.*, 1971; Waris *et al.*, 1971; Sodermark *et al.*, 1975). At present the efficacy of this therapy in the prevention of relapse after reversion of atrial fibrillation is highly controversial. Indeed, results obtained vary from author to author, ranging from 40 to 68 per cent success rate at 1 year, and from 20 to 53 per cent at 2 years (Killip and Yormak, 1965; Jouve *et al.*, 1966; Morris, Peter, and McIntosh, 1966; Bjerkelund and Orning, 1968; Colin *et al.*, 1968; Hall and Wood, 1968; Waris *et al.*, 1971; Jacques *et al.*, 1973). Sokolow and Ball (1956) considered this therapy effective since, in their experience, relapse of arrhythmia occurred in 85 per cent of cases in the absence of treatment and in only 21 per cent with a daily dose of 1.6 g quinidine. Hurst *et al.* (1964) shared this opinion, for they observed 77 per cent of immediate relapse of atrial fibrillation after discontinuance of quinidine maintenance therapy. Similarly, Cramer (1968) found a lower incidence of relapse, both early and late, with a daily dose of quinidine equal to or exceeding 1.2 g. On the other hand, Oram and Davies (1964), Halmos (1966), Hall and Wood (1968), and Waris *et al.* (1971) found no significant difference between the results obtained with or without maintenance therapy with short-acting quinidine. It must be pointed out, however, that in none of these studies, whether favourable to the action of quinidine or not, were patients allocated randomly to quinidine or control groups, except that by Oram and Davies (1964).

Most recent comparative trials agree in acknowledging the efficacy of long-acting quinidine preparations in the maintenance of sinus rhythm after conversion of atrial fibrillation. Byrne-Quinn and Wing (1970), in a double-blind trial, obtained a success rate of 16 per cent after 15 months with placebo and 45 per cent with a long-acting preparation of quinidine bisulphate ($P < 0.01$). In another randomized trial, Hillestad *et al.* (1971) found that 15 per cent of patients subjected to DC shock remained in sinus rhythm after 1 year in the absence

of maintenance therapy, compared with 31 per cent of those given long-acting quinidine ($P < 0.05$). The difference was particularly clear cut when the onset of atrial fibrillation was less than 1 year previously. Szekely *et al.* (1970) also obtained a higher success rate with long-acting quinidine than without treatment, in an unrandomized trial. Korsgren *et al.* (1965) found a fairly definite correlation between the duration of the maintenance of sinus rhythm and the assiduity with which quinidine treatment was followed. Very recently, Sodermark *et al.* (1975) in a multicentre controlled study found that after one year 51 per cent of the patients in the quinidine treated group remained in sinus rhythm, compared with 28 per cent in the control group.

On the other hand, Resnekov *et al.* (1969) consider that long-acting quinidine provides no distinct benefit in maintaining sinus rhythm. These authors compared the duration of maintenance of sinus rhythm after two successive DC conversions in the same patients, without maintenance therapy after the first and with long-acting quinidine after the second conversion. It must be pointed out, however, that quinidine therapy was prescribed systematically after the second conversion and not in random order. In addition, mean duration of the maintenance of sinus rhythm observed in this trial suggests that the main goal of the authors was the prevention of the early relapse of the arrhythmia. Gunning *et al.* (1970) found no difference between the long-term results obtained with and without quinidine bisulphate in patients subjected to conversion of atrial fibrillation after cardiac surgery.

Like most authors (Killip and Yormak, 1965; Korsgren *et al.*, 1965; Halmos, 1966; Jouve *et al.*, 1966; Bjerkelund and Orning, 1968; Byrne-Quinn and Wing, 1970; Gunning *et al.*, 1970; Hillestad *et al.*, 1971; Sodermark *et al.*, 1975), we found a high incidence of relapse within the first month of DC shock. This incidence was lower with long-acting than with conventional quinidine (7 or 35% compared with 8 or 44%), but the difference was not significant. These results suggest that the efficacy of the long-acting preparation is reflected mainly in the prevention of long-term relapse; in particular, it was surprising to find that almost all patients who were given this preparation and were still in sinus rhythm after 1 month of treatment, remained so subsequently. In the group given conventional quinidine, the percentage of patients remaining in sinus rhythm decreased progressively after the first month. These findings are similar to those of Hillestad *et al.* (1971) but different from those of Byrne-Quinn and Wing (1970) and Hartel *et al.*

(1970) who found that long-acting quinidine also prevented short-term recurrence.

Some authors have abandoned the use of quinidine to prevent relapse of atrial fibrillation because of the risk of sudden death (Oram and Davies, 1964; Killip and Yormak, 1965; Bjerkelund and Orning, 1968; Radford and Evans, 1968; Waris *et al.*, 1971). This drug is well known for its capacity to induce serious ventricular arrhythmias (Thomson, 1956) and the incidence of these is thought to be directly related to blood quinidine levels (Sokolow and Ball, 1956; Bjerkelund and Orning, 1968). We have observed no such arrhythmias, but had to decrease the dose of conventional quinidine in four cases because of the appearance of a conspicuous quinidine effect on the electrocardiogram. We observed no electrocardiographic changes of this type with long-acting quinidine, because this preparation makes it possible to obtain comparatively stable blood quinidine levels without unduly high peak concentration (Renaiss *et al.*, 1971; Salvador *et al.*, 1971). Similarly, Gunning *et al.* (1970), Hartel *et al.* (1970), and Hillestad *et al.* (1971), had no deaths that could be attributed to long-acting quinidine. However, Byrne-Quinn and Wing (1970) mentioned a case of sudden death in the course of treatment: it was not proved that this was related to therapy, as it occurred in a patient with severe ischaemic heart disease, though the previous finding of a high blood quinidine level suggests that it may have been. Thus, though accidents seem to be rarer with long-acting quinidine, they nevertheless remain possible.

In conclusion, it follows from this work that long-acting quinidine preparations have several advantages over conventional quinidine. They are more effective in maintaining sinus rhythm after conversion from atrial fibrillation. The convenience of twice daily administration results in their being more readily accepted by patients who therefore follow their treatment more regularly. Lastly, they may reduce the risk of serious arrhythmias by avoiding sharp rises to very high peak levels.

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Requests for reprints to J. P. Normand, Hôpital Ambroise-Paré, 9 Avenue Charles-de-Gaulle, 92100 Boulogne, France.