Comparison of lidoflazine and quinidine in prophylactic treatment of arrhythmias

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The efficacy of quinidine versus lidoflazine therapy was compared in the maintenance of sinus rhythm after electrical cardioversion for atrial flutter or fibrillation in a group of 35 patients. Both quinidine and lidoflazine were relatively ineffective in maintaining sinus rhythm after cardioversion. Lidoflazine was also used to prevent supraventricular and ventricular tachycardias in a miscellaneous group of patients; one of these with paroxysmal supraventricular tachycardia developed runs of ventricular tachycardia soon after starting lidoflazine. The trial was stopped after 4 patients died while receiving lidoflazine, on the suspicion that their deaths may have been related to drug-induced arrhythmias. The arrhythmogenic potential of lidoflazine when used in patients with supraventricular arrhythmias contrasts with reports of its apparent safety in large numbers of patients with angina pectoris.

Despite the high initial success rate in the treatment of atrial flutter and atrial fibrillation by electrical cardioversion, it has been the experience of most workers that sinus rhythm can be expected to persist in only approximately 20 per cent of patients at the end of one year (Coelho *et al.*, 1967; Bjerke-lund and Orning, 1968; Radford and Evans, 1968; Södermark *et al.*, 1975). Our similarly unsatisfactory results despite the use of maintenance quinidine gluconate and a recent report of sinus rhythm in 90 per cent of patients at one year after cardioversion while receiving maintenance lidoflazine (Batlouni, 1970) led us to undertake a comparison of its efficacy with that of quinidine gluconate.

Lidoflazine is the generic name of 1-(4, 4-di-(fluoro-phenyl)-butyl)-4-(2,6-dimethyl-anilino-carbonyl)-methyl-piperazine with the following structural formula (Fig. 1).

Fig. 1 Chemical formula.

It has been shown in animal experiments to have a prolonged coronary vasodilator effect by direct action on the smooth muscle of the coronary arteries (Schaper *et al.*, 1965, 1966), and its antiarrhythmic properties in animals have been described by Carmeliet and Xhonneux (1971). It has been extensively used clinically in the treatment of angina pectoris and in the conversion of atrial fibrillation to sinus rhythm.

Subjects and methods

Patients entering the trial were under 70 years of age and had to remain in sinus rhythm for at least 24 hours after cardioversion. Patients with recent myocardial infarction, active myocarditis, cardiac surgery less than one month previously, known sensitivity to lidoflazine or quinidine, a blood urea above 60 mg/100 ml (9.9 mmol/l), a platelet count under 100 000/mm³, or serum potassium levels under 4.0 mmol/l were excluded. Patients with ventricular premature systoles occurring more frequently than 5 times per minute or where the ventricular extrasystoles were multifocal, consecutive, or had a QR/QT ratio less than 1 were also excluded. Relapse after previous cardioversion did not exclude patients from entry to the trial.

Before cardioversion patients underwent routine physical examination, 12-lead electrocardiogram with 12-second rhythm strip, and chest x-ray examination. Blood was checked for electrolytes,

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urea, creatinine, and platelets. Digoxin was withheld for at least 12 hours before cardioversion. After cardioversion, a test dose of quinidine sulphate (200 mg) or lidoflazine (60 mg) was given in all cases.

Therapy was designed so that patients were randomly allocated after electrical cardioversion to either a low-dose lidoflazine (60 mg 8-hourly) or quinidine gluconate (324 mg 8-hourly) group. If relapse occurred on this therapy, the higher dose of the same drug (lidoflazine 120 mg 8 hourly or quinidine gluconate 648 mg 8-hourly) was then prescribed after reconversion. Further relapse resulted in the patient being switched to the opposite drug group at low dosage after cardioversion, and finally a further relapse necessitated repeat cardioversion and the higher dosage of the opposite drug.

Follow-up examinations were undertaken at 1, 3, 6, and 12 months after cardioversion, with the intention to continue them for 2 years if the trial had run its course. The electrocardiogram, blood electrolytes, urea, creatinine, and platelets were checked at each outpatient visit after cardioversion. Patients were removed from the trial where symptoms were thought to be attributable to side-effects of the drug. Patients who failed to take their drugs as prescribed were also removed from the trial, as were patients in whom the electrocardiogram showed widening of the QRS complex, atrio-ventricular dissociation, or the development of ventricular extrasystoles fulfilling the original criteria preventing inclusion in the trial.

Twenty-two patients received low dose quinidine gluconate and three subsequently received the higher dosage after a second cardioversion, having relapsed into atrial flutter/fibrillation. Fourteen patients received low dose lidoflazine and one of these went on to the higher dosage after relapse and repeat cardioversion. Two patients received low dose lidoflazine, after reversion to atrial flutter/fibrillation on both low and high dose quinidine gluconate.

The average age of the patients allocated initially to quinidine gluconate therapy (37.9 years) did not differ significantly from that of the group receiving lidoflazine therapy (44.4 years). Just over half the patients in each group had underlying rheumatic heart disease while the remainder had an approximately equal distribution of either cardiomyopathy, ischaemic, congenital, hypertensive, or no apparent underlying heart disease. The cardi thoracic ratio exceeded 50 per cent in exactly half the patients in each group. The duration of the atrial flutter/fibrillation was 3 months or longer in 11 of the patients treated initially with quinidine gluconate and 9 of those treated initially with lidoflazine. Atrial fibrillation had been present for 6 months or more in 6 patients in each group and for one year or longer in 4 patients in each group.

Results

The Table illustrates the proportion of patients holding sinus rhythm at varying periods after cardioversion and takes into account the diminishing population over the months resulting from patients defaulting or stopping therapy because of side-effects and eventually from the trial being stopped. It will be seen that approximately half of the patients on low dose lidoflazine or quinidine were still in sinus rhythm 6 months after cardioversion. Of the 3 patients who failed to maintain sinus rhythm on high dose quinidine, 1 failed to reconvert, 1 became depressed after 2 weeks on lidoflazine, and the third maintained sinus rhythm for the 16 weeks she received it. Of the 2 patients who failed to maintain sinus rhythm while on low dose lidoflazine, 1 patient was switched to high dose lidoflazine but died shortly after.

Five of the patients receiving quinidine gluconate and 1 of the patients receiving lidoflazine stopped treatment. Three other patients discontinued quinidine gluconate therapy because of gastrointestinal side-effects, 1 developed cinchonism, one developed thrombocytopenic purpura, and quini-

Table

	No. of patients		Time after conversion					
			1 month	2 month	3 month	4 month	5 month	6 month
Low dose quinidine	22	{ In sinus rhythm	13	11	10	7	4	4
		{ Relapsed	2	2	2	2	2	2
High dose quinidine	3	{ In sinus rhythm	2	1	0			
		{ Relapsed	1	1	2			
Low dose lidoflazine	14	{ In sinus rhythm	8	7	5	3	2	2
		{ Relapsed	1	1	2	2	2	2
High dose lidoflazine	1	{ In sinus rhythm	0					
		{ Relapsed	0					

dine was withdrawn in one because of development of frequent ventricular extrasystoles. One patient developed a desquamative rash on the palms of the hands while receiving quinidine and later when he was switched to lidoflazine therapy as well. One patient on lidoflazine treatment became depressed.

Among those taking lidoflazine 4 died suddenly and unexpectedly between eight days and 25 weeks after starting therapy. Three of them were receiving low dose lidoflazine and the other one was on the higher dose regimen. These deaths led to the trial being abandoned at the advice of the Hospital Pharmaceutical Advisory Committee and the Faculty Review Committee for Clinical Research Investigation. Case summaries for the 4 patients concerned are reported in detail.

CASE 1

This 67-year-old woman had been followed for 9 years with hypertension, diabetes, and severe peripheral vascular disease for which bilateral above-the-knee amputations had been performed. Her hypertension was severe, requiring methyldopa and Rautrax, while her diabetes was mild and was controlled on oral therapy plus diet. She had well-controlled cardiac failure for which she received digoxin and frusemide with potassium supplements. Since 1964 she had been known to have an electrocardiogram showing left bundle-branch block with left axis deviation, and in December 1968 she presented with a history of syncope and was shown on Holter monitoring to have periods of sinus bradycardia as low as 37/minute, periods of atrial fibrillation, and periods of sinus rhythm with first degree block in addition to her left bundle-branch block and left axis deviation. A permanent transvenous pacemaker was implanted resulting in control of her syncopal attacks. Thereafter she was found to be in sinus rhythm on all subsequent follow-up visits to the Pacemaker Clinic. In December 1971 she had a transient cerebrovascular accident from which she made a good recovery. In August 1973 she presented in rapid atrial fibrillation and was given digitalis. Despite this, dyspnoea failed to improve and atrial fibrillation persisted. She was, therefore, cardioverted on 22 October 1973 at which time she had serum potassium values between 4.4 and 5.1 mmol/l. After cardioversion her electrocardiogram showed sinus rhythm at 70/minute, PR interval 0.20 s, left axis deviation, and complete left bundle-branch block. She was discharged on frusemide 80 mg daily, potassium chloride 1200 mg t.d.s., phenformin HCl 50 mg daily, and lidoflazine 60 mg 8 hourly. It was learnt subsequently that she died 8 days after cardioversion. Since her cardioversion she had been resting

at home and complained of occasional chest pain. She spent the day alone and was found lying dead on the floor that evening, having fallen from her wheelchair. Necropsy was not obtained.

CASE 2

This 42-year-old woman was first seen in April 1969 after a transient cerebrovascular accident resulting from presumed cerebral embolism complicating atrial flutter/fibrillation with underlying mitral stenosis and trivial aortic regurgitation. She was cardioverted for the first time in July 1969 and again in February 1973 for recurrence of atrial fibrillation and on each of these occasions she was maintained on quinidine sulphate 400 mg 8 hourly after conversion. In October 1973 she was cardioverted for a third time after which she received lidoflazine 60 mg 8 hourly, diazepam 2 mg t.d.s. while warfarin was continued. At that stage she was asymptomatic, with signs of non-critical mitral stenosis and trivial aortic regurgitation and her electrocardiogram showed sinus rhythm with a PR interval of 0.20 s, left axis deviation, and complete left bundle-branch block. When seen at follow-up 1 month and 3 months after cardioversion she was well and was taking her therapy. Her electrocardiogram showed sinus tachycardia on each occasion with a normal PR interval and persistent left axis deviation and complete left bundle-branch block. The QT interval varied from 0.36 to 0.37 s. Serum potassium level at her last follow-up visit was 4.6 mmol/l. Two days before her death she was seen by her general practitioner who said that she appeared well with a normal pulse rate. Twenty-five weeks after cardioversion she was seen by her family at 7 a.m. and appeared to be well but was found dead in bed 20 minutes later. There were no preceding warning symptoms of syncope or palpitations to suggest an arrhythmic mode of death. Necropsy was not obtained.

CASE 3

This man was 33 years old when he developed palpitations. His referring physician found him to have tachycardia and started him on propranolol 40 mg daily and frusemide 40 mg on alternate days. There was a history of an acute myocardial infarction at the age of 30 years confirmed by review of the electrocardiograms at that time. After his infarct he had led an active life without restriction during the 3 years before his death and he was not unduly disturbed by the development of the arrhythmia.

On physical examination he appeared to be nervous and his electrocardiogram showed evidence of atrial flutter with 4:1 atrioventricular block. He was cardioverted and started on lidoflazine 60 mg

8 hourly on 7 December 1973. After cardioversion, clinical examination indicated cardiomegaly with a loud third heart sound and a grade 2/6 systolic ejection murmur at the base. Chest x-ray examination confirmed the presence of significant cardiomegaly. A clinical diagnosis of thyrotoxicosis was suggested and serum T3 and T4 were sent for analysis. The possibility of alcoholic cardiomyopathy was also entertained as there was a history of excessive alcoholic intake over many years. At the time of discharge on lidoflazine therapy alone his serum potassium was 4.0 mmol/l and his discharge electrocardiogram showed a sinus tachycardia of 108/minute with a normal PR interval, normal frontal axis, left atrial and left ventricular enlargement which had not been present at the time of his previous myocardial infarction; the QT interval was 0.36 s.

It was learnt that the patient died suddenly 31 days later. His wife said that he started making noises during the night and she awoke to find him unconscious and cyanosed; by the time the doctor arrived he was dead. He had been seen by several people during the days before his death and he was described as being asymptomatic and in apparent good health. In particular there was no story of syncope or dizzy spells before his death. After his death results of thyroid function tests became available which were clearly abnormal with a T3 value of 58 µg/100 ml and T4 of greater than 25 µg/100 ml. In retrospect, he presumably had thyrotoxic as well as ischaemic heart disease. Necropsy was not obtained.

CASE 4

This 49-year-old woman had been followed for 11 years with mitral regurgitation which had first been detected at the age of 15 years. She had grade 2/4 effort intolerance for which she had been given digitalis and she had received frusemide 80 mg daily and potassium chloride 1200 mg t.d.s. She first went into atrial fibrillation in August 1974 and was started on lidoflazine 60 mg 8 hourly plus her other medications after cardioversion in November 1974. She underwent dilatation and curettage for irregular menstrual bleeding three weeks later having previously undergone a similar operation uneventfully in 1968. Because she had relapsed into atrial fibrillation since her previous cardioversion she was cardioverted later on the day of operation and restarted on lidoflazine at the higher dosage of 120 mg 8 hourly. After cardioversion she was in sinus rhythm with a normal PR interval and slight non-specific QRS widening of 0.10 s, with additional electrocardiographic evidence of left atrial and left ventricular enlargement. Chest x-ray

examination showed left ventricular cardiomegaly. Her postoperative recovery was uneventful until the morning of the third postoperative day when she was due to be discharged from hospital. When her routine temperature was taken at 5 a.m. she was found to be well but 30 minutes later she collapsed and died. Permission for necropsy was refused. A serum potassium performed the previous month had been 4.2 mmol/l. Review of her drug chart indicated that she had been receiving her lidoflazine therapy in a dose of 60 mg 8 hourly as prescribed, and that after cardioversion the dosage was increased to 120 mg 8 hourly which she received until the night before her death at 10 p.m. This meant that her previous dose had been given seven and a half hours before her death and that the increased dosage of lidoflazine had been administered for two and a half days before she died.

Discussion

A valid comparison of the efficacy of quinidine versus lidoflazine in maintaining sinus rhythm after cardioversion for atrial flutter and atrial fibrillation in the two groups of patients could not be made in this abortive trial and a limited number of patients only received both quinidine and lidoflazine. Though less than half the patients who remained in the trial were still in sinus rhythm 6 months after cardioversion the numbers are far too small for comparison of the relative effectiveness of the two drugs. As seen in previous trials, however, the relapse rate was higher in the first three months than in the second three months after cardioversion (Coelho *et al.*, 1967; Bjerkelund and Orning, 1968; Cramér, 1968). Comparison between the patients entering the two groups in terms of the nature of underlying heart disease, cardiac size, and previous duration of atrial fibrillation, factors known to influence the duration of sinus rhythm after cardioversion, indicated a surprising similarity in this small group of patients.

Side-effects were seen in patients on both drugs and most of these were well-recognised complications such as gastrointestinal upsets, cinchonism, rash, and thrombocytopenic purpura with quinidine therapy. The occurrence of rash or depression with lidoflazine therapy, however, has not previously been described to my knowledge.

The most striking feature that emerged from this trial and the reason for abandoning it before completion was the unexpected occurrence of 4 deaths among the patients receiving lidoflazine, while none of the patients receiving quinidine succumbed. Most patients qualifying for entry to such a trial have serious underlying heart disease and are at risk

of sudden death from a variety of mechanisms related to their disease processes (Cramér, 1968; Takkunen *et al.*, 1970).

The phenomenon of quinidine-induced ventricular tachycardia and ventricular fibrillation is a well-documented one (Oram and Davies, 1964; Selzer and Wray, 1964; Bjerkelund and Orning, 1968; Cramér, 1968; Radford and Evans, 1968) and constitutes a rare but well-recognised cause of sudden death (Maurice *et al.*, 1956; Radford and Evans, 1968). There have been similar previous reports of syncope, paroxysmal ventricular tachycardia or ventricular fibrillation, and sudden death in patients receiving lidoflazine therapy (Miyahara *et al.*, 1969; Batlouni, 1970; Piessens *et al.*, 1970; Bortoluzzi and Rodrigues, 1971; Schlepper and Derro, 1972; Czerny *et al.*, 1975). In all instances lidoflazine was being given, in order to convert atrial tachyarrhythmias to sinus rhythm, in similar doses to those used to maintain sinus rhythm in this study. Among the 206 patients in these six reports the incidence of these problems was 14 per cent. There are other reported series, however, comprising a total of 57 patients without any of the above dangerous complications (De Vil and Bruyneel, 1974; Bruyneel *et al.*, 1975; Lehmann and Hochrein, 1975). Among the numerous reported series of patients receiving quinidine for medical cardioversion the highest reported incidence of syncope is 6.8 per cent among 237 patients (Cramér, 1968). Though the comparative risks of lidoflazine versus quinidine therapy have not been systematically evaluated these reports plus the present one suggest that lidoflazine is the more hazardous of the two drugs.

During the course of this trial we tried the effect of lidoflazine in the same dosage in a miscellaneous group of 14 patients consisting of 3 with paroxysmal supraventricular tachycardia, 3 with paroxysmal ventricular tachycardia, and 8 who had been electively cardioverted from atrial flutter/fibrillation but who could not enter the trial because of previously known gastrointestinal intolerance to quinidine. Though there were no deaths in this group, one 75-year-old woman with paroxysmal supraventricular tachycardia and occasional ventricular extrasystoles developed runs of self-limiting ventricular tachycardia during lidoflazine therapy (Fig. 2). Lidoflazine was stopped and lignocaine administered with adequate control of her arrhythmia. Serum potassium was checked and found to be above 5 mmol/l on several occasions. Eighteen hours after stopping lidoflazine a test dose of 200 mg quinidine sulphate and 8 hours later quinidine gluconate 648 mg 8 hourly was begun. Lignocaine had now been withdrawn

and on quinidine therapy extrasystoles again increased as did frequent runs of ventricular tachycardia. She developed paroxysms of ventricular fibrillation, one of which was persistent with loss of consciousness requiring defibrillation. Quinidine was immediately withdrawn and intravenous lignocaine restarted, with signs of ventricular irritability subsiding within the next few days. Paroxysmal supraventricular tachycardia was eventually controlled on practolol 100 mg 12 hourly without any recurrence of ventricular arrhythmias.

The mechanism of ventricular tachycardia and fibrillation in patients receiving quinidine is thought to be related to prolongation of the relative refractory period of the ventricles whereby a ventricular extrasystole can occur during the vulnerable

Fig. 2 Electrocardiograms in patient after institution of lidoflazine and subsequent quinidine therapy. Times and doses of lidoflazine and quinidine are illustrated in relation to rhythm strips. Daily serum potassium levels are recorded.

period more readily. Lidoflazine, which prolongs the QT interval, may provoke ventricular arrhythmias in similar fashion. Carmeliet and Xhonneux (1971) have shown that the rate of pacemaker activity and depolarisation, the amplitude of the action potential, and the conduction velocity of *in vitro* cardiac muscle are reduced by lidoflazine, while the duration of the action potential and the effective refractory period are prolonged. Lidoflazine may thus be compared to local anaesthetic and other antiarrhythmic drugs such as quinidine. At therapeutic dose levels it does not produce blockade of adrenergic beta receptors. It is believed to interfere directly with the transmembrane conduction processes of electrolytes, particularly calcium and potassium. Where intracellular potassium is diminished and the driving force for repolarising current is lowered lidoflazine may disturb the repolarisation process by further reducing conductance and its use is contraindicated in the presence of hypokalaemia (Batlouni 1970; Carmeliet and Xhonneux, 1971).

In the patient who developed ventricular tachycardia the serum potassium was normal on several occasions and it was previously normal in all 4 patients who subsequently died. The 2 patients who died shortly after starting lidoflazine therapy or shortly after increasing the dosage, however, were both receiving diuretics. Despite potassium supplements and a normal serum potassium level, they may have had an overall total body deficit of potassium.

Therapy with digitalis preparations has been blamed for ventricular arrhythmias in patients receiving lidoflazine. In Batlouni's series (1970), 4 of 18 patients receiving lidoflazine plus digitalis manifested syncope, while only 1 of 32 receiving lidoflazine alone showed this complication. Two patients reported by Miyahara and colleagues (1969) who developed ventricular tachycardia and ventricular fibrillation were both on digitalis, but it is not clear from the report how many of the remaining patients were also receiving digitalis. All 5 of the patients in the report by Piessens and co-workers (1970) who developed ventricular tachycardia, ventricular fibrillation, or sudden death were receiving digitalis, but so were 12 of the remaining 21 who did not develop ventricular tachyarrhythmias. In the series of 30 patients reported by Schlepper and Derro (1972), 21 were on digitalis and of these 15 developed ventricular extrasystoles among whom 5 went on to syncope; none of the 9 patients not receiving digitalis developed ventricular arrhythmias. Czerny *et al.* (1975), however, concluded that digitalis therapy was not related to the occurrence of complicating

ventricular arrhythmias in their series of patients. The single patient who showed paroxysmal ventricular tachycardia in that report was receiving only lidoflazine at the time of her arrhythmias, and none of the 4 patients who died was receiving digitalis at the time of their death.

The duration of lidoflazine treatment varied from 8 days to 25 weeks in our 4 patients who died. In 4 of the 6 reported series which describe the time of syncope or ventricular tachyarrhythmias during lidoflazine therapy, the attacks occurred between the first and seventh day after starting treatment. If death were on a similar arrhythmic basis it would seem likely that, as in the case of quinidine syncope or sudden death, it would have occurred within a short time of starting treatment with lidoflazine. The first patient (Case 1) died 8 days after starting therapy and the fourth patient (Case 4) 2½ days after increasing her dosage. It seems reasonable therefore to invoke the drug as possibly being responsible for both these deaths. The other two (Cases 2 and 3), however, died 4 and 25 weeks, respectively, after starting lidoflazine and seem less likely, therefore, to have died from a drug-related arrhythmia.

The nature of the underlying heart disease varied from patient to patient but all 4 patients had intraventricular conduction disturbances including left anterior hemiblock, left bundle-branch block, and non-specific QRS widening. In the report of Piessens and colleagues (1970) only 1 of 5 patients with syncope or sudden death had a conduction disturbance. In the other reports of patients with syncope on lidoflazine it is not clear whether there was a higher incidence of intraventricular conduction disturbances among those experiencing syncope.

An unexplained aspect of the arrhythmogenic potential of lidoflazine is its remarkable safety in the treatment of patients with angina pectoris. In 7 reported series (Verhaeghe, 1969; Batlouni, 1970; Schwalb, 1971; Bernstein and Peretz, 1972; Piessens and De Geest, 1972; Aravanis *et al.*, 1973; Vohra and Sloman, 1973), comprising 247 patients treated with doses equivalent to those used to convert fibrillation, there are no recorded instances of ventricular tachyarrhythmias or syncope. Batlouni (1970) quotes a colleague, however, who treated 2 patients with angina and congestive cardiac failure on digitalis and intensive diuretic treatment with lidoflazine both of whom experienced syncope. In one of these multifocal ventricular extrasystoles were recorded, while in the other ventricular tachycardia was shown subsequent to the syncopal episode. With these 2 exceptions, it is difficult to reconcile the difference in the tendency to ventricular arrhythmias in patients with angina

and those with atrial fibrillation treated with lidoflazine.

Analysis revealed a statistical difference with a probability of 8.2 per cent calculated by the exact probability test (Armitage, 1971) in the death rate between the 23 patients receiving quinidine and the group of 28 receiving lidoflazine, including the 14 miscellaneous patients. In view of the fact that the death rate on lidoflazine was approaching the usually accepted statistical significance level of 5 per cent and another patient had sustained dangerous ventricular tachyarrhythmias on lidoflazine therapy, it was decided to terminate the trial. These results, in conjunction with the unacceptably high risk of syncope caused by documented or presumed ventricular tachyarrhythmias in patients receiving lidoflazine for arrhythmias, lead us to the conclusion that it is not an acceptable form of therapy in the treatment or prophylaxis of arrhythmias.

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