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CARDIOVASCULAR MEDICINE

Sinus rhythm maintenance following DC cardioversion of atrial fibrillation is not improved by temporary precardioversion treatment with oral verapamil

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Objective: To evaluate prospectively the effects of pretreatment with verapamil on the maintenance of sinus rhythm after direct current (DC) cardioversion.
Design: Randomised, active control, open label, parallel group comparison of verapamil versus digoxin.
Settings: Multicentre study in three teaching and three non-teaching hospitals in Sweden.
Patients: 100 consecutive patients with atrial fibrillation (AF) of at least four weeks' duration and indications for cardioversion were assigned randomly to two groups, one treated with verapamil (verapamil group) and the other with digoxin (digoxin group) before cardioversion. Fifty patients were assigned randomly to each treatment arm. After dropout of four patients from the digoxin group and seven patients from the verapamil group, data obtained from 89 patients were analysed.
Interventions: After randomly assigned pretreatment with either verapamil or digoxin for four weeks, DC cardioversion was performed. If sinus rhythm was restored then verapamil treatment was discontinued.
Main outcome measures: The rate of AF recurrence was assessed one, four, eight, and 12 weeks after cardioversion.
Results: 6 patients in the verapamil treated group and none in the digoxin treated group reverted to sinus rhythm spontaneously ($p < 0.05$). DC cardioversion restored sinus rhythm in 24 of 37 (65%) patients in the verapamil group and 41 of 46 patients (89%) in the digoxin group ($p < 0.05$). After 12 weeks' follow up 28% (13 of 46) of digoxin pretreated patients versus 9% (four of 43) of verapamil pretreated patients remained in sinus rhythm ($p < 0.05$).
Conclusion: Pretreatment with verapamil alone does not improve maintenance of sinus rhythm after DC cardioversion in patients with AF. The rate of spontaneous cardioversion may be improved by verapamil.

Atrial fibrillation (AF) is a common arrhythmia in clinical practice with a prevalence in the general population of 0.4–0.9%. The incidence of AF increases with age resulting in a prevalence of 2–4% in the population over 60 years.[1–3] Long term maintenance of sinus rhythm after successful cardioversion is difficult, mainly because of the high incidence of recurrence in the first month after cardioversion. The duration of AF is one of the most important factors affecting successful cardioversion.[4 5] The concept of electrical remodelling of the atria is a possible explanation: AF causes progressive electrophysiological and structural changes of the atria, which in turn promote the initiation and perpetuation of AF.[6]

Several experimental studies showed that electrical remodelling of the atria during AF may be caused by intracellular calcium overload and hence attenuated by calcium channel blockers.[7–9] On the other hand, in long lasting AF, pretreatment with verapamil does not prevent electrophysiological changes caused by AF[10] and may, in fact, result in a shortening of the refractory periods.[11] Clinical studies aimed at testing the hypothesis that verapamil may reduce early recurrence of AF after cardioversion have also had conflicting results.[12–18]

The planning of this study was based on the theoretical knowledge of atrial remodelling gained from experimental investigations and limited clinical studies.[19–22] Its aim was to compare in a patient group the effects of pretreatment with oral verapamil on sinus rhythm maintenance after direct current (DC) cardioversion of chronic AF with a control group in which ventricular rate control was achieved with digoxin.

PATIENTS AND METHODS

Patient population

From January 1998 to March 2000, we recruited 100 consecutive patients admitted for elective DC cardioversion of their persistent AF for a study in six medical centres in southern Sweden. Persistent AF was defined in accordance with American College of Cardiology/American Heart Association/European Society of Cardiology guidelines for the management of patients with AF.[23] To be enrolled in the study patients had to have, firstly, persistent AF for more than one month but less than three years and, secondly, clinical indications for DC cardioversion according to local practice. Patients with the following criteria were not included in the study: (a) AF for longer than three years; (b) DC cardioversion at any time before inclusion; (c) untreated hyperthyroidism; (d) planned intervention of cardiac surgery; (e) treatment with calcium channel blockers or β blockers within one month before inclusion; and (f) concomitant use of any antiarrhythmic drugs other than digoxin.

Abbreviations: AF, atrial fibrillation; DC, direct current; VERDICT, verapamil versus digoxin cardioversion trial

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Study protocol

All patients gave written informed consent before participating in the study. The study was approved by respective local ethics committees and complied with the requirements of the Declaration of Helsinki.

Clinical examination included standard 12 lead ECG at rest, transthoracic cardiac echocardiography, chest radiography, thyroid function tests, and routine blood chemistry to confirm patient eligibility.

Randomisation was by the closed envelopes technique. Study treatment was assigned in an open label fashion, patients being assigned to either the verapamil group or to the digoxin group before the scheduled cardioversion. The doses of either of the administered medications were adjusted to keep the ventricular rates in the interval between 50–75 beats/min.

In the verapamil group, verapamil in a slow release form was used. Initially, verapamil was administered as 120 mg twice daily. The doses were adjusted up to the maximum of 240 mg twice daily, depending on the ventricular rate. If rate control was not achieved by verapamil alone, digoxin was added. In the digoxin group, if medically indicated, digoxin was the only drug used for rate control. The starting dose was in the range of 0.13–0.25 mg/day. In both groups, if digoxin was used to reach adequate heart rates at rest, it was withdrawn if the heart rate decreased below 75 beats/min. Participants were pretreated for a minimum of four weeks before DC cardioversion.

If patients were treated with β blockers for control of ventricular rate during AF, concurrent arterial hypertension, or other conditions, the medication was washed out before initiating pretreatment with the study drug under the strict control of their clinical condition.

Anticoagulation was achieved with oral warfarin, which was initiated, if not already in use, on the day of inclusion. DC cardioversion was performed when the international normalised ratio had been within the therapeutic range (2.0–3.0) for three to four weeks. Warfarin treatment continued for at least four weeks after DC cardioversion.

DC cardioversion was performed while patients were heavily sedated with propofol at a dose of 2 mg/kg. Up to four synchronised external monophasic shocks (100, 200, 360, 360 J) were delivered to restore sinus rhythm. If sinus rhythm was restored either during the pretreatment period or after DC cardioversion, the study treatment was discontinued.

The success rates of both spontaneous and DC cardioversion and subsequent sinus rhythm maintenance were assessed by documenting cardiac rhythm with ECG recordings at rest taken immediately after cardioversion and subsequently at one, four, eight, and 12 weeks.

If AF was documented at any point during the study, treatment was discontinued. Such patients were then managed in accordance with local practice (fig 1).

Table 1 Baseline patient characteristics

	Digoxin treatment (n = 50)	Verapamil treatment (n = 50)
Sex (male/female)	37/13	33/17
Age (years)*	72 (7)	66 (10)
Smokers	5	7
AF duration (months)	7.5 (6.0)	10.7 (8.5)
LVEF >55%	42	44
AF rate at DC conversion >90 beats/min*	15	5
Structural heart disease	27	21

Data are numbers or mean (SD).
*p<0.05 for comparisons between the groups.
AF, atrial fibrillation; DC, direct current; LVEF, left ventricular ejection fraction.

Statistical analyses

The difference in outcomes between the groups was analysed by Fisher's exact test. The non-parametric Mann-Whitney U test for unpaired variables was used to compare patient characteristics between the groups. StatView 4.5 (Abacus Concepts, Berkeley, California, USA) was used for statistical analysis. All results are expressed as mean (SD). Significance was indicated by $p < 0.05$.

RESULTS

Baseline characteristics

The 100 patients enrolled in the study were distributed equally between the groups: 50 were pretreated with verapamil and 50 with digoxin (table 1). Four patients (three from the digoxin group and one from the verapamil group) were excluded from the analysis according to the inclusion and exclusion criteria at enrolment.

Of the 47 patients remaining in the digoxin group, one did not receive DC cardioversion because of gastrointestinal haemorrhage. Thus, only 46 patients in the digoxin group were DC converted and followed up through week 12. Forty two of them were treated with digoxin at the time of cardioversion. The other four did not require rate control.

Of the 49 patients remaining in the verapamil group, three chose not to continue participating in the study during the

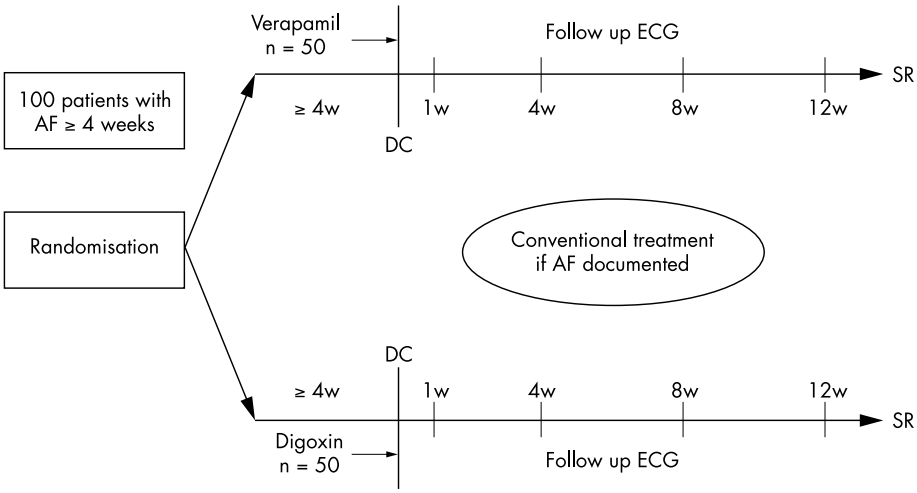

Figure 1 Protocol flow chart. Pretreatment with verapamil or digoxin was discontinued after restoration of sinus rhythm (SR). If atrial fibrillation (AF) was documented at any time during follow up (study end point) then patients were treated according to local practice. w, weeks.

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pretreatment period and three did not receive the DC cardioversion because of worsening of heart failure (two patients) or allergic reaction (one patient), thus leaving 43 eligible for rhythm conversion for the 12 week follow up. Among those, spontaneous restoration of sinus rhythm was observed in six patients during pretreatment with verapamil. The remaining 37 patients in the verapamil group underwent DC cardioversion.

There was no significant difference between the groups as regards sex, weight, duration of AF, or left ventricular function. Twenty one patients in the verapamil group and 27 patients in the digoxin group had structural heart disease.

Seventy per cent of the randomly assigned patients were men and 30% were women. The duration of AF ranged between 1–30 months with a mean of 8.4 months. Eighty six per cent of all patients had ejection fraction exceeding 55%. Twenty five per cent of the population studied were smokers, equally distributed between the groups.

There was, however, a significant difference in the ages of the groups, the population assigned to the verapamil group being somewhat younger than that in the digoxin group (table 1).

Duration of pretreatment and rate control

The mean time from inclusion to DC cardioversion was 78 (47) days in the digoxin treated group and 89 (59) days in the verapamil treated group. The duration of the pretreatment period was influenced by the time required to achieve international normalised ratios sufficient for safe cardioversion.

The ventricular rate of AF at the time of DC cardioversion also varied between the groups. Although the study drug was administered to a maximum predefined dose, 15 patients in the digoxin group had ventricular rates exceeding 90 beats/min compared with five in the digoxin group (table 1). However, five patients in the verapamil treated group required the concomitant use of digoxin to reach ventricular rate control.

Main findings

Six patients (mean duration of AF 7.6 (8.9) months, range 2–24 months) in the verapamil group but none in the digoxin group reverted to sinus rhythm spontaneously before the scheduled cardioversion ($p < 0.05$).

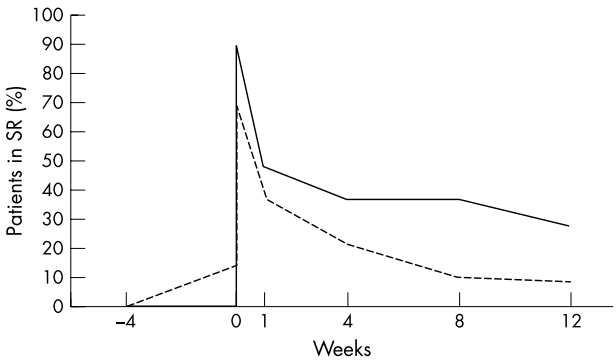

Figure 2 Maintenance of sinus rhythm after DC cardioversion during the 12 week follow up period. Solid line corresponds to the digoxin pretreated group and dashed line to the verapamil pretreated group. Week 0 is the time of spontaneous or electrical cardioversion. Week 4 is time of randomisation and the beginning of the pretreatment period. The proportion of patients remaining in sinus rhythm was greater for patients pretreated with digoxin than for verapamil pretreated patients at weeks 8 and 12 ($p < 0.05$ for both comparisons). Note that 14% (6 of 43) of verapamil treated patients converted to sinus rhythm spontaneously before DC cardioversion.

DC cardioversion resulted in restoration of sinus rhythm in 24 of 37 patients (67%) in the verapamil group, which was lower than for the digoxin group, in which 41 of 46 patients (89%) converted to sinus rhythm ($p < 0.05$).

There was no significant difference in the rate of sinus rhythm maintenance between the groups at one or four weeks after DC cardioversion (fig 2). However, already at week 8 a significantly greater proportion of patients in the digoxin group than in the verapamil group remained in sinus rhythm (17 of 46 *v* 7 of 43, $p = 0.033$). At the end of the follow up period after DC cardioversion, 13 of the 46 patients in the digoxin group remained in sinus rhythm versus four of 43 in the verapamil group ($p = 0.031$).

DISCUSSION

Why verapamil? Studies of atrial remodelling

Persistent AF is characterised by a high incidence of recurrence, especially during the first weeks after restoration of sinus rhythm.[12] AF of long duration is one of the few factors that worsens the prognosis of sinus rhythm maintenance after successful cardioversion achieved either pharmacologically or by DC cardioversion.[4 5]

The mechanism for these early subacute relapses of AF is thought to be related to increased atrial vulnerability during the first weeks of sinus rhythm due to the remaining arrhythmogenic substrate and arrhythmia triggers favoured by atrial remodelling developed during AF.[24–27] Atrial electrical remodelling develops quickly, is progressive, and may be persistent. Shifts in autonomic tone, atrial stretch, and depletion of high energy phosphates do not contribute significantly to the phenomenon.[27]

Interest in the use of calcium lowering agents in an attempt to improve the effectiveness of cardioversion and reduce the rate of early recurrence appeared after the first experimental studies of atrial remodelling in AF, which suggested that intracellular calcium overload is one of the mechanisms involved in the electrical remodelling process.[7–9] In a series of experiments verapamil was shown to attenuate the shortening of the action potential duration[8] and the atrial effective refractory period[9] as indices of electrical remodelling caused by short term rapid atrial pacing. Experimental studies of long term pacing in animal models of AF, however, showed that verapamil not only does not prevent tachycardia induced changes of atrial electrophysiological properties but also may shorten the atrial refractory period and even increase the duration of AF in dogs.[10 11]

Nevertheless, clinical studies showed that, in patients with persistent AF, atrial refractory periods that have been shortened by longstanding AF[28] may be prolonged by oral verapamil.[29] Studies showed that verapamil reduced atrial vulnerability by shortening the conduction delay zone and prolonging the atrial refractory period in patients with paroxysmal AF.[19] Verapamil also increased spontaneous conversion rates when given in combination with amiodarone.[30]

These theoretical considerations of the potential beneficial effect of verapamil on atrial remodelling caused by AF served as the background for the planning of this clinical study.

Study procedures

Selection of the comparator

Testing the hypothesis of the possible beneficial effect of verapamil pretreatment on the outcome of DC cardioversion posed strict requirements on the choice of comparator. Since the vast majority of patients with AF require medications for ventricular rate control, the best comparison would be with a drug that does not affect the restoration of sinus rhythm and can control ventricular rate. For these reasons antiarrhythmic agents of classes I and III could not be used. β Blockers were

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an alternative to calcium channel blockers in terms of rate control agent. However, they may also affect myocardial electrophysiology in a potentially favourable way[31] and could therefore have influenced the interpretation of the results. On the other hand, digoxin, a classical rate control agent in AF, does not affect the restoration of sinus rhythm[21 32 33] and acts oppositely to verapamil by increasing intracellular calcium concentrations and increasing the atrial effective refractory period.[34] Several other studies have also compared digoxin with verapamil.[21 35 36]

Doses of study drug

Low tolerance to high doses of verapamil can potentially limit the beneficial effects of the drug. We aimed at achieving calcium channel blockage by treating patients with a maximum of 240 mg twice daily. Mainly because of the tendency to bradycardia or atrioventricular blockade, very few patients reached this dose and several patients received only 80 mg daily. At the time of DC cardioversion the mean (SD) dose of verapamil was 260 (110) mg/day (range 80–480 mg).

Spontaneous cardioversion

A significantly higher proportion of the patients in the verapamil group converted spontaneously to sinus rhythm before DC cardioversion than in the digoxin group. This observation was even more surprising in that no beneficial effect on either the DC cardioversion success rate or sinus rhythm survival was observed in the verapamil treated group. The high spontaneous cardioversion rate in the verapamil group can of course be explained by inclusion of patients with paroxysmal AF in the study. However, at the time of inclusion, there were no reasons to question the presence of persistent AF. Spontaneous reversion to sinus rhythm was one of the end points of the recently presented VERAF (verapamil in atrial fibrillation) study.[36] The same trend supporting favourable effects of verapamil was observed. De Simone and colleagues[37] in their recently published study also described a significantly higher rate of spontaneous cardioversion in patients pretreated with verapamil. Since in our study none of the patients randomly assigned to the digoxin group converted spontaneously to sinus rhythm, we believe that the spontaneous conversion observed may be a true effect of verapamil. Available data on the prolongation of the atrial refractory period in humans with persistent AF also favour this explanation.[29]

Efficacy of DC cardioversion

The finding that the efficacy of DC cardioversion was lower in the verapamil group than in the digoxin group is surprising and contradicts the results of several recently published studies comparing the effects of verapamil and digoxin on the efficacy of electrical cardioversion.[35 36] Innes and colleagues[21] earlier found that the quinidine–verapamil combination was superior to quinidine–digoxin for restoration of sinus rhythm in patients with recent onset paroxysmal AF. De Simone and colleagues,[37] however, did not report any benefits of pretreatment with verapamil for the immediate outcome of electrical cardioversion.

Sinus rhythm maintenance

When the present study was designed, knowledge of the effects of pretreatment with verapamil on sinus rhythm maintenance was limited. Lamberti and colleagues[22] showed that pretreatment with calcium antagonists may prevent atrial electrical remodelling. By using transtelephonic monitoring, Tieleman and associates[20] showed that the use of intracellular calcium lowering drugs during AF was the only significant variable related to maintenance of sinus rhythm after cardioversion. This retrospective study was, however, not randomised and enrolled a limited number of patients. The group of calcium lowering drugs consisted of all calcium channel blockers and β adrenergic receptor blockers. Many of the patients also took calcium channel blockers for treatment of hypertension before the start of the latest AF episode. On the contrary, Shenasa and colleagues[38] in a small series reported that verapamil prolonged the duration of induced AF in patients with spontaneous paroxysms of AF. Rinkenberger and colleagues[39] observed no effect of verapamil on either AF duration or recurrence.

The present study was a prospective randomised study in which concomitant use of any other antiarrhythmic drugs or calcium channel blockers was a criterion for exclusion. Despite the benefit observed in terms of ventricular rate control, our finding that verapamil unfavourably influences sinus rhythm maintenance contradicts the results of several studies. De Simone and colleagues[12] showed that short term administration of verapamil before and after electrical cardioversion has a beneficial effect on arrhythmia recurrence during the first week after restoration of sinus rhythm. In that study, however, the treatment also was combined with the IC class drug propafenone. The same group recently studied the effects of short time pretreatment with verapamil on the outcome of a second electrical cardioversion caused by the early recurrence of AF. They showed that combinations of verapamil with class IC and III antiarrhythmic agents are safe and effective in reducing AF relapses in those patients,[37] a finding that supports earlier observations of Tieleman and colleagues.[30]

The efficacy of standalone verapamil in reducing AF recurrence was studied in the recent VERAF study, in which the effect of verapamil was maximal for reducing immediate recurrence—that is, during first week after cardioversion. Concomitant use of digoxin by patients not treated with verapamil did not interfere with the outcome of electrical cardioversion.[36] Daoud and colleagues[40] showed that verapamil given intravenously reduced the recurrence of AF and extended the duration of sinus rhythm in patients with immediate recurrence of AF.

On the other hand, our negative findings are in accordance with the recently published results of VERDICT (verapamil versus digoxin cardioversion trial), in which stand alone verapamil administered for one month before and one month after electrical cardioversion did not enhance either the outcome of cardioversion or arrhythmia recurrence.[35] Pretreatment with verapamil did not affect the AF relapse rate in patients with persistent AF taking amiodarone in the study of Bertaglia and colleagues.[13] In both these studies, however, verapamil was continued for one month after electrical cardioversion, whereas we studied the ''pure'' pretreatment effect of verapamil, which was not continued after electrical cardioversion.

It is well known that the duration of AF has an important impact on the success of DC cardioversion and subsequent maintenance of SR. The study protocol allowed for inclusion of patients with arrhythmia for up to three years, which may therefore have directly affected the benefit of pretreatment. However, the design of our study did not permit analysis of the subgroup of patients with shorter arrhythmia duration (for example, less than six months).

Electrical remodelling starts immediately after the initiation of AF.[26] It is therefore possible that, as suggested by several experimental studies,[8 9] verapamil can protect only if it is initiated early in the course of AF. It is also not clear whether verapamil should be continued after successful electrical cardioversion. In our study, the drug was discontinued immediately after the restoration of sinus rhythm. However, studies in which verapamil was

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continued after effective cardioversion have had conflicting results.[35 36]

Is there a place for verapamil in cardioversion and rhythm control?

Despite the number of studies, evidence relating to the use of verapamil for preventing the recurrence of arrhythmia in patients with AF is limited and contradictory. On the basis of the available clinical information[35] and the results of our study, the use of stand alone verapamil cannot be justified for improving the outcome of DC cardioversion and reducing early relapses of AF after rhythm conversion. However, a substantial number of studies advocate the use of calcium antagonists in addition to the class I and III antiarrhythmic drugs, since verapamil may strengthen the preventive effects of these drugs.[16 30 37] Repeated observations of increased rates of spontaneous restoration of sinus rhythm in patients pretreated with verapamil[36 37] offer an additional rationale for including verapamil in the arrhythmia pretreatment schemes before scheduled cardioversion of persistent AF.

Limitations of this study

In one centre, the availability of immediate transoesophageal echocardiography guided DC cardioversion prevented some of the patients from entering the present study. This may have introduced a bias in patient selection. The need for adding digoxin to the treatment regimen of five patients in the verapamil group could also have affected the results.

Administration of antiarrhythmic agents after successful cardioversion would perhaps have improved sinus rhythm maintenance in our series. However, that the majority of patients had no previous history of DC conversion meant that they were having their first episode of AF, for which prophylactic antiarrhythmic treatment is not routinely indicated.

Conclusion

Pretreatment with oral verapamil does not improve sinus rhythm maintenance after cardioversion in patients with persistent AF who are not given other antiarrhythmic medications. The rate of spontaneous cardioversion can be increased by verapamil.

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