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Modulation of Ventricular Rate in Permanent Atrial Fibrillation: Randomized, Crossover Study of the Effects of Slow-Release Formulations of Gallopamil, Diltiazem, or Verapamil

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Summary

Background: The management of permanent atrial fibrillation (PAF) consists primarily of long-term anticoagulation with either aspirin or warfarin to prevent systemic embolization, and modulation of ventricular rate (VR) to improve cardiac function by prolonging the ventricular diastolic filling time.

Hypothesis: The effects of slow-release formulations of gallopamil (100 mg b.i.d.), diltiazem (120 mg b.i.d.), or verapamil (120 mg b.i.d.) on VR were evaluated in 18 patients with PAF without organic heart disease.

Methods: In all patients, each treatment was administered randomly, was compared with oral digoxin, and was assessed by 24-h Holter monitoring during daily life and by a 6-min walking test.

Results: There were no significant differences in mean and minimum VR recorded during 24-h Holter monitoring among the four treatments. Peak heart rates recorded during the 6-min walking test with digoxin treatment was 167 ± 12 beats/min. This was significantly reduced by gallopamil (149 ± 23 beats/min, $p = 0.01$), diltiazem (142 ± 24 beats/min, $p < 0.001$), and verapamil (137 ± 30 beats/min, $p < 0.001$). There were no significant differences in peak VR during the walking test among the three calcium antagonists. Pauses of > 3 s were observed in 3 of 18 (17%) patients who received digoxin (max 3.4 s) and in 5 of 18 (28%) patients who received diltiazem (max 3.4 s); p = NS. Periods of bradycardia < 30 beats/min were observed in 5 of 18 (28%) patients during digoxin treatment, and in 3 of 18 (17%) patients during treatment with gallopamil, diltiazem, and verapamil; p = NS.

Conclusion: Gallopamil, diltiazem, or verapamil are superior to digoxin in controlling VR during mild exercise in patients with PAF without organic heart disease. The reduction of peak VR is obtainable without further slowing of resting VR. However, gallopamil appears to be the least effective calcium blocker at controlling resting and exercise VR; thus, there are no advantages over the other calcium blockers in its use in the clinical setting.

Key words: atrial fibrillation, ventricular rate control, digoxin, calcium-channel blockers

Introduction

Permanent atrial fibrillation (PAF) is a common cardiac arrhythmia. It is particularly frequent in the elderly and in patients with heart disease.[1] In the Framingham study, there was a 2% risk of developing PAF over two decades, and its presence was associated with a doubling in mortality.[2] Two-thirds of patients with PAF require long-term drug therapy to avoid symptoms and systemic complications and to maintain optimal cardiac function. The management of PAF consists primarily of long-term anticoagulation with either aspirin or warfarin to prevent systemic embolization, and modulation of ventricular rate (VR) to improve cardiac function by prolonging the ventricular diastolic filling time.[3,4]

Digitalis glycosides have been used traditionally as a drug of choice for control of VR in patients with atrial fibrillation (AF),[5] but because the predominant effect of digoxin on resting heart rate is mediated by enhanced vagal tone, the beneficial effects frequently may not be maintained during exercise or other stress-related situations when vagal influences are withdrawn.[6,7] Previous studies have demonstrated that the

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direct effect of the calcium-channel blockers verapamil and diltiazem on slowing atrioventricular (AV) nodal conduction results in a better control of exercise heart rate in patients with AF.[8–11] Gallopamil (D 600), a methoxy derivative of verapamil, is a calcium-channel blocker reported to be 2.5 times more potent than verapamil, as shown by the results of in vitro studies.[12] The effect of gallopamil on heart rate reduction in patients with AF and rapid ventricular response has been previously reported.[13] Information on the antiarrhythmic effect of one nondihydropirydine calcium-channel blocking agent compared with another, in the context of PAF, has not been published.

In this randomized, crossover study, prolonged ambulatory electrocardiographic (ECG) monitoring was used to evaluate the effects of slow-release (SR) formulae of gallopamil, diltiazem, or verapamil on resting and mild exercise-provoked heart rate in nonhospitalized patients with PAF.

Materials and Methods

The study population consisted of 15 men and 3 women aged 54 to 72 years (mean age 66 ± 9 years), with documented history of stable PAF (>6-month duration). All patients had AF without significant structural heart disease: 8 (44%) in association with arterial hypertension and 10 (56%) with lone AF. Patients were required to demonstrate resting heart rate in excess of 100 beats/min (without any heart rate-modifying drug) and good exercise tolerance (New York Heart Association functional class I). In all subjects, thyroid function tests gave normal results. Exclusion criteria included renal failure, congestive heart failure, left ventricular ejection fraction <40%, angina or recent myocardial infarction (<6 months), preexcitation syndrome, electrolyte imbalance, uncontrolled hypertension (systolic blood pressure >160 mm/Hg and diastolic blood pressure >100 mm/Hg), and concomitant therapy with antiarrhythmic agents. Patients receiving heart rate modifying drugs that are not antiarrhythmic (e.g., bronchodilators) were also excluded. The necessity of digoxin therapy or the presence of contraindications to calcium-channel blockers similarly excluded patients from the study. The clinical characteristics of our study population are shown in Table I. Each patient studied gave informed consent.

The study protocol is outlined as follows: The 4-week study period was divided into weekly treatment periods. On Day 7 of drug treatment, an ambulatory ECG monitoring assessment was made.

The drugs and oral dosages used for the AV nodal blocking regimens were (1) SR formulation of gallopamil, 200 mg daily, 100 mg b.i.d.; (2) SR formulation of diltiazem, 240 mg daily, 120 mg b.i.d.; (3) SR formulation of verapamil, 240 mg daily, 120 mg b.i.d.; (4) digoxin, once daily, according to serum concentration, ranging from 0.8 to 1.4 μg/ml, measured by radioimmunoassay (digoxin daily mean dose was 0.254 ± 0.007 mg). Each drug was administered randomly in the same patients, in a crossover fashion, for a 7-day period. Patient compliance was evaluated by pill counting.

Twenty-four-h ambulatory ECGs were recorded for all subjects on the last day of each treatment period. Recordings were starting at 7.30 A.M.; during the period from 8 A.M. to 2 P.M., the patient followed standard activity and performed a 6-min walking test as described by Lipkin *et al.*[14] The test was carried out in a 20 m long corridor, and each patient was instructed to cover as much ground as possible in 6 min.

Holter monitoring tapes were made by means of an Avionics two- or three-channel recorder and were analyzed by trained physicians, in a blinded fashion, on a visual and computerized scanning system (Model 563, Del Mar Avionics, Irvine, Calif., USA). We evaluated (1) mean VR over 24 h; (2) minimum VR during nighttime; (3) peak VR during the walking test; and (4) impairment of VR calculated as percentage between peak VR during the walking test and theoretical age-adjusted maximum rate (220 minus age). Heart rate was calculated from the number of QRS complexes in 1 min. We also evaluated the number of RR cycles >2 s and the number of phases of bradycardia <50 beats/min, calculated over four consecutive RR cycles. Possible adverse events were recorded by means of active questioning.

Student's *t*-test was used for statistical analysis and a p value of <0.05 was considered statistically significant.

Results

All 18 patients completed the study. Pill counting indicated that they had taken the tablets as directed.

Ambulatory Electrocardiographic Recording

Heart rate both at rest and after exercise varied widely between treatments. The results of Holter monitoring during the four treatment periods are shown in Figures 1 and 2. There were no significant differences in mean and in minimum VRs among the four treatments (Fig. 1). However, peak heart rates recorded during the 6-min walking test were significantly lower with calcium-channel blockers than with digoxin (Fig. 2). During treatment with digoxin, peak heart rate during the 6-min walking test was 167 ± 12 beats/min (range 149–185 beats/min). This was significantly reduced by calcium-chan-

TABLE I Clinical characteristics of study patients

Patients (male)	15 (83%)
Age (years)	66 ± 9
Heart disease	
None	10 (56%)
Arterial hypertension	8 (44%)
Echocardiogram	
LVEF	54 ± 8
LVEF <50%	2 (11%)
Left atrium >40 mm	3 (17%)
Mitral regurgitation (1–2/4)	5 (28%)

Abbreviation: LVEF = left ventricular ejection fraction.

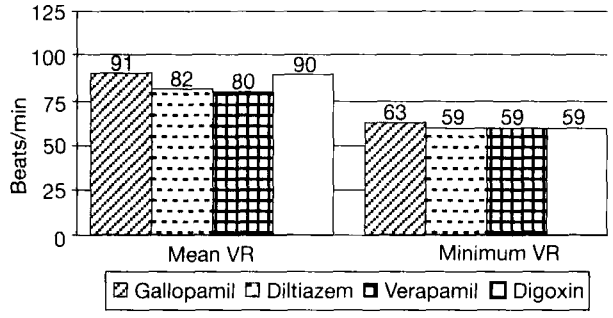

FIG. 1 Effect of modulating drugs on ventricular rate: Holter monitoring parameters. VR = ventricular rate.

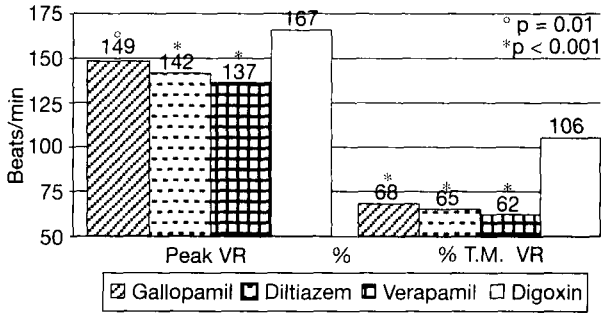

FIG. 2 Effect of modulating drugs on ventricular rate: 6-min walking-test parameters. VR = ventricular rate, T.M. VR = theoretical age-adjusted maximum rate.

nel blockers: gallopamil 149 ± 23 beats/min (range 105–176 beats/min), p = 0.01, versus digoxin; diltiazem 142 ± 24 beats/min (range 114–173 beats/min), p < 0.001, versus digoxin; verapamil 137 ± 30 beats/min (range 90–182 beats/min), p < 0.001, versus digoxin. There was no significant difference in peak ventricular rates during the walking test among these three calcium-channel blockers, but there was a significant difference in VR impairment percentage between digoxin and the three calcium-channel blockers (Fig. 2). The percentage between peak VR during the walking test and theoretical age-adjusted maximum rate (220 - age) was 106 ± 6% during treatment with digoxin. This was significantly reduced by gallopamil (mean 68 ± 10%, p < 0.005, vs. digoxin), diltiazem (mean 65 ± 11%, p < 0.001, vs. digoxin) and verapamil (mean 62 ± 14%, p < 0.001, vs. digoxin).

The number of RR cycles > 2 s and the number of phases of bradycardia < 50 beats/min were not significantly different among the four treatment groups (Table II).

Side Effects

None of the study patient experienced serious adverse effects with any treatment. The incidence of RR cycles > 3 s and the number of bradycardia phases < 30 beats/min were not significantly different among the four treatments. RR cycles > 3 s were observed in 3 of 18 (17%) patients who received digoxin (longest pause 3.4 s) and in 5 of 18 (28%) patients who received diltiazem (longest pause 3.4 s); p = not significant (NS). Periods of bradycardia < 30 beats/min were observed in 5 of 18 (28%) patients during treatment with digoxin (lowest VR 27 beats/min), and in 3 of 18 (17%) patients each during treatment with gallopamil (lowest VR 29 beats/min), diltiazem (lowest VR 27 beats/min), and verapamil (lowest VR 29 beats/min); p = NS.

TABLE II Bradyarrhythmic events

	Digoxin	Gallopamil	Diltiazem	Verapamil
PAU	137 ± 191	125 ± 206	254 ± 380	203 ± 332
BRD	170 ± 229	168 ± 278	261 ± 347	262 ± 421

All p values = not significant.

Abbreviations: PAU = RR cycles > 2 s, BRD = period of bradycardia < 50 beats/min.

Discussion

Management of PAF consists primarily of long-standing anticoagulation with either aspirin or warfarin to prevent systemic embolization, and modulation of VR.[3,4] The aim of modulating therapy is to reduce the ventricular response rate by increasing the AV conduction delay.

Digoxin is widely used in the treatment of PAF and increases the AV conduction block by potentiating vagal tone and by reducing adrenergic activity at the node.[15] However, during exercise, intrinsic vagal tone is withdrawn and adrenergic activity increases so that the efficacy of digoxin is reduced. Thus, digoxin fails to control VR during exercise, and it has been argued that this may lead to impairment of exercise tolerance.[6,7] During the digoxin period, mean peak heart rate during the 6-min walking test rose quickly to 167 ± 12 beats/min, ranging from 149 to 185 beats/min despite therapeutic digoxin concentration. This high ventricular response during mild effort confirms the above-mentioned hypothesis. Nevertheless, this is comparable with those reported by others who have performed similar studies using bicycle or treadmill ergometry.[7,8]

The optimal rate in terms of cardiac function is, however, unknown. In animal studies, increasing heart rate is associated with improved cardiac output up to a critical point at which cardiac output starts to decline.[16] The value of this critical point in human AF is uncertain. All calcium-channel blockers chosen for this study are recognized AV nodal blocking agents[10,17] which, by increasing AV nodal refractoriness, may be expected to reduce VR during AF.[18] Rate-limiting calcium entry blocking drugs such as verapamil and diltiazem achieve better control of exercise-induced tachycardia than digoxin in PAF,[8–11] and the effect of gallopamil on heart rate reduction in patients with AF and rapid ventricular response has been previously reported.[13] The present study demonstrated that not

only diltiazem and verapamil, but also gallopamil, were more effective than digoxin alone in controlling VR during mild effort. The influence of gallopamil, diltiazem, or verapamil on VR during exercise was not statistically different. However, gallopamil appears to be the least effective calcium-channel blocker for controlling exercise VR among the rate-modulating calcium blockers, although we cannot rule out the possibility that the dosage chosen for gallopamil was inadequate.

There was no evidence that treatment with rate-limiting calcium-channel blockers was associated with excessive bradycardia, as the minimum VRs recorded during ECG monitoring were similar with digoxin and calcium antagonists. Moreover, the number of RR cycles >2 s and the number of phases of bradycardia <50 beats/min were not significantly different among the four treatments.

None of the study patients experienced serious adverse effects with any treatment, and the incidence of RR cycles >3 s and the number of bradycardia phases <30 beats/min were not significantly different among the four drugs. In any case, discontinuation of the treatment because of advanced bradyarrhythmic events was unnecessary.

For assessment of heart rate, continuous 24-h ECG monitoring is superior to intermittent rhythm strip recording,[19] in that the effects of a full range of physical activities may be observed during the recording. However, unsupervised subjects may, for various reasons, limit their activity during the monitor period.[20] This difficulty was overcome by performing a 6-min walking test during the day of recording, thus allowing direct comparison among different treatment regimens.

Conclusions

Slow-release formulations of gallopamil, diltiazem, and verapamil are effective agents in the treatment of patients with PAF. Their effect on modulation of VR during mild effort is significantly superior when compared with the effectiveness of digoxin. The reduction of peak VR is obtainable without further slowing of resting VR; however, gallopamil appears to be the least effective calcium-channel blocker in controlling resting and exercise VR among the rate-modulating calcium blockers. Thus, this drug is not superior to the two drugs we currently use for this purpose, and there are not clear advantages over the other calcium blockers in its use in the clinical setting.

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