Clinical Research

Efficacy and Safety of Oral Amiodarone in Controlling Heart Rate in Patients with Persistent Atrial Fibrillation who have Undergone Digitalisation

George E. Kochiadakis, Emmanuel M. Kanoupakis, Nikolaos E. Igoumenidis, Hercules E. Mavrakis, Panagiotis K. Kafarakis, Panos E. Vardas

Department of Cardiology, Heraklion University Hospital, Crete, Greece

Key words:
Amiodarone, rate control, atrial fibrillation.

Introduction: Oral amiodarone has been suggested by some authors for rate control in patients with persistent atrial fibrillation. In this study we evaluated the efficacy and safety of oral amiodarone versus placebo for rate control during exercise and daily activities in patients with chronic atrial fibrillation who had undergone digitalisation.

Methods: The study group consisted of 53 patients (35 men, mean age 65 ± 9 years) with persistent atrial fibrillation (mean duration 17 ± 7 months). All patients had therapeutic levels of digitalis and were under anticoagulation treatment with acenocoumarol. Twenty-eight of them were treated with amiodarone (200 mg per day orally) and 25 received placebo. All patients were assessed with 24-hour ECG monitoring, a maximal symptom-limited cardiopulmonary exercise test and evaluation of adverse events.

Results: The mean exercise duration was similar in both groups. Amiodarone produced a lower heart rate than placebo at all exercise levels ($p<0.0001$ for all). VO_2 was similar in both groups whereas O_2 pulse was higher in the amiodarone group at all exercise levels. During daily life, heart rate showed a significant circadian pattern in both groups, with higher values during the day than at night (time effect for both $p<0.001$). The mean value of heart rate under amiodarone was lower than for placebo (75 ± 10 vs. 86 ± 12 /min, $p<0.001$) but this difference was due to a significant difference during the day ($p<0.001$) that was not present during the night ($p=0.48$).

Conclusions: Oral amiodarone is very effective when combined with digoxin for control of heart rate in patients with chronic atrial fibrillation and it should be considered as an alternative treatment when more traditional drugs, such as Ca^{+2} inhibitors or b-blockers have proven ineffective or are contraindicated.

Manuscript received:
April 13, 2005;
Accepted:
July 20, 2005.

Address:
George E. Kochiadakis

Cardiology Department,
Heraklion University Hospital,
P.O. Box 1352
Stavrakia,
711 00 Heraklion
Crete, Greece
e-mail:
cardio@med.uoc.gr

Oral amiodarone, an agent with a complex electrophysiological profile and multiple modes of action, has been suggested by some researchers for rate control in patients with persistent atrial fibrillation.[1-3] However its efficacy and safety when used for this purpose have not yet been studied sufficiently.

In light of the above we evaluated the efficacy and safety of oral amiodarone versus placebo for rate control during exercise and daily activities in patients with persistent atrial fibrillation who had undergone digitalisation.

Methods

Patients

The study group was recruited from patients with persistent atrial fibrillation (mean duration 17 ± 7 months) who were taking part in placebo-controlled studies in our clinic for

Table 1. Baseline patient characteristics. There were no significant differences between the two groups.

	Amiodarone (n=28)	Placebo (n=25)
Sex (male/female)	18/10	17/8
Age (years)	64 ± 8	67 ± 8
Left ventricular ejection fraction (%)	50 ± 12	51 ± 12
Atrial fibrillation duration (months)	18 ± 6	16 ± 7
Underlying heart disease (%)	16 (57.1%)	15 (60%)

the evaluation of the effectiveness of long-term amiodarone administration in the conversion of persistent atrial fibrillation to sinus rhythm and who had not converted after at least one month of treatment. The inclusion and exclusion criteria for these studies have already been published elsewhere.[4,5]

All 53 patients (35 men, mean age 65 ± 9 years) who qualified as above participated in this sub-study. Twenty-eight of them were under treatment with amiodarone (200 mg per day orally) and 25 were receiving placebo. No adverse effects necessitating drug discontinuation had occurred. All patients had therapeutic levels of digitalis and were under anticoagulation treatment with acenocoumarol (INR: 2-3). Any other agent with an antiarrhythmic effect was stopped at least 5 half lives before the patient entered the substudy.

Holter recordings - cardiopulmonary exercise test

All patients were assessed with 24-hour ECG monitoring, a maximal symptom-limited cardiopulmonary exercise test and evaluation of adverse events.

Patients exercised on a motor-driven treadmill (Max-1, Marquette, Milwaukee, USA) with an incremental exercise workload using a modified Naughton protocol. During testing, the patients breathed atmospheric air through a low-resistance mask. The partial pressures of respiratory O_2 and CO_2 were measured using a special gas analyser (Oxycon A, Mijnhard). The gas analyser was calibrated with standard gases immediately before each test. Gas exchange variables were measured continuously and averaged at 30-second intervals during the 2-minute rest period and throughout the test. The variables measured included VO_2 (ml/kg/min), respiratory exchange ratio (VCO_2/VO_2) and oxygen pulse (oxygen uptake/ heart rate). These parameters were determined at submaximal exercise (speed 3 mph, 0% grade), at the anaerobic threshold and at peak exercise. The gas exchange anaerobic threshold, determined as outlined by Beaver et al,[6] was taken as the mean of estimations performed by two independent observers who were unaware of the patients' treatment or other data.

Statistical analysis

Continuous data are summarised as mean ± standard deviation. The effect of the 2 different treatment schemes on changes in heart rate over time was assessed using repeated measures analysis of variance with 2 factors: one for temporal effect (at 24 levels for the circadian variation, 4 levels for the exercise test) and one for treatment effect. The exercise test had 4 levels: resting, submaximal exercise, anaerobic threshold and maximal exercise. In case of significant findings post-hoc tests were also performed. Separate sub-analyses were also performed to examine the day (7:00-23:00) and night (23:01-6:59) effect. A p value <5% was the criterion for significance in all statistical comparisons.

Results

All patients completed the sub-study uneventfully. The clinical characteristics of the two patient groups were similar (Table 1).

The mean exercise parameters and gas exchange variables at different exercise levels are shown in table 2. The mean exercise duration was similar in both groups. Amiodarone produced a lower heart rate than placebo at all exercise levels ($p<0.0001$ for all). Mean blood pressure was lower in the amiodarone group, but not significantly so, at all exercise levels. VO_2 was similar in both groups whereas O_2 pulse was higher in the amiodarone group at all exercise levels.

During daily life, heart rate showed a significant circadian pattern in both groups, with higher values during

Table 2. Exercise parameters and gas exchange variables at rest, submaximal exercise, anaerobic threshold and maximal exercise.

	Amiodarone	Placebo
Resting		
HR (beats/min)	71 ± 11*	95 ± 8
Systolic BP (mm Hg)	128 ± 12	139 ± 17
Submaximal exercise		
VO_2 (ml/kg/min)	14.4 ± 2	15.3 ± 2
O_2 pulse (ml/beat)	8.5 ± 1*	7.6 ± 1
HR (beats/min)	127 ± 9*	146 ± 10
Systolic BP (mm Hg)	146 ± 25	149 ± 19
Anaerobic threshold		
Time (s)	402 ± 37	410 ± 41
VO_2 (ml/kg/min)	17.5 ± 1.2	18.1 ± 2
O_2 pulse (ml/beat)	9.3 ± 1*	8.2 ± 0.8
HR (beats/min)	142 ± 8*	159 ± 12
Systolic BP (mm Hg)	150 ± 17	155 ± 12
Maximal exercise		
Time (s)	655 ± 52	688 ± 62
VO_2 (ml/kg/min)	23.7 ± 1.3	24.4 ± 1.4
O_2 pulse (ml/beat)	10.3 ± 0.8*	9.1 ± 0.6
HR (beats/min)	160 ± 18*	189 ± 12
Systolic BP (mm Hg)	172 ± 20	181 ± 18

*: $p < 0.05$ amiodarone vs. placebo
BP – blood pressure; HR – heart rate; VO_2 – oxygen uptake

the day than at night (time effect for both $p<0.001$). The mean value of heart rate under amiodarone was lower than for placebo (75±10 vs. 86±12 bpm, $p<0.001$) but this difference was due to a significant difference during the day ($p<0.001$) that was not present during the night ($p=0.48$) (Figure 1).

Discussion

Traditionally, the drug used for heart rate control in patients with persistent atrial fibrillation is digitalis. However, as our own results and previous findings from other studies have shown, this agent is ineffective in situations with elevated sympathetic tone, such as during exercise or stress, and it is thus often necessary to use an additional antiarrhythmic agent for better heart rate control.[1-3]

The results of this study suggest that oral amiodarone, which increases the refractory period of the atrioventricular node and slows atrioventricular nodal conduction time, could be used for this purpose.[7] More precisely, according to our results the addition of amiodarone to digoxin produces a lower heart rate than digoxin alone at all levels of exercise, as well as during daily activities when sympathetic tone is increased.

It is also of clinical importance that, in spite of the lower heart rate achieved when amiodarone is given along with digoxin, during exercise the exercise capacity is unaffected. As oxygen pulse, which reflects stroke volume, increased under amiodarone, this suggests that the study population are able to use their stroke volume reserve to compensate for the negative chronotropic effect of amiodarone. It is likely that this is due both to the peripheral vasodilatory properties of oral amiodarone and to the fact that, unlike the other drugs already used for this purpose, such as b-blockers or Ca^{+2} inhibitors, amiodarone exhibits little or no negative inotropic effect.[8,9]

It should be noted at this point that one previous study showed that amiodarone used on its own has a similar efficacy to digoxin in the control of heart rate during ambulatory activity and exercise.[10] This allows us to hypothesise that a combination of the two drugs is needed for a good clinical result, reflecting a synergistic effect on the atrioventricular node of the effects of amiodarone and the vagomimetic actions of digoxin.

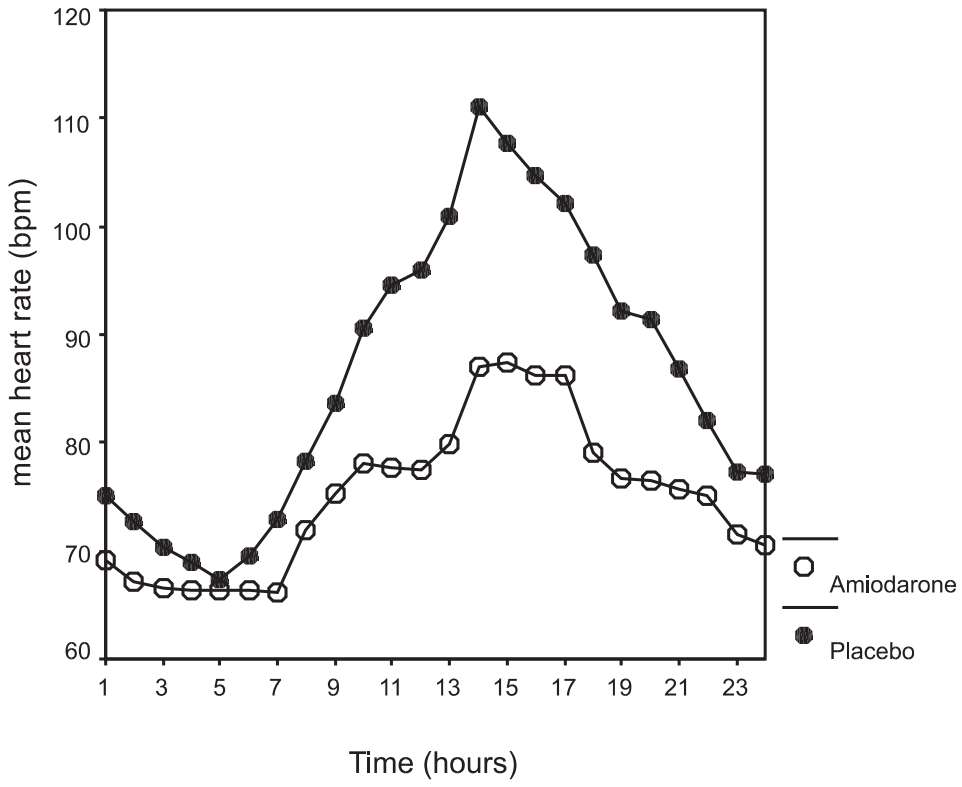

Figure 1. Mean hourly ventricular rate over 24 hours under the two treatments. The circadian pattern is apparent in both cases and the difference between the groups is clear during the day.

Oral amiodarone was quite safe and well tolerated in our patients. However this result should be viewed with care. Amiodarone is a drug that has been implicated in many cardiac and non-cardiac side effects that have been proved to be related to the dose and the duration of treatment; thus the absence of side effects in our patients was probably due to the small dosage and the relatively short time of administration.[11]

Conclusion

Oral amiodarone is very effective when combined with digoxin for control of heart rate in patients with persistent atrial fibrillation. However, although its use appeared safe in the present study, the cardiac and non-cardiac side effects reported elsewhere from its long term use mean that it should only be considered as an alternative treatment when more traditional drugs, such as Ca^{+2} inhibitors or b-blockers have proven ineffective or are contraindicated.

References

1. Blitzer M, Costeas C, Kassotis J, Reiffel JA: Rhythm management in atrial fibrillation—with a primary emphasis on pharmacological therapy: Part 1. Pacing Clin Electrophysiol 1998; 21: 590-602.
2. Jung F, DiMarco JP: Treatment strategies for atrial fibrillation. Am J Med 1998; 104: 272-286.
3. Fuster V, Ryden LE, Asinger RW, et al: ACC/AHA/ESC Guidelines for the Management of Patients With Atrial Fibrillation: Executive Summary. A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the European Society of Cardiology Committee for Practice Guidelines and Policy Conferences (Committee to Develop Guidelines for the Management of Patients With Atrial Fibrillation) Developed in Collaboration With the North American Society of Pacing and Electrophysiology. Circulation 2001; 104: 2118-2150.
4. Kochiadakis GE, Igoumenidis NE, Parthenakis FI, Chlouverakis GI, Vardas PE: Amiodarone versus propafenone for conversion of chronic atrial fibrillation: results of a randomized, controlled study. J Am Coll Cardiol 1999; 33: 966-971.
5. Kochiadakis GE, Igoumenidis NE, Solomou MC, Kaleboubas MD, Chlouverakis GI, Vardas PE: Efficacy of amiodarone for the termination of persistent atrial fibrillation. Am J Cardiol 1999; 83: 58-61.
6. Beaver WL, Wasserman K, Whipp BJ: A new method for detecting anaerobic threshold by gas exchange. J Appl Physiol 1986; 60: 2020-2027.
7. Connolly SJ: Evidence-based analysis of amiodarone efficacy and safety. Circulation 1999; 100: 2025-2034.
8. Bourke JP, Cowan JC, Tansuphaswadikul S, Campbell RW: Antiarrhythmic drug effects on left ventricular performance. Eur Heart J 1987; 8 Suppl A: 105-111.

9. Gill J, Heel RC, Fitton A: Amiodarone. An overview of its pharmacological properties, and review of its therapeutic use in cardiac arrhythmias. Drugs 1992; 43: 69-110.
10. Tse HF, Lam YM, Lau CP, Cheung BM, Kumana CR: Comparison of digoxin versus low-dose amiodarone for ventricular rate control in patients with chronic atrial fibrillation. Clin Exp Pharmacol Physiol 2001; 28: 446-450.
11. Vorperian VR, Havighurst TC, Miller S, January CT: Adverse effects of low dose amiodarone: a meta-analysis. J Am Coll Cardiol 1997; 30: 791-798.