CARDIOVASCULAR EFFECTS OF AQ-A 39 IN HEALTHY VOLUNTEERS

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- 1 Ten healthy male volunteers performed maximal exercise tests on a bicycle ergometer. A control reading was obtained; at a second session propranolol 80 mg was given, and then placebo, 100 mg or 200 mg AQ-A 39 were administered in a randomised double-blind manner.
- 2 At peak exercise, the heart rate averaged 191.6 beats/min during the control test, 185.8 beats/min after placebo, 172.4 beats/min with 100 mg of AQ-A 39 (-10%), 166.0 (beats/min) with 200 mg of AQ-A 39 (-13.4%); with 80 mg of propranolol, the heart rate averaged 132.8 beats/min and the workload accomplished was substantially lower than that accomplished with AQ-A 39 and placebo which remained the same as in the control test.
- 3 No effect on blood pressure was observed.
- 4 The rate pressure product was significantly reduced with AQ-A 39.

Keywords AQ-A 39 cardiovascular effects exercise testing

Introduction

AQ-A 39 (5,6-dimethoxy-2-[3[[α -(3,4-dimethoxy)-phenylethyl]methylamino]propyl]phtalimidine) induces a decrease in the heart rate of animals and reduces myocardial oxygen demand without affecting cardiac contractility (Dämmgen *et al.*, 1981; Kobinger & Lillie, 1981).

The bradycardic effect of AQ-A 39 is due to its direct action on the sinus node: the drug decreases the slope of the diastolic depolarization and prolongs the duration of the action potential. In terms of ionic currents, these effects have been explained by a frequency and voltage dependent blockade of the slow inward current and a blockade of potassium outward currents respectively (Osterrieder *et al.*, 1981). Further electrophysiological properties not yet completely explained probably contribute to the negative chronotropic effects of AQ-A 39 both on the sinus node and on Purkinje fibres (Hohnloser *et al.*, 1982; Lillie & Kobinger, 1983).

The aim of the present study was to investigate the effects of orally administered AQ-A 39 on the heart rate of healthy subjects both at normal levels during rest and at high levels during exercise.

Methods

Volunteers

Ten healthy male volunteers with a mean age of 24.5 (22-27) years consented to and participated in the study, which had been approved by the Ethical Committee of Haut Lévêque's Hospital.

The exercise tests

Volunteers performed standardized exercise tests on an Elema-Siemens bicycle ergometer. Cycling was maintained at 60 rev/min. The initial workload was started at 30 Watts and was increased by 30 Watts every 3 min until exhaustion.

Procedure

The day before the trial began (D0), a preliminary test was made to familiarize the participants with the laboratory conditions and to minimize the possibility of tachycardia due to anxiety. The control test was performed on the first day (D1). The same test was performed on the second day after oral administration of propranolol (2 tablets of 40 mg). No tests were

made on the third day (D3). On D4, D5 and D6, the tests were performed after administration under randomized double-blind conditions of 100 mg of AQ-A 39 (1 capsule of 100 mg), of 200 mg of AQ-A 39 (1 capsule of 200 mg) and of placebo (1 capsule).

Propranolol was chosen as a reference β -adrenoceptor blocker; it was not administered in a double-blind fashion because it was not possible to reproduce the same galenic presentation as AQ-A 39. The dose of 80 mg was chosen as it is a usual therapeutic dose which can be tolerated by a healthy subject. The trials were suspended on D3 to ensure the complete elimination of the propranolol. On the other hand, pharmacodynamic data showed that AQ-A 39 could be administered daily without risk of the effects being carried over from one day to the next (Benedikter, unpublished observations).

Based on pharmacokinetic data, the tests were carried out 2 h after drug administration. From experience it was found that tests were best performed towards the end of the morning. The drugs were therefore administered at 09.00 h and the exercise tests took place at 11.00 h.

Variables analysed

The ECG was monitored and recorded continuously throughout the study. The following data were thus obtained: heart rate, electrocardiographic events, systolic and diastolic blood pressure, maximal workload. Heart rate was assessed at rest, at each level of exertion (statistical analysis was made for exercise levels of 150 Watts 2 min and 180 Watts 2 min corresponding respectively to a total of 7,200 and 10,260 kpm), and also at peak exercise. Systolic and diastolic blood pressure were always measured by the same investigator, at the second minute of each exercise level, by the arm-cuff method using a sphygmomanometer and a stethoscope for auscultation. Workload was expressed in kpm and the rate pressure product was calculated.

Statistical analysis

The reported values are expressed as mean $\pm$ s.d. and were compared by non-orthogonal analysis of variance, taking into account that each subject was his own control. Tests were made to see whether there was an interaction between sequence and treatment to ensure there was no carry over of the effects of the drug from the previous day.

Results

Maximal workload

The highest average workload was achieved during the control test ($21,735 \pm 5,385$ kpm, i.e. 25 min 42 s

Table 1 Heart rate (beats/min) during the test. Mean $\pm$ s.e. mean values were calculated for ten subjects. Changes in percentages and *P* values are given from control.

	Control	Propranolol	Placebo	AQ-A 39 100 mg	AQ-A 39 200 mg
		P	P	P	P
Rest	78.7 $\pm$ 12.2	59.1 $\pm$ 14.6	78.1 $\pm$ 14.3	73.8 $\pm$ 8.6	72.4 $\pm$ 8.0
150 Watts 2 min	142.6 $\pm$ 13.1	110.7 $\pm$ 8.8	138.2 $\pm$ 10.6	129.3 $\pm$ 9.8	124.3 $\pm$ 8.2
180 Watts 2 min	158.4 $\pm$ 12.5	118.5 $\pm$ 8.6	154 $\pm$ 11.3	142.5 $\pm$ 9.9	135.7 $\pm$ 9.5
Peak exercise	191.6 $\pm$ 8.7	132.8 $\pm$ 9.2	185.8 $\pm$ 10.3	172.4 $\pm$ 9.1	166.0 $\pm$ 8.9
		< 0.001	NS	NS	NS
		< 0.001	NS	< 0.001	< 0.001
		< 0.001	NS	< 0.001	< 0.001
		< 0.001	NS	< 0.001	< 0.001

of exercise). After placebo ($20,218 \pm 5,474$ kpm, i.e. 23 min 54 s of exercise), after 100 mg AQ-A 39 ($20,349 \pm 4,676$ kpm, i.e. 24 min 24 s) and after 200 mg AQ-A 39 ($20,664 \pm 4,709$ kpm, i.e. 24 min 36 s), the average workload achieved was slightly but not significantly lower. However, after propranolol (80 mg), the workload attained averaged only $16,419 \pm 3,724$ kpm, i.e. 21 min 28 s of exercise, 24.5% less than control value; this decrease is statistically significant ($P < 0.001$).

Heart rate

The results are summarized in Table 1 and Figure 1. At rest, slightly lower results than control value were obtained after placebo, 100 mg AQ-A 39 and 200 mg AQ-A, but these variations were not statistically significant. On the other hand, after 80 mg propranolol the heart rate at rest was significantly lower (25% less than control value).

Figure 1 Heart rate at maximal exercise after placebo, 100 and 200 mg AQ-A 39. Graphical representation of individual subjects values.

Maximal heart rate: at peak exercise, the heart rate after placebo was slightly lower than control value, whereas after 100 mg AQ-A 39 it was significantly lower (-10%) and even lower after 200 mg AQ-A (-13.4%); after propranolol the heart rate at peak exercise was even lower than after 200 mg AQ-A (-30.7%).

At submaximal exercise: the results at 150 Watts 2 min and 180 Watts 2 min are shown in Table 1 and Figure 1. From the lower exertion levels and for each exertion level, the heart rate of each subject after placebo was identical or slightly, but not significantly, lower than during the control test. The heart rate after 100 mg AQ-A 39 was always significantly lower than after placebo and after 200 mg AQ-A 39 the heart rate was even lower. After 80 mg propranolol, the heart rate was always significantly lower than after 200 mg of AQ-A 39.

Blood pressure and rate pressure product

Results at peak exercise are shown in Figure 2. Slight but not significant changes in systolic blood pressure were observed after placebo and after AQ-A 39, whereas 80 mg propranolol caused a significant decrease in systolic blood pressure at rest and throughout exercise.

Some variations were observed in diastolic pressure which must be interpreted with reserve, given the difficulty in obtaining precise results by auscultation.

The rate pressure product was not significantly different from control after placebo. A statistically significant fall in rate pressure product was seen after 100 mg AQ-A 39 and it was more pronounced after 200 mg AQ-A 39. The decrease in rate pressure product was much more substantial after propranolol (42% lower than control at peak exercise).

Discussion

The cause of exertional angina is an increase in myocardial oxygen requirements which cannot be supplied by the atherosclerotic arteries of the heart, unlike unstable angina, more often caused by coronary spasm which suddenly reduces oxygen delivery (this distinction is in any case schematic as the two phenomena are often combined).

To reduce myocardial oxygen consumption, drugs have to act on some of its determining factors: heart rate, wall tension (linked to systolic blood pressure and to the radius of the ventricular cavity), myocardial contractility, time intervals of the heart cycles (Braunwald, 1970).

Two simple indexes are used to determine myocardial oxygen consumption: the 'rate pressure product' 'heart rate $\times$ systolic blood pressure' and the tension time index 'heart rate $\times$ systolic blood pressure $\times$ left ventricular ejection time'.

The results above show that, for each subject and for each exertion level, heart rate can be related to the drug and the dosage. From these results, it may be concluded that oral administration of 100 mg AQ-A 39 significantly decreases heart rate during exertion (at peak exercise it is 10% lower than control) and

Figure 2 Blood pressure and rate pressure product at maximal exercise. control (I), 80 mg propranolol (II), placebo (III), 100 mg AQ-A 39 (IV) and 200 mg AQ-A 39 (V).

that this decrease is even more pronounced with 200 mg AQ-A 39 (13.4% lower than control at peak exercise). Its action on heart rate, a determining factor of myocardial oxygen consumption, could make AQ-A 39 a potential anti-anginal agent.

A similar action on heart rate has been demonstrated with another compound, alinidine (Nicholls *et al.*, 1983; Harron *et al.*, 1982), although the two substances are chemically quite different. The action of these two compounds on the sinus node is not fully known but the electrophysiological properties of AQ-A 39 are better known.

The effect of 50 mg alinidine on tachycardia at submaximal effort was compared to that of 40 mg propranolol and found to be equivalent (Harron *et al.*, 1981). It would have been relevant to make such a comparison of AQ-A 39 and propranolol in doses which would produce the same reduction in heart rate, i.e. by giving higher doses of AQ-A 39 and lower doses of propranolol.

The doses chosen for AQ-A 39 were calculated according to data obtained from animal pharmacology, toxicology and from first clinical trials and the oral administration of more than 200 mg in a single dose raises ethical questions (Benedikter, unpublished observations).

Conversely, lower doses of propranolol could have been used. In this study, heart rate reduction is greater after propranolol and as, moreover, it reduces blood pressure, the decrease in rate-pressure product is more substantial than after AQ-A 39. Thus it would

appear that propranolol acts more effectively on myocardial oxygen consumption. However its action is accompanied by a decrease in myocardial contractility which does not occur with AQ-A 39 (Kobinger & Lillie, 1981; Lillie & Kobinger, 1981) and could explain why the workload achieved after AQ-A 39 is maintained whereas it is considerably reduced (by 24.5%) after propranolol. Thus, when the heart rate reduction produced by propranolol and AQ-A 39 is equal, the haemodynamic conditions are nevertheless completely different.

Moreover propranolol induces a decrease in heart rate at rest and during exercise, whereas AQ-A 39 does not exert its action at rest but only during exercise, and in a rate dependent manner. Therefore the dose of propranolol required to produce the same decrease in heart rate as a given dose of AQ-A 39 would depend on the workload. For this reason, it seemed advisable not to take only heart rate into consideration but to compare a realistically therapeutic dose of AQ-A 39 with a commonly used therapeutic dose of propranolol.

Furthermore, the next step in the clinical evaluation of AQ-A 39 should be a trial in patients suffering from exertional angina, comparing the drug with a therapeutic dose of propranolol.

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