Effect of cicloprolol in intraocular pressure in healthy vounteers

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Two oral doses of cicloprolol (50 mg and 100 mg), a β_1 -adrenoceptor partial agonist, were administered to nine healthy volunteers in a double-blind placebo-controlled study. Intraocular pressure (IOP) and exercise heart rate were reduced while the resting heart rate and blood pressure remained unchanged. The responses to the two different doses of cicloprolol were similar.

Introduction

Cicloprolol is a selective β_1 -adrenoceptor partial agonist (Cavero *et al.*, 1985). It has been given to healthy volunteers in oral doses of 25–100 mg and was shown to be well tolerated (McCaffrey *et al.*, 1987). β -adrenoceptor blocking effects on heart rate, blood pressure and tremor were seen for at least 3 h after dosage.

The aim of this study was to investigate whether cicloprolol has any ocular hypotensive effect after administration of single oral doses of 50 and 100 mg. Cardiovascular effects were monitored by measurement of resting and exercise heart rates and blood pressure.

Methods

Nine healthy volunteers of either sex (one female) aged 18–26 years participated in this study. Each attended on three occasions at the same time of the day separated by at least 1 week. On each occasion, baseline measurements were taken, then one tablet of either cicloprolol 50 mg, cicloprolol 100 mg or placebo was given. The volunteers arrived fasting and nothing, except water, was allowed until 3 h after dosing. The treatments were given in a double-blind design, partially balanced on the basis of three latin squares.

The measurements taken were resting heart rate (after sitting for 5 min), blood pressure (under the same conditions), IOP and exercise heart rate, in that order, before (baseline) and at 1, 2, 3 and 6 h after dosing. Exercise heart rate

was not measured at 1 h after dosing, i.e. only at times 0, 2, 3 and 6 h.

Heart rate was measured by counting the radial pulse rate for 1 min, blood pressure by a standard mercury sphygmomanometer and IOP by non-contact tonometry (Grolman, 1972). Exercise heart rate was induced by exercising the subjects on an electrically-braked bicycle ergometer. The work load necessary to increase the heart rate to 160 beats min^{-1} in the last 15 s of 3 min exercise was determined before starting the study.

Statistical analysis

The baseline values were first analysed by analysis of variance to test the differences between the different study days. There was no statistical difference between the pre-treatment values of IOP, resting and exercise heart rates. Post-treatment values were then analysed as follows: The areas under the response *vs* time curve of the post-treatment values for each subject on each treatment were calculated and then compared by analysis of variance.

Results

Intraocular pressure

Both doses of cicloprolol reduced intraocular pressure significantly in both eyes ($P < 0.005$).

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The maximal reduction was reached in 2 h and was still there 6 h after dosing (Figure 1). There was no statistical difference between the responses to the two doses of cicloprolol.

Resting heart rate

The resting heart rate was not changed after either of the doses of cicloprolol (Figure 2).

Exercise heart rate

A significant reduction of the exercise heart rate was detected with both doses of cicloprolol ($P < 0.001$). Maximal reduction was reached by 2 h and was still there 6 h after dosing (Figure 2). There was no significant difference between the responses to 50 mg and 100 mg of cicloprolol.

Blood pressure

Systolic and diastolic blood pressures were not changed significantly after either of the doses of cicloprolol.

Discussion

This experiment has demonstrated that cicloprolol possesses an ocular hypotensive action after oral administration of two doses (50 mg and 100 mg). Other β -selective adrenoceptor antagonists, such as atenolol (Elliot *et al.*, 1975), acebutolol (Welsh *et al.*, 1983) and betaxolol (Caldwell *et al.*, 1984), also possess this pharmacological effect.

Administration of oral cicloprolol was not associated with changes in resting heart rate. This is probably due to its potent β -adrenoceptor partial agonist activity balancing its antagonist action (McCaffrey *et al.*, 1987). However, exercise heart rate was inhibited to a significant degree by both doses of this agent.

The reduction in IOP and exercise heart rate were not affected by increasing the dose of cicloprolol indicating that we were probably at the plateau stage of the dose response curve.

Administration of these doses of cicloprolol was not associated with changes in blood pressure.

Until recently, timolol was the only β -adrenoceptor antagonist available in a topical

Figure 1 IOP changes (mean $\pm$ s.e. mean) after (○) 50 mg cicloprolol, (□) 100 mg cicloprolol and (●) placebo.

Figure 2 Resting and exercise heart rates (mean $\pm$ s.e. mean) after (○) 50 mg cicloprolol, (□) 100 mg cicloprolol and (●) placebo.

preparation for the treatment of glaucoma in the United Kingdom. Carteolol was introduced in mid 1986. Both are non-selective antagonists and carteolol has partial agonist and local anaesthetic actions as well (Gorgone *et al.*, 1983). The use of timolol has been associated with instances of severe bronchoconstrictor reactions (Fraunfelder & Barker, 1984). Caution is therefore necessary in asthmatic patients. Cicloprolol is a β_1 -selective adrenoceptor antagonist, a characteristic which may make it safer in the treatment of glaucoma in patients with obstructive

airways disease. It is also a long acting agent which may increase patient compliance.

This drug is in the early stage of its development and a topical preparation is not available yet. However, it was possible to demonstrate its ocular hypotensive action after oral administration and development of a topical preparation for further study should be considered.

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