Exercise and the pharmacokinetics of propranolol, verapamil and atenolol

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Summary. The volumes of distribution of the β-adrenoceptor blocking agents propranolol and atenolol, and the calcium antagonist verapamil, during exercise have been investigated. Changes in the plasma concentrations of atenolol and propranolol during exhaustive exercise at 70% of maximal aerobic power were compared after 1 week of oral treatment (propranolol 80 mg b.d. and atenolol 100 mg once daily) in 12 healthy volunteers. In a second study the effect of 10 min exercise at 50% of maximal aerobic power on steady state plasma concentrations of propranolol, atenolol and verapamil was compared in 7 healthy subjects. The drugs were administered by a continuous intravenous infusion.

The plasma concentration of atenolol was not changed by exercise in either study, but the plasma concentrations of propranolol and verapamil were significantly increased in both studies. However, after correction for changes in plasma volume during exercise, the plasma propranolol concentration was not significantly elevated in the second study.

From the results it is concluded that exercise led to a reduction in the volume of distribution of propranolol during prolonged exercise (25 min) at 70% Wmax, which was not clearly demonstrable during 10 min exercise at 50% Wmax. The volume of distribution of verapamil was reduced during 10 min exercise at 50% Wmax. No change in the volume of distribution of atenolol during exercise could be shown. The changes in the volumes of distribution of propranolol and verapamil during exercise may contribute to preventing an increase in the half-life of these drugs in patients performing prolonged physical exercise.

Keywords: Propranolol, Atenolol, Verapamil; pharmacokinetics, exercise

Subjects and methods

Two separate studies were performed. In the first the drugs were administered orally, and in the second intravenously.

Subjects

The first study was done 12 healthy, male volunteers (age 20 to 27 y); in the second study 7 healthy volunteers (age 20 to 23 y; 3 m, 4 f) took part. The protocol of the studies was approved by the Ethics Committee of the University of Limburg, and all subjects gave their written informed consent to it.

Protocol of the studies

The first study was performed as part of a larger study of the effects of β-adrenoceptor blockers on endurance exercise performance. The subjects came to the laboratory three times. On the first occasion...
maximal aerobic power (\(W_{max}\)) on a cycle ergometer (Lode, Groningen, The Netherlands) was determined in an incremental exercise test done to exhaustion. Before the next two visits, the subjects were given either propranolol (80 mg b.d.) or atenolol (100 mg) p.o. each for one week, in random order. The subjects took the last dose 1 h before coming to the laboratory. Treatment periods were separated by at least one drug-free week. On arrival in the laboratory catheters were inserted into forearm veins in each arm. A continuous infusion of saline (2.5 ml.min\(^{-1}\)) was started and was continued until the end of the recovery period. After 30 min at rest, the subject performed a submaximal endurance exercise test at 70% \(W_{max}\) until exhaustion. Before and after the initial 30 min rest period (t = -30 and 0 min), after 10 and 20 min of exercise (t = 10 and 20 min), at the moment of exhaustion, and after 3, 6 and 10 min of recovery, venous blood samples were obtained for determination of haematocrit haemoglobin concentration, and plasma drug concentration.

In the second study all subjects came to the laboratory three times after an overnight fast. On each occasion the subjects were given an intravenous infusion: propranolol, atenolol or verapamil, in random order. There was an interval of at least 1 week between tests.

After arrival in the laboratory venous catheters were inserted into forearm veins in each arm. A bolus injection of the drug (propranolol 195 \(\mu g\cdot kg^{-1}\); verapamil 225 \(\mu g\cdot kg^{-1}\); atenolol 35 \(\mu g\cdot kg^{-1}\)) was administered over 5 min, followed by continuous infusion (propranolol 42 \(\mu g\cdot min^{-1}\); verapamil 60 \(\mu g\cdot min^{-1}\); atenolol 5 \(\mu g\cdot min^{-1}\)) until the end of the experiment. The doses of the bolus and the infusion were chosen to obtain steady-state plasma concentrations of the three drugs of approximately 50 ng.m\(^{-1}\).

After 90 min of the infusion, an incremental exercise test to exhaustion was performed on a cycle ergometer (Lode, Groningen, The Netherlands) to determine the maximal aerobic work capacity (\(W_{max}\)). After further 60 min at rest, the subject exercised for 10 min on the cycle ergometer at 50% of \(W_{max}\).

Venous blood samples for determination of the plasma concentrations of the drugs were obtained after 150, 175 and 190 min of the infusion (t = -30, -15 and 0 min), and during the 1st, 3rd, 5th and 10th min of exercise (t = 1, 3, 5, 10 min) and recovery (t = 11, 13, 15, 20 min). Haematocrit and haemoglobin concentrations were also measured.

**Methods**

Haemoglobin concentration was determined with the OSM2 haemoximeter (Radiometer, Copenhagen) and haematocrit by micro-centrifugation. From changes in haemoglobin and haematocrit, changes in plasma volume were calculated [Dill and Costill 1974]. Propranolol, verapamil and atenolol concentrations were determined by HPLC with fluorimetric detection. The methods for propranolol and verapamil have previously been described [Mooij et al. 1987]. For atenolol the procedure was after addition of 1N NaOH 200 \(\mu l\) and 230 ng procainamide, as internal standard, to 1 ml plasma, the plasma was extracted with 6 ml dichloromethane:1-butanol (19:1). The organic phase was dried in a water bath under N\(_2\) and the residue dissolved in 100 \(\mu l\) eluent water:acetic acid:Bic B-7 (23:75:0.8:1.5). The solution was subjected to HPLC with a \(\mu\)Bondapack C18 column (Waters Inc., The Netherlands). For fluorimetric detection the excitation wavelength was set at 222 nm and the emission filter at 320 nm. The interassay coefficient of variation of the procedure was 6.2%.

**Data analysis**

Data are presented as mean with (SD). Statistical analysis was performed by two-tailed Student t-tests for paired observations. In the second study analysis of variance with repeated measurements was used to analyze differences between the three drugs; post-hoc pairwise comparisons between drug treatments were performed by Scheffe's F-test. \(P < 0.05\) was considered statistically significant.

**Results**

Plasma concentrations of propranolol and atenolol in the first study are shown in Fig. 1. The plasma concentration of propranolol did not change significantly between t = -30 min and t = 0 min (Fig. 1). Similar results were obtained for the plasma atenolol concentration. During exercise, however, the plasma concentration of propranolol rose significantly, from 168 (113) ng.m\(^{-1}\) to 202 (125) ng.m\(^{-1}\) at 20 min exercise (\(P = 0.01\)). In contrast, the plasma concentration of atenolol did not change during exercise [265 (115) ng.m\(^{-1}\) at t = 0 min and 270 (100) ng.m\(^{-1}\) at t = 20 min] (Fig. 1). Within the 10 min recovery period, the plasma propranolol concentration had returned to the pre-exercise level. The plasma atenolol concentration, on the other hand, rose during the recovery period [from 267 (100) ng/ml at exhaustion to 292 (107) ng.m\(^{-1}\) at 6 min recovery, \(P = 0.01\)]. The changes in the plasma volume during exercise were within 5% after each drug. Correction of the plasma concentration of the drug for the change in plasma volume did not yield significantly different results.

The results of the incremental maximal exercise test in the second study were: maximal heart rate was 144 (9) beats.min\(^{-1}\) during propranolol, 172 (8) beats.min\(^{-1}\) during atenolol, and 182 (10) beats.min\(^{-1}\) during verapamil infusion (\(P < 0.001\)). Differences between the pairs of treatments were also significant. Maximal power output (\(W_{max}\)) was 212 (46) W during propranolol, 234 (51) W during atenolol and 224 (44) W during the verapamil infusion (\(P < 0.01\)). Pairwise comparisons revealed that only the difference between propranolol and atenolol was significant.

In the second study, the plasma concentrations of propranolol and verapamil were similar at rest, and that of atenolol was significantly lower (\(P < 0.05\)). During the 10 min exercise period the concentrations of verapamil and propranolol increased significantly [propranolol from 51.9 (12.5) ng.m\(^{-1}\) (t = 0 min) to 59.6 (10.6) ng.m\(^{-1}\) (t = 10 min), \(P < 0.01\); verapamil from 50.9 (15.2) ng.m\(^{-1}\) (t = 0 min) to 70.1 (10.6) ng.m\(^{-1}\) (t = 10 min, \(P < 0.001\)).]