Clinical Pharmacology of a New β-Adrenoceptor Blocking Drug, Befunolol

Cross-Over Comparison with Propranolol on Repeated Administration

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Summary. Repeated doses of a new β-adrenoceptor blocking agent, befunolol, were administered orally to adult male volunteers for a cross-over comparison with propranolol. The β-adrenoceptor blocking activity of befunolol was greater than that of propranolol when assessed by the percentage reduction in exercise-induced tachycardia. The elimination half-life of drug was significantly prolonged on repeated administration of propranolol, but not of befunolol. The percentage reduction in exercise-induced tachycardia was highly correlated with the log plasma level of each drug. Both drugs produced a significant reduction in pre-exercise systolic and diastolic blood pressure, and significant attenuation of exercise-induced rise in systolic blood pressure.

Key words: befunolol, propranolol; pharmacokinetics, pharmacodynamic effects, beta-adrenoceptor blocking agent

Befunolol hydrochloride (2-acetyl-7-[2-hydroxy-3-isopropylaminopropoxy]benzofuran hydrochloride) is a new β-adrenoceptor blocking drug (Fig. 1). Experiments on the pharmacokinetics of befunolol in rats and rabbits showed high, rapid absorption from the intestine after oral administration, resulting in a wide distribution in various organs. Particularly high tissue concentrations were found in the liver, kidney and lung [1-3]. Being only slightly lipid-soluble, it is minimally distributed in the central nervous system and little passes through the placenta.

The β-adrenoceptor blocking activity of befunolol has been shown to be 2 to 10 times that of propranolol when compared in isolated organs and in situ [4]. Befunolol is considered to be devoid of intrinsic sympathomimetic activity [4] and have less membrane-stabilizing activity than propranolol [5].

Pharmacokinetic studies of befunolol in man after single oral administration have been reported [6, 7]. As drugs of this type are usually administered repeatedly in clinical practice, the present study was designed to investigate the pharmacokinetics and pharmacodynamics of befunolol in comparison with propranolol in adult male volunteers given ten oral doses.

Subjects and Methods

Subjects

9 subjects, aged 22 to 42 y and weighing 52 to 65 kg, were selected by physical and laboratory examination. Prior to admission to the study, the subjects were given a full explanation of the purpose and procedure of the trial, as well as of side-effects which might occur in association with the drug. Written consent was obtained from each subject.

Fig. 1. Structure of befunolol and its metabolite, M1
Table I. Dosage scheme

<table>
<thead>
<tr>
<th>Group</th>
<th>Subject</th>
<th>Test period I</th>
<th>Wash-out period</th>
<th>Test period II</th>
</tr>
</thead>
<tbody>
<tr>
<td>Befunolol-propranolol</td>
<td>A, B, C, D</td>
<td>Befunolol 20 mg every 6 h (a total of 10 doses)</td>
<td>1 month</td>
<td>Propranolol 20 mg every 6 h (a total of 10 doses)</td>
</tr>
<tr>
<td>Propranolol-befunolol</td>
<td>E, F, G, H, I</td>
<td>Propranolol 20 mg every 6 h (a total of 10 doses)</td>
<td></td>
<td>Befunolol 20 mg every 6 h (a total of 10 doses)</td>
</tr>
</tbody>
</table>

Test Drugs

The drugs used were capsules containing befunolol hydrochloride 10 mg and tablets containing propranolol hydrochloride 10 mg (Inderal®).

Treatment

9 subjects were divided into 2 groups at random, as shown in Table 1. The first group received befunolol during Period I and propranolol during Period II, and the second group received the drugs in the reverse order. Both drugs were administered as ten doses of 20 mg every 6 h. A wash-out period of 1 month was interposed between the 2 treatment periods. All subjects had 3 meals a day and were given a snack 2 h before the first and tenth doses of each drug. Smoking, caffeine or alcohol-containing beverages were not permitted during the study.

Examinations

Urinalysis, routine haematological examinations, blood biochemical tests, chest X-ray and electrocardiography were performed before the start and at the end of Periods I and II. Physical check-ups were performed daily at 7:00 a.m. during the test periods. Body temperature, weight, pulse rate and blood pressure were measured at the same time. In addition, the following examinations were carried out in each subject:

1. Determination of Plasma Drug Concentration.
   Blood was collected 1, 2, 3, 4 and 6 h after the first dose and immediately before and 1, 2, 3, 4, 6, 8, 11, 18 and 24 h after the tenth dose for determination of the plasma level of befunolol and MI (Fig.1), the main metabolite of befunolol in man [8], by gas-chromatography [6], and the plasma level of propranolol by radioimmunoassay [9].

2. Exercise Test. Exercise tests were carried out using a Jonas® 990 bicycle ergometer, to assess effects on heart rate and blood pressure just before and just after exercise at a submaximal work load. Control values were determined on the day before drug administration. Submaximal work load was measured at the point at which the heart rate exceeded 160 beats/min and plateaued. The work load used in this study was 105.6 ± 5.6 watts for 2.21 ± 0.17 min (mean ± SE, n = 9). Heart rate was determined by a telemetric tachometer (Nippon Koden, RT-5) with synchronization to the R-waves of the ECG. Blood pressure was recorded with an Arteriosonde® 1015 several times before and immediately after the exercise test, which was carried out before and 1.5, 3.5 and 5.5 h after the first and the tenth doses. Blood pressure was measured in 5 cases.

Pharmacokinetic Analysis

A graphical simulation of the time-course of plasma drug concentrations was performed up to 6 h after oral administration, by application of one- or two-compartment open models with an absorption phase, as represented by the following general expression deduced from the plot of the measured values in each subject.

When $t < t_L$, $C = Coe^{-\alpha t} [\text{ng/ml}]$

and when $t \geq t_L$, $C = Coe^{-\alpha t} + Ae^{-\beta(t-t_0)} + Be^{-\beta(t-t_L)} - (A + B)e^{-K(at-t_0)} [\text{ng/ml}]$

where

- $\alpha$: exponential coefficient [h⁻¹] of $\alpha$ phase,
- $\beta$: exponential coefficient [h⁻¹] of $\beta$ phase,
- $K$: absorption rate constant [h⁻¹],
- A: intercept of monoexponential $\alpha$ line with ordinate (ng/ml),
- B: intercept of the back-extrapolated monoexponential declining line with the ordinate [ng/ml],
- Co: hypothetical drug concentration at time 0, obtained by back-extrapolation of the monoexponential declining line [ng/ml],
- $t_L$: absorption time lag [h].

The analysis was carried out on a DEC®-RT 11 computer according to the formula of Berman et al. [10].

Pharmacodynamic Analysis

The $\beta$-adrenoceptor blocking effect was expressed as the percentage reduction in exercise-induced tachycardia (%R) using the following formula: