Impairment of Antipyrine Clearance in Humans by Propranolol

DAVID J. GREENBLATT, M.D., KATE FRANKE, DAVID H. HUFFMAN, M.D.

SUMMARY The effect of propranolol on antipyrine clearance in humans was evaluated in six healthy volunteers who received single 1.4 to 1.5 g doses of intravenous antipyrine on two occasions. The first (control) antipyrine trial was without concurrent drug administration; the second trial was done during treatment with therapeutic doses of propranolol (40 mg every 4 to 6 hours). Antipyrine elimination half-life (t1/2), volume of distribution (Vd), and total clearance were determined after each trial. In all subjects isoproterenol sensitivity decreased markedly during propranolol treatment, indicating a high degree of beta blockade produced by the drug. Mean antipyrine t1/2 during the propranolol treatment period was significantly prolonged, and total clearance significantly reduced, over the control values. Twenty-four-hour urinary excretion of 4-hydroxyantipyrine, the major metabolite of antipyrine, likewise was reduced from 23.6% of the dose on the control trial to 14.8% of the dose during propranolol coadministration (0.1 < P < 0.2). Vd however, was nearly identical during both trials (0.62 L/kg). Thus propranolol prolongs the half-life and reduces the clearance or biotransformation rate of antipyrine, a drug whose clearance is independent of hepatic blood flow. Propranolol may influence the activity of hepatic microsomal enzymes responsible for drug hydroxylation.

PROPRANOLOL IS CURRENTLY APPROVED for clinical use in the treatment of cardiac arrhythmias, angina pectoris, and hypertension. In these settings it is commonly coadministered with other pharmacologic agents, but there is little information available on possible pharmacokinetic interactions of propranolol with other drugs used to treat these disease states. Such interactions could be of considerable clinical importance if they lead to decreased efficacy or enhanced toxicity of other coadministered drugs. The present study assessed the interaction of propranolol with antipyrine, a compound that shares with many other drugs a primary biotransformation pathway involving hydroxylation by the liver. As such, the pharmacokinetic profile of antipyrine is extensively used as an index of drug-metabolizing capacity in humans, and appears to be sensitive to factors that stimulate or inhibit drug metabolism.
Subjects

Six healthy male and female volunteers, aged 21 to 30 years, participated after giving written informed consent. All were free of identifiable medical disease (including cardiac disease, asthma, or diabetes), and none was taking any medications on a chronic basis.

Procedure

Each subject received single intravenous doses of antipyrine on two occasions separated by at least one week. On the first (control) trial, antipyrine was given without concurrent drug administration. On the second trial, subjects ingested propranolol, 40 mg every 4 to 6 hours, beginning 12 hours prior to antipyrine infusion, and continuing for 24 hours after antipyrine dosage. The total dose of propranolol over the 36-hour period was 400 mg.

Antipyrine was prepared in a sterile aqueous solution of 200 mg/ml. A quantity of this solution containing 1.4 to 1.5 g of antipyrine was diluted to 50 ml with 5% dextrose in water and infused into an antecubital vein over a period of 5 minutes by a constant-rate infusion pump. Venous blood samples were drawn from the contralateral arm into heparinized tubes prior to drug administration, at the termination of the infusion, and at 5, 15, 30, 45 minutes, 1 hour, 1.5, 2.0, 2.5, 3.4, 6.8, 12, 18, and 24 hours after the infusion. In addition, a 24-hour urine collection commenced at the start of the infusion. Plasma samples and aliquots of urine were frozen until the time of assay.

The degree of beta adrenergic sensitivity (or blockade) was assessed just prior to both antipyrine administration trials in each subject using the isoproterenol infusion technique. Under continuous electrocardiographic monitoring, incremental bolus doses of intravenous isoproterenol were administered every 2 to 3 minutes until a transient increase in ventricular rate of at least 30 beats per minute over the baseline control value was noted. The sequence of isoproterenol doses was as follows: 0.1 μg, 0.2, 0.5, 1.0, 2.0, 5.0, 10.0, 20.0, 50.0, 100.0, and 200.0 μg. When the end point was reached, no further doses were given and the antipyrine infusion trial was begun.

Analysis of Samples

Plasma concentrations of antipyrine were determined by spectrophotometric assay. Urinary excretion of unchanged antipyrine and of its metabolite, 4-hydroxyantipyrine, were determined by gas chromatography using acetaminophen as an internal standard. The presence of propranolol in plasma did not interfere with the assay for antipyrine.

Table 1. Effect of Propranolol Coadministration on Antipyrine Pharmacokinetics

<table>
<thead>
<tr>
<th>Subject</th>
<th>Elimination half-life</th>
<th>Volume of distribution</th>
<th>Clearance</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>control (hr)</td>
<td>with propranolol</td>
<td>control (L/kg)</td>
</tr>
<tr>
<td>1</td>
<td>13.3</td>
<td>14.0</td>
<td>.64</td>
</tr>
<tr>
<td>2</td>
<td>12.4</td>
<td>16.7</td>
<td>.61</td>
</tr>
<tr>
<td>3</td>
<td>8.9</td>
<td>15.7</td>
<td>.63</td>
</tr>
<tr>
<td>4</td>
<td>12.6</td>
<td>17.3</td>
<td>.68</td>
</tr>
<tr>
<td>5</td>
<td>11.7</td>
<td>13.3</td>
<td>.61</td>
</tr>
<tr>
<td>6</td>
<td>6.1</td>
<td>12.4</td>
<td>.55</td>
</tr>
<tr>
<td>Mean</td>
<td>10.8 (±1.1)</td>
<td>14.9 (±0.8)</td>
<td>.62 (±.02)</td>
</tr>
</tbody>
</table>

| paired t | 4.01 | 0.17 | 2.93 |
| level of significance | $P \sim .01$ | NS | $P < .05$ |
Analysis of Data

For each subject-trial, the slope of the terminal log-linear portion of the plot of antipyrine plasma concentration versus time was determined by least-squares regression analysis. The slope and intercept of the least-squares line was used to determine the antipyrine elimination half-life, volume of distribution, and clearance. Differences in these variables between the control and propranolol conditions were analyzed using Student's paired t-test.

The degree of beta adrenergic sensitivity (or blockade) was determined from a graph of the increase in ventricular rate over the pre-isoproterenol baseline value versus the logarithm of the isoproterenol dose. The slope and intercept of this line were used to determine the 30-beat chronotropic dose (CD-30).

The beta blockade index for each subject was defined as the ratio of the CD-30 during ingestion of propranolol divided by the CD-30 in the control state.

Results

A high degree of beta blockade was achieved in all subjects by propranolol administration. The mean (± standard error) CD-30 during the control period was 2.6 ± 0.4 µg of isoproterenol, as compared with 77.2 ± 18.2 µg during propranolol treatment (fig. 1). The mean beta blockade index was 33.1 ± 10.1, with a range of 17.0 to 41.8.

Table 1 shows pharmacokinetic variables for antipyrine during the control period and during propranolol administration. The apparent volume of antipyrine distribution was nearly identical during both treatments (0.62 L/kg). However, the antipyrine elimination half-life was prolonged from a mean of 10.8 ± 1.1 hr during the control period to 14.9 ± 0.8 during propranolol treatment (P < 0.01), and antipyrine clearance reduced from 0.71 to 0.41 ml/min/kg (P < 0.05) (table 1, fig. 2). In addition, the 24-hour urinary excretion of 4-hydroxyantipyrine (fig. 3) fell from a mean of 23.6 ± 4.9% of the dose during the control period to 14.8 ± 0.8% during propranolol treatment (paired t = 1.86, 0.1 < P < 0.2). There was also a trend toward an increase in the 24-hour urinary excretion of unchanged antipyrine during the propranolol trial (from 3.9 ± 0.6 to 4.7 ± 0.8% of the dose). None of the changes in the pharmacokinetic variables was correlated with the beta blockade index.

Discussion

Administration of therapeutic doses of propranolol to healthy individuals in the present study had no apparent effect upon the volume of distribution of a single intravenous dose of antipyrine, but significantly prolonged antipyrine elimination half-life, and significantly reduced its total metabolic clearance. There was also a trend toward a decrease in urinary excretion of 4-hydroxyantipyrine, the major metabolite of this compound formed by a hydroxylation reaction in the liver. Thus propranolol coadministration appears to reduce the rate of antipyrine biotransformation. It is very unlikely that this interaction is attributable to chance, since the pharmacokinetic profile of antipyrine in animals and humans is quite reproducible upon repeated
testing in the same subject in the absence of exogenous factors that influence antipyrine metabolism. Although antipyrine itself is not generally used as a therapeutic agent in clinical practice, it is widely utilized as a marker for drug metabolizing capacity.1-6 Thus, the findings may have relevance to interactions of propranolol with other compounds.

The exact mechanism of the propranolol-antipyrine interaction is not established by our study. Assuming hepatic blood flow in a healthy individual to be approximately 21 ml/kg/min, the hepatic extraction ratio for antipyrine, estimated as the ratio of its clearance divided by hepatic blood flow,8, 12 averaged only about 4% in the control state. Thus, although propranolol has the ability to reduce cardiac output and hepatic blood flow in healthy individuals,12 it is unlikely that a change in hepatic blood flow could account for the reduction in antipyrine clearance attributable to propranolol.12-14 A previous report in fact indicated that the clearance of morphine, a compound with a much higher hepatic extraction ratio than that of antipyrine, was not influenced by propranolol.15 It is therefore likely that propranolol has a direct influence on the activity of the hepatic microsomal enzymes responsible for drug hydroxylation.14 Further studies on the mechanism and clinical implications of this interaction are necessary. Studies are also needed to establish the time-course of interaction following propranolol discontinuation, since we assessed only those effects attributable to concurrent propranolol treatment.

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