Effects of pyrazinamide, probenecid, and benzbromarone on renal excretion of oxypurinol

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Abstract
The effects of pyrazinamide, probenecid, and benzbromarone on renal excretion of oxypurinol were investigated. Pyrazinamide decreased the mean (SEM) fractional clearance of oxypurinol from 19.2 (2.1) to 8.8 (1.5). Probencid increased the fractional clearance of oxypurinol from 14.1 (3.5) to 24.8 (4.1). Benzbromarone increased the fractional clearance of oxypurinol from 15.6 (2.3) to 33.8 (2.8). These results suggest that oxypurinol may be secreted by a 'an organic acid system' and that oxypurinol is reabsorbed at a putative postsecretory site of the renal tubules.

Oxypurinol is a major metabolite of allopurinol, which is now widely used for the control of uric acid production in patients with gout. Oxypurinol is a strong inhibitor of xanthine oxidase, its inhibitory potency being similar to that of allopurinol, and it has a longer half life (13–18 hours) than allopurinol (0.6–1.6 hour). Therefore, the effect of allopurinol on uric acid production can be attributed almost entirely to oxypurinol. In normal subjects and patients with gout allopurinol is mainly converted to oxypurinol by xanthine oxidase, and oxypurinol is then excreted unchanged by the kidney. The concentration of serum oxypurinol is directly related to the renal clearance of oxypurinol, which increases or decreases under various conditions. For treatment of patients with gout, therefore, it is important to understand the renal excretion of oxypurinol. The renal excretion of oxypurinol seems to be similar to that of uric acid, but the renal transport mechanism(s) of oxypurinol has not yet been clearly elucidated. Probenecid and benz bromarone are two uricosuric agents, which seem mainly to inhibit the renal reabsorption of uric acid at the postsecretory site (fig 1). Pyrazinamide is an antituberculous agent and is well known to inhibit the renal secretion of uric acid (fig 1). These three agents have therefore been used to study the renal transport of uric acid. As the renal excretion of oxypurinol is similar to that of uric acid, in this study we investigated the renal excretion of oxypurinol using these drugs (pyrazinamide, probenecid, and benz bromarone).

Materials and methods

CHEMICALS
Oxypurinol and allopurinol were kindly provided by Tanabe (Osaka, Japan). Pyrazinamide, benz bromarone, and probenecid were kindly provided by Sankyo (Tokyo, Japan), Torii (Tokyo, Japan), and Banyu Pharmaceutical (Tokyo, Japan) respectively. Other chemicals were obtained from Wako Pure Chemical Industries (Osaka, Japan).

ANALYSES OF PLASMA AND URINE SAMPLES
Plasma and urinary creatinine concentrations were measured with a Wako creatinine test kit. Oxypurinol in plasma and urine samples was measured by high performance liquid chromatography. The chromatography method described previously was modified by combining two reversed phase columns (C18 microsphere column in series, 2,3-Pyrazinedicarboxamide, purified as reported previously, was used as an internal standard for measuring plasma oxypurinol.

SUBJECTS AND PROTOCOL
Studies were made on 15 men, 26 to 39 years old with no clinical history and who appeared healthy on physical examination, giving normal results in urine analyses, complete blood counts, and routine blood chemical analyses. They received only water for 12 hours before the study and were divided into three groups of five. Allopurinol (300 mg) was given orally to all groups. After three and a half hours urine was completely voided and then urine samples were collected twice at 30 minute intervals. Blood samples were taken twice at the midpoints.

Figure 1. Renal transport of uric acid in humans. Probenecid and benz bromarone each inhibit uric acid transport at (3). Pyrazinamide inhibits uric acid transport at (2).
between collections of urine samples with a heparinized syringe. The plasma was promptly separated. After the second urine sample had been taken the three groups received 2·0 g of probenecid, 300 mg of benzbromarone, or 3·0 g of pyrazinamide respectively. One and a half hours later urine was completely voided and then urine samples were collected twice at 30 minute intervals. Blood samples were taken twice at the midpoints between collections of urine samples. This protocol was based on the results of a preliminary study which showed that the plasma concentration of oxypurinol was not significantly different four and six hours after the intake of 300 mg of allopurinol. The oxypurinol concentration of each sample was measured and the percentage ratio of oxypurinol clearance/creatinine clearance (fractional oxypurinol clearance, F_{ox}) was calculated. The means of variables in the control period and in the period after treatment with test drugs were calculated.

**STATISTICAL ANALYSES**

Values are shown as means (SEM). Significances of differences in the means of variables in the control period and in the period after treatment with test drugs were analysed by the two tailed, paired t test. The variables examined were the plasma oxypurinol concentration, urinary ratio of oxypurinol to creatinine (U_{ox}/U_{cr}), and F_{ox}.

**Results**

**EFFECT OF PYRAZINAMIDE ON OXYPURINOL**

Figure 2 shows mean values of various indices in the control period and after administration of pyrazinamide. After pyrazinamide treatment the plasma concentration of oxypurinol did not change, but U_{ox}/U_{cr} and F_{ox} decreased from 0·98 (0·24) to 0·45 (0·13) (p<0·05) and from 19·2 (2·1) to 8·8 (1·5) (p<0·005) respectively.

**EFFECT OF PROBENECID ON OXYPURINOL**

Figure 3 shows mean values of various indices in the control period and after the probenecid treatment. Probenecid treatment did not affect the plasma concentrations of oxypurinol, but it caused an increase in U_{ox}/U_{cr} from 0·72 (0·11) to 1·17 (0·07) (p<0·005) and an increase in F_{ox} from 14·1 (3·5) to 24·8 (4·1) (p<0·005) respectively.

**EFFECT OF BENZBROMARONE ON OXYPURINOL**

Figure 4 shows mean values of various indices in the control period and after benzbromarone treatment. This drug did not affect the plasma concentration of oxypurinol but caused an increase in U_{ox}/U_{cr} from 0·87 (0·14) to 1·67 (0·26) (p<0·005) and an increase in F_{ox} from 15·6 (2·3) to 33·8 (2·8) (p<0·005) respectively.

**Discussion**

There are reports that oxypurinol, like uric acid, is reabsorbed by the renal tubules in...
Renal excretion of oxypurinol

Figure 5 Hypothetical renal transport of oxypurinol in humans.

Humans and dogs, that pyrazinamide inhibits the secretion of uric acid by the renal tubules in humans, and that oxypurinol has a $pK_a$ of 7-7 and would thus not be transported by the 'organic acid system' of tubular secretion in humans. These previous reports suggest that pyrazinamide does not affect the renal excretion of oxypurinol. In this study, however, we found that pyrazinamide caused a decrease in $F_{ox}$ (fig 2), suggesting that oxypurinol may be secreted at the secretory site because at the pH of plasma a weak acid with a $pK_a$ of 7-7 would be ionised to an appreciable extent (fig 3). Probenecid is a uricosuric agent and at normal dose it mainly inhibits the tubular reabsorption of uric acid at the postsecretory site, suggesting that it may inhibit the tubular reabsorption of oxypurinol at that site. Its effect in increasing $F_{ox}$ in normal subjects (fig 3) supports this possibility and is consistent with the results in subjects with gout. Benz bromarone, like a normal dose of probenecid, seems mainly to inhibit postsecretory reabsorption of uric acid. Therefore, benz bromarone probably also increases $F_{ox}$. A pharmacokinetic interaction between benz bromarone and oxypurinol has been suspected, but this interaction was not detected in previous studies, except in the study by Colijn et al., which showed that oral administration of 100 mg/day or 20 mg/day of benz bromarone for seven days increased $F_{ox}$ in normal subjects. Colijn et al suggested that the absence of an observed pharmacokinetic interaction between benz bromarone and oxypurinol in previous studies was due to the slow onset of action of benz bromarone because all previous studies had been conducted using a single high dose schedule (allopurinol 300 mg, benz bromarone 60 mg). Their speculation led us to suspect that even a single dose of benz bromarone might increase $F_{ox}$ if it exerted a sufficiently strong uricosuric action. Therefore, we tested the effect of a single very high dose schedule (allopurinol 300 mg, benz bromarone 300 mg) and found that benz bromarone did in fact increase $F_{ox}$ (fig 4), indicating that the hypouricaemic effect of combination therapy with allopurinol and benz bromarone on plasma uric acid may be less than additive, as reported by von Loffler et al. and that oxypurinol may be reabsorbed at least at a postsecretory site of the tubules (fig 5).
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