

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). Probenecid 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 '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).¹⁻⁵ 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.² The concentration of serum oxypurinol is directly related to the renal clearance of oxypurinol,⁴ which increases or decreases under various conditions.⁴⁻⁶ 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,^{4,7} but the renal transport mechanism(s) of oxypurinol has not yet been clearly elucidated. Probenecid and benzbromarone are two uricosuric agents, which seem mainly to inhibit the renal reabsorption of uric acid at the postsecretory site⁸⁻¹⁰ (fig 1). Pyrazinamide is an antituberculous agent and is well known to inhibit the renal secretion of uric acid⁸ (fig 1). These three agents have therefore been used to study the renal transport of uric acid.^{11,12} As the renal excretion of oxypurinol is similar to that of uric acid,⁴ in this study we investigated the renal excretion of oxypurinol using these drugs (pyrazinamide, probenecid, and benzbromarone).

Materials and methods

CHEMICALS

Oxypurinol and allopurinol were kindly provided by Tanabe (Osaka, Japan). Pyrazinamide, benzbromarone, 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 previously¹³ was modified by combining two reversed phase columns (C₁₈ microsphere column) in series. 2,3-Pyrazinedicarboxamide, purified as reported previously,¹⁴ 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

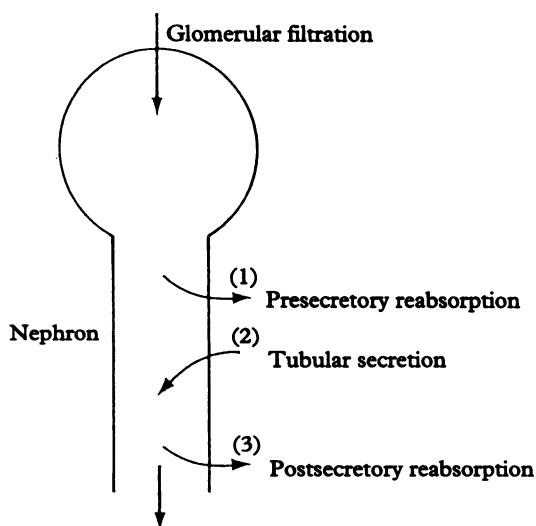


Figure 1 Renal transport of uric acid in humans. Probenecid and benzbromarone each inhibit uric acid transport at (3). Pyrazinamide inhibits uric acid transport at (2).

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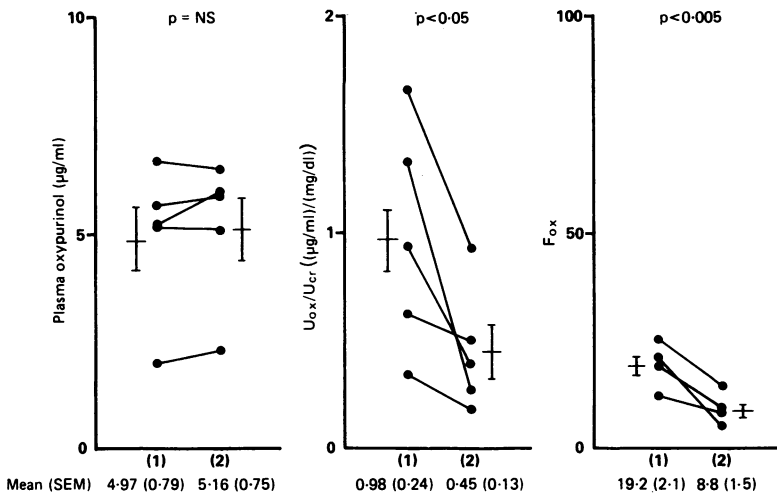


Figure 2 Effects of pyrazinamide on plasma oxypurinol, urinary ratio of oxypurinol to creatinine (U_{ox}/U_{cr}), and fractional oxypurinol clearance (F_{ox}). (1)=control period; (2)=after pyrazinamide treatment.

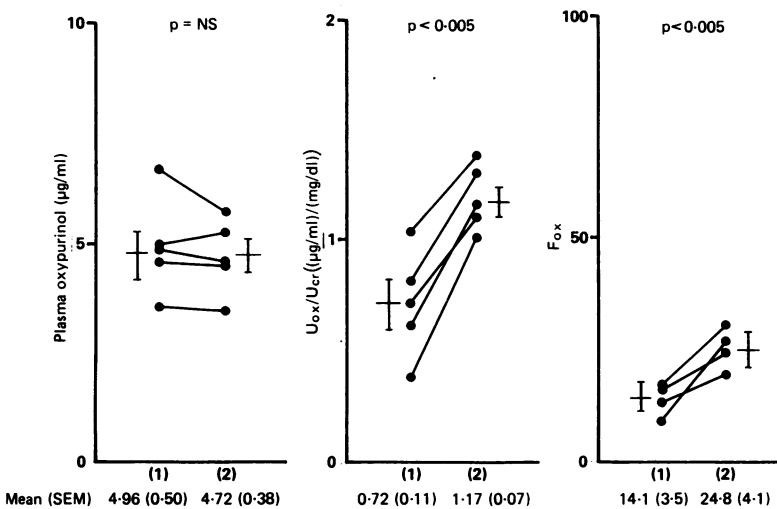


Figure 3 Effects of probenecid on plasma oxypurinol, urinary ratio of oxypurinol to creatinine (U_{ox}/U_{cr}), and fractional oxypurinol clearance (F_{ox}). (1)=control period; (2)=after probenecid treatment.

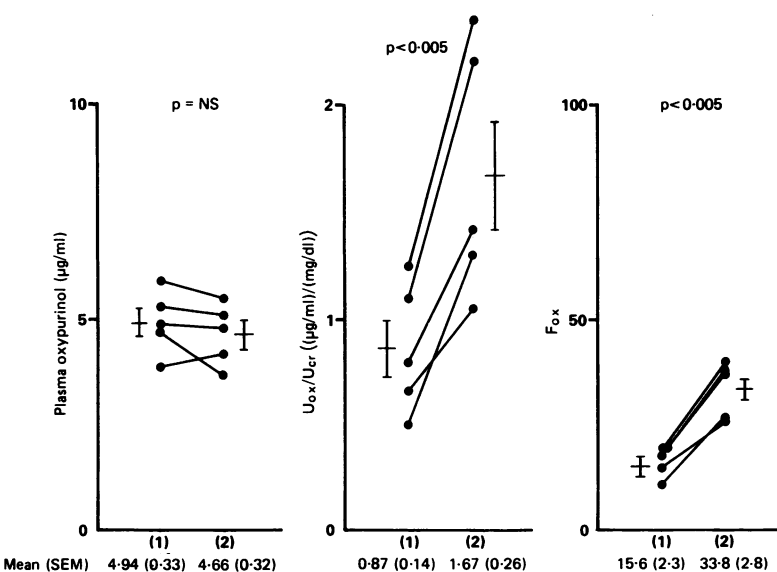


Figure 4 Effects of benzbromarone on plasma oxypurinol, urinary ratio of oxypurinol to creatinine (U_{ox}/U_{cr}), and fractional oxypurinol clearance (F_{ox}). (1)=control period; (2)=after benzbromarone treatment.

between collections of urine samples with a heparinised 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.¹⁵ 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 OXPURINOL

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 OXPURINOL

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 OXPURINOL

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

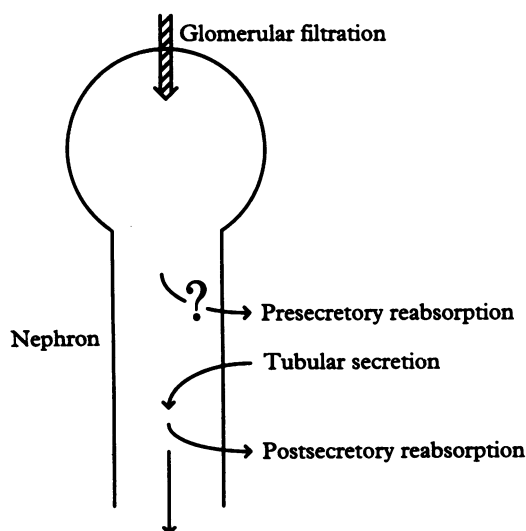


Figure 5 Hypothetical renal transport of oxypurinol in humans.

humans and dogs,⁴ that pyrazinamide inhibits the secretion of uric acid by the renal tubules in humans,⁸ 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.⁵ 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 5). Probenecid is a uricosuric agent and at normal dose it mainly inhibits the tubular reabsorption of uric acid at the postsecretory site,⁸ 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.⁴ Benzbromarone, like a normal dose of probenecid, seems mainly to inhibit postsecretory reabsorption of uric acid.¹⁰ Therefore, benzbromarone probably also increases F_{ox} . A pharmacokinetic interaction between benzbromarone and oxypurinol has been suspected, but this interaction was not detected in previous studies,^{16, 17} except in the study by Colin *et al*,⁷ which showed that oral administration of 100 mg/day or 20 mg/day of benzbromarone for seven days increased F_{ox} in normal subjects. Colin *et al* suggested that the absence of an observed pharmacokinetic interaction between benzbromarone and oxypurinol in previous studies was due to the slow onset of action of

benzbromarone because all previous studies had been conducted using a single high dose schedule (allopurinol 300 mg, benzbromarone 60 mg).^{16, 17} Their speculation led us to suspect that even a single dose of benzbromarone 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, benzbromarone 300 mg) and found that benzbromarone did in fact increase F_{ox} (fig 4), indicating that the hypouricaemic effect of combination therapy with allopurinol and benzbromarone on plasma uric acid may be less than additive, as reported by Von Loffler *et al*¹⁸ and that oxypurinol may be reabsorbed at least at a postsecretory site of the tubules (fig 5).

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