Renal Handling of Uric Acid in Man*

DENNIS J. LEVINSON, M.D., F.A.C.P., DOUGLAS E. DECKER, B.S.,
and LEIF B. SORENSEN, M.D.

Division of Rheumatology,
Department of Medicine,
Michael Reese Hospital and Medical Center,
Chicago, IL 60616

ABSTRACT

The uricosuric response to 80 mg of micronized Benzbromarone was employed to assess the renal tubular secretory site for uric acid in patients with primary gout. Since Benzbromarone† selectively inhibits tubular reabsorption of secreted urate, the maximum uricosuria induced by this drug can be equated with the minimal secretory rate. Furthermore, a significant relationship was noted in normal controls between urate secretion and the plasma urate concentration (r = 0.956, p < 0.005). Using the Benzbromarone response as a measure of tubular secretion, gouty patients with normal production hyperuricemia had a significantly lower secretory rate by comparison to patients with overproduction of uric acid. These data indicate that in patients with primary normal production hyperuricemia, the renal tubular defect is related to a decreased secretory response for a given plasma concentration of uric acid.

Introduction

Bi-directional renal urate transport, studied by both clinical and pharmacologic means, reveals a four-component system including complete filtration of uric acid at the glomerulus, virtually complete reabsorption of filtered urate, a distal secretory site, and further reabsorption of secreted urate. Net tubular urate excretion amounts to approximatley 10 percent of the filtered load.8

Praetorius and Kirk presented evidence for tubular secretion of uric acid in man when they reported a patient with a urate clearance that was 46 percent greater than a simultaneously determined endogeneous glomerular filtration rate.11 This finding was interpreted as indicating not only a defect in urate reabsorption but also the existence of tubular secretion of uric acid. Subsequently, Gutman and coworkers demonstrated net tubular urate secretion in some patients with a modest decrease in renal function.
by the administration of sulfinpyrazone during osmotic diuresis and urate loading. Under these experimental conditions, urate excretion exceeded the filtered load by approximately 20 percent. On the basis of these observations, Gutman and Yü proposed a three-component hypothesis for the renal handling of urate. Accordingly urate was completely filtered at the glomerulus and subsequently underwent both reabsorption and secretion. Furthermore, these authors speculated that excreted urate might represent urate that had been secreted in the tubule.

In recent years, evidence has accumulated indicating that urate secretion is far greater than heretofore believed and that most of the secreted uric acid is reabsorbed at a distal post-secretory site.

Indirect evidence favoring the existence of reabsorption of secreted urate has arisen from studies of patients with Hodgkin's and Wilson's disease who have hypouricemia related to defective tubular urate reabsorption. When these patients were given pyrazinamide, a compound known to block tubular secretion of uric acid, the urine became almost free of urate, indicating that their inappropriate response did not result from a defect in the tubular reabsorption of filtered urate.

Analogous to these cases, a report was made by us of a 26-year old woman who was found to have a defect in reabsorption of uric acid localized solely to the post-secretory site, and in whom no underlying disease could be demonstrated. Perhaps, the most compelling argument for reabsorption of secreted uric acid has been gathered from pharmacologic studies using pyrazinamide and uricosuric drugs. For example, it has been shown that the uricosuric response to Benzbromarone was completely abolished when tubular urate secretion was blocked by prior administration of pyrazinamide. Similar, but quantitatively less dramatic responses were observed with Probencid, uricosuric doses of chlorothiazide and benziodarone, after inhibition of tubular secretion by either pyrazinamide or low dose salicylates.

The finding that the uricosuric response to Benzbromarone could be eliminated by prior pyrazinamide administration indicated that uricosuric drugs were acting distal to the secretory site by inhibiting reabsorption of secreted uric acid. This observation implies that the magnitude of tubular urate secretion can be determined if it is possible to block distal reabsorption completely. Benzbromarone is especially suitable for this purpose since it is not excreted by the renal organic anion transport system and, therefore, does not interfere with the tubular secretion of uric acid. To the extent that Benzbromarone selectively inhibits post-secretory reabsorption of uric acid, it is possible to assess tubular secretion by measuring the maximum rate of urate excretion following administration of a suitable dosage of the drug. Based upon these observations, the maximal uricosuric response to the minimal secretory rate of uric acid in normal and gouty subjects has been equated by us.

Methods

The tubular secretory rate was assessed in eight healthy volunteers and 11 patients with primary gout, all of whom had a normal glomerular filtration rate. Three patients in the gouty group were urate overproducers, while eight patients had normal production but low urinary uric acid excretion relative to plasma urate levels. All medications were discontinued 14 days prior to studies, which were conducted in the morning following an overnight fast. Informed consent was obtained from both healthy volunteers and the gouty patients.
Following a control period during which baseline values for plasma and urinary uric acid were obtained, 80 mg of micronized Benzbromarone were given in a single oral dose. Urate excretion was determined hourly and expressed as µg per min and, where indicated, divided by the endogenous creatinine clearance to correct for differences in nephron mass. Maximum uricosuria was usually obtained during the fourth hour following drug administration. Adequate diuresis was accomplished with tap water given at half-hour intervals, and urine specimens were obtained by spontaneous voiding at hourly intervals. Plasma samples were obtained at the mid-point of each collection period.

Plasma and urine urate determinations were performed by the enzymatic spectrophotometric method of Praetorius, while creatinine was assayed on an SMA 660.*

**Result**

A typical study in a healthy volunteer showing the maximum uricosuric response to 80 mg oral Benzbromarone is presented in figure 1. During the control period, urate excretion was 495 µg per min with a plasma urate value of 5.32 mg per dl. At the height of the Benzbromarone response, i.e., maximum uricosuria, urate excretion had risen to 2780 µg per min while plasma urate had fallen to 4.20 mg per dl. Urate clearance rose from 9.3 ml per min during the control period to 66.3 ml per min following drug administration.

In figure 2 are depicted the baseline excretion and the uricosuric response to Benzbromarone for eight normal volunteers and three patients with primary gout in whom increased production of uric acid had previously been demonstrated in turnover studies with 14C-uric acid. Baseline urine urate excretion val-

---

* Tarrytown, NY.
values during the control period and the maximum uricosuric response to Benzbroromarone are plotted against plasma urate values over a range between 2.05 mg per dl to 10.72 mg per dl. These studies demonstrate a significant functional relationship between urate secretion and plasma urate concentrations ($r = 0.956$, $p < 0.005$). Since Benzbroromarone selectively inhibits reabsorption of secreted uric acid, the differences between secreted and excreted uric acid becomes a valid measure of urate reabsorption distal to the secretory site.

The response to Benzbroromarone has been used to define the renal defect in primary gout characterized by a normal production of uric acid. The results of studies in eight patients are shown in figure 3, superimposed on values obtained for the normal population shown previously. In conformity with previous observations, it can be seen that gouty normal producers require a higher plasma urate concentration to excrete a quantity of uric acid in the urine comparable to healthy controls. Although, all of the patients showed a significant uricosuric response to Benzbroromarone, urate secretion was distinctly lower in gouty normal producers than in gouty patients with overproduction of uric acid. This indicated that the defect in the former group is related to a decreased secretory response for a given plasma concentration of uric acid.

Discussion

Interpretation of these data is based on the assumption that pyrazinamide causes a selective and complete block in urate secretion distal to the nephron segment where filtered uric acid is reabsorbed and, further, that Benzbroromarone, in the dosage used, causes virtually a complete inhibition of reabsorption of secreted uric acid. Although the validity of both assumptions may be questioned, the use of both pyrazinamide and Benzbroromarone represents the most sensitive tools available at present for the pharmacological characterization of the bi-directional renal urate transport system. The majority of patients with primary gout have normal urate production and require an elevated plasma urate concentration to obtain a normal level of urate excretion. The technique of measuring the uricosuric response to Benzbroromarone has allowed identification of a defect in the renal handling of uric acid in these patients, which can be localized to the secretory site. Although, gouty normal producers can be characterized as having a subnormal response to Benzbroromarone, this drug, as is the case with other uricosuric agents, decreases post-secretory fractional reabsorption of uric
acid, resulting in a lowering of plasma urate levels.

The exact mechanism and site(s) of tubular urate transport in man remain to be clarified. Recent, micropuncture studies in the rat indicate substantial urate reabsorption in the loop of Henle. Variation in urine flow exerts a moderate effect on urate excretion in man suggesting that a reabsorptive site is also present in the distal tubule or collecting ducts.

In summary, the magnitude of urate secretion in gouty patients has been determined by measuring the maximum uricosuric response to Benzbromarone. In normal subjects and gouty patients with overproduction of uric acid, urate secretion is a linear function of plasma urate concentration. Patients with primary gout who have a normal production of uric acid appear to have a diminished tubular secretion of uric acid as the underlying basis for their hyperuricemia. The exact site(s) for this bi-directional tubular urate transport systems remains to be clarified.

References


