Uric Acid Transport in Fanconi Syndrome with Marked Renal Hypouricemia: Analysis Using Pyrazinamide and Benzbromarone

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Dear Sir,

Fanconi syndrome is a nonselective proximal tubule dysfunction, characterized by amino aciduria, glycosuria, phosphaturia, renal tubular acidosis and hypouricemia. There have been few detailed clearance studies on the disturbance of the uric acid transport system in Fanconi syndrome [1-3], although increased uric acid clearance has been reported [4]. Therefore, to clarify the defective site(s) of the renal uric acid transport system, we studied a patient with Fanconi syndrome showing marked renal hypouricemia, using pyrazinamide (PZA) and benzbromarone (BZB).

The patient was a 15-year-old male, referred to us because of glycosuria and hypouricemia. He had been hospitalized in a local care institution for 15 years for cerebral palsy and mental retardation with vegetative state, and was fed by gastrostomy tube. Review of his medical record showed that his serum uric acid level ranged from 2.5 to 4.0 mg/dl 3 years before. His fasting blood glucose level was 98 mg/dl and HbA_{1c} was 4.4%. Urinalysis revealed glycosuria, pro-teinuria and amino aciduria. The early morning urine constantly showed a pH > 7.0. Serum uric acid levels were 0.4-0.8 mg/dl on several occasions. Daily urinary uric acid excretion was about 213 mg. Plasma hypo-xanthine and xanthine concentrations were 0.08 and 0.07 µg/ml, respectively, and daily urinary hypoxanthine and xanthine excretions were 3 and 3.9 mg, respectively, excluding xanthinuria. Uric acid clearances ranged from 31.3 to 38.0 ml/min. Fractional

clearances of uric acid (C_{ua}/C_{cr}) were markedly increased with values between 0.729 and 0.847 (0.773 ± 0.050 , $n = 3$). Serum creatinine was 0.5-0.6 mg/dl and sodium 134 mEq/l, chloride 105 mEq/l, calcium 7.7 mg/dl and inorganic phosphate 1.1 mg/dl. Tubular reabsorption of phosphate was 80% (normal 85-95%). Serum alkaline phosphatase activity

was 23.6 BLU (normal 0.8-2.9). A percutaneous renal biopsy specimen showed no definite evidence of interstitial nephritis. The diagnosis of Fanconi syndrome was made, although the cause remained undetermined.

The BZB loading test (fig. 1a) and the PZA + BZB loading test (fig. 1b) were performed as previously described with a minor modification [5]. C_{ua}/C_{cr} of each period was calculated. The serum concentrations of PA (one of the metabolites of PZA) and BZB were determined by high-performance liquid chromatography (HPLC) as described previously [6, 7]. BZB did not increase C_{ua}/C_{cr} at all. Neither PZA nor PZA + BZB produced any appreciable changes in C_{ua}/C_{cr} at any clearance period. The results of the two loading tests are summarized in table 1. Plasma BZB concentration, measured 6 h after the administration of BZB, by HPLC was 5.0 $\mu\text{g/ml}$. Plasma concentration and urinary excretion of PA, measured 180 min after the administration of PZA by HPLC, was 3.2 $\mu\text{g/ml}$ and 3.9 mg/h, respectively.

The four-compartment theory has been widely supported clinically as a model of the renal handling of uric acid [8, 9]. On the

Table 1. Changes in fractional uric acid clearance (C_{ua}/C_{cr}) after BZB loading test and PZA + BZB loading test

Patient

Control (n = 4)

BZB loading test

0.070 ± 0.032 0.166 ± 0.101 0.389 ± 0.062 0.337 ± 0.090

0.842

0.857

0.857

0.765

0.058 ± 0.027

0.0070 ± 0.0033

0.0064 ± 0.0024

0.029 ± 0.021

0.062 ± 0.037

PZA + BZB loading test

0.868

0.878

0.849

1.012

0.929

basis of the response to the drugs, the defect(s) of the proximal tubule causing renal hypouricemia are classified as follows:

presecretory reabsorption defect type;

postsecretory reabsorption defect type;

enhanced secretion type, and (4) combined reabsorption defect type. Recently, extensive uric acid transport defect along proximal tubules has been advocated by Shichiri et al. [10]. In this type, neither probenecid (PB) nor BZB and PZA altered uric acid clearance, which did not exceed creatinine clearance.

The present case did not show any significant changes in C_{ua}/C_{cr} in spite of sufficient

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BZB 100 mg

1

-60 0

390 min

PZA 60 mg/kg-60 0 90

BZB 100 mg150 210

300

360

420

480 min

Fig. 1. Protocol of BZB loading test (a) and PZA + BZB loading test (b).

P2

Pa

P5

plasma concentrations of PA and BZB obtained after the administration of PZA and BZB, with C_{ua}/C_{Cr} not exceeding unity, suggesting the defect involving extensive uric acid transport rather than presecretory reabsorption. The defective mechanism(s) of uric acid transport system in Fanconi syndrome are not completely understood. In a previous study [1], a clearance study was conducted in a 48-year-old female patient with Fanconi syndrome using PZA and PB, who responded to PZA but not to PB, demonstrating the defective site to be either enhanced secretion or postsecretory reabsorption, while other studies [2, 3] demonstrated patients with Fanconi syndrome who had high C_{ua}/C_{Cr} above unity with lack of response to PB, suggesting complete failure of uric acid reabsorption. These cases seem to belong to combined reabsorption defect type. Thus, there seem to exist various defective types in uric acid transport system in Fanconi syndrome. Although the reason for such variability in the defective mechanisms of uric acid transport in Fanconi syndrome remains unclear, this defect may be related either to stage or etiology of the syndrome. On the other hand, there may exist subtypes of uric acid transport defect in Fanconi syndrome as in idiopathic renal hypouricemia. Accumulation of similar new cases with clearance studies might shed light on this issue.

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