Hypouricemia due to Increased Tubular Urate Secretion

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Dear Sir,

Shichiri et al. [1] in the January 1987 issue of the Journal describe a case of renal hypouricemia associated with normal suppression of uric acid excretion after pyrazinamide (PZA) but a remarkable increase after probenecid (PB). In the same issue Nakajima et al. [2] describe three additional hypouricemic patients with normal (or nearly normal) response to PZA and normal, or slightly increased, response to PB. The authors of these two papers suggest that an increase in urate secretion by the renal tubule is the underlying defect in the presented patients. Although this is a most likely explanation, their data do not allow one to exclude that presecretory urate reabsorption could also be impaired in their patients. In fact a normal inhibition of urate excretion with the PZA test does not exclude reduced presecretory urate reabsorption: when the tubular load of urate is consistently reduced by PZA, unreabsorbed urate along the presecretory sites could still undergo reabsorption along the postsecretory sites, thus allowing for a normal PZA suppression test. In this context, PB-induced uricosuria would also be increased.

To validate this possibility, we performed separately a PZA test either alone or 2h after the administration of 2 g PB (PZA + PB) in 7 patients with tubular hypouricemia [3]. The theoretical assumptions of the combined test were that the contemporary inhibition of both urate secretion by PZA and of postsecretory reabsorption by PB

would allow a more correct evaluation of presecretory urate reabsorption than the two separate tests. In all the patients, presecretory reabsorption was markedly lower after the combined PZA + PB test ($67.1 \pm 12.5\%$ of filtered urate) than after PZA test alone ($86.7 \pm 15.6\%$, $p < 0.005$).

Moreover, no consistent differences were observed in 9 hyperuricemic patients and 8 healthy controls, thus excluding pharmacological interactions as a possible explanation of the observed results in hypouricemic patients. Three hypouricemic patients showed a normal response to PZA, but in all the patients the response to the combined PZA + PB test was abnormal. Two conclusions can be drawn from our data: first, in patients with reduced presecretory urate reabsorption some unreabsorbed urate can further undergo reabsorption along the postsecretory sites, at least during PZA-induced decrease of urate secretion; second in patients with tubular hypouricemia a normal PZA test cannot allow reduced presecretory reabsorption to be excluded. Like the patients described by Shichiri et al. [1] and Nakajima et al. [2], one of our patients showed increased PB-induced uricosuria (85.4%, normal values $52.8 \pm 15\%$) and an almost normal inhibition of fractional urate clearance after PZA to a value of 4.3% (normal values $2.1 \pm 1.6\%$); however, fractional urate clearance after the combined PZA+PB test remained increased

to 12% (normal values $4.9 \pm 2.5\%$), indicating that the increased PB-induced uricosuria was not related to increased secretion but more likely to decreased presecretory reabsorption.

236

Colussi/Rombolà/DeFerrari/Minetti

We agree that the data presented by Shichiri et al. [1] are unlikely to be accounted for only by reduced presecretory reabsorption, since a 227.8% fractional urate clearance after PB is more than the sum of filtered and secreted urate; nevertheless, its coexistence cannot be excluded. We strongly believe that the combined PZA+ PB test is a more appropriate tool for the evaluation of tubular urate reabsorption processes in patients with abnormal tubular urate handling than classical PZA and PB tests performed alone.

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References

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