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Metabolic Consequences of Rifampin-Mediated Enzyme Induction During Treatment for Tuberculosis

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The combined effect of a hepatic enzyme-inducing drug and an enzyme-inhibiting drug, rifampin and isoniazid, on indirect biochemical indices of enzyme induction was studied during treatment of tuberculosis. Most pharmacological studies concentrate on the effect of a single drug in normal healthy volunteers, and it is difficult to know their relevance when applied to a situation in which compound therapy is used in patients.

Plasma gamma-glutamyl transpeptidase (γGT) was advocated by Rosalki et al. (15) as a simple test of enzyme induction during anticonvulsant therapy. We compared γGT levels in a control group which had completed treatment (mean ± SD, 27.1 ± 23.7 IU/liter; $n = 27$) and in the treatment group after 3 months of rifampin (450 to 600 mg) and isoniazid (300 mg) daily (47.9 ± 56.1 IU/liter; $n = 69$) ($P < 0.02$). However, two patients among the controls and 9 of 15 patients in the treatment group with abnormally raised values (males, >60 IU/liter; females, >50 IU/liter) gave a history of high alcohol intake. When they were excluded, there was no significant difference between the control (23.5 ± 18.2 IU/liter; $n = 25$) and treatment (32.2 ± 19 IU/liter; $n = 60$) ($P > 0.1$) groups. This

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confirmed our previous report in which raised plasma lyososmal enzymes, β-glucuronidase and β-*N*-acetylglucosaminidase, were the striking effect of rifampin (12).

Hunter et al. (8) showed that urinary D-glucaric acid is a further useful screening test of enzyme induction. In an earlier paper (11), we showed a complete suppression by isoniazid of rifampin induction of urinary D-glucuric acid excretion and that finding is confirmed in this study (Fig. 1) and extended to 69 patients (Fig. 2). The probable reason is the inhibiting effect by isoniazid on hepatic microsomal enzymes (3, 13). This brings into question the value of the urinary D-glucaric acid index during compound therapy when drugs may have opposing actions on enzyme induction.

Plasma antipyrine half-life and 6β-hydroxycortisol (6β-OHF) are useful tests of drug-mediated changes in the mixed-function oxidase system of liver microsomes (2). Although isoniazid may have an inhibiting effect on plasma half-life in individual patients (11), there was a significant decline in half-life when rifampin was combined with either streptomycin or isoniazid (Fig. 3). In the rifampin-streptomycin group urinary D-glucaric acid was increased (Fig. 1), and when plasma antipyrine half-life was tested at the same time interval, a significant correlation was found ($r = 0.7614$, $P < 0.05$). This adds some evidence to the view that induction of the cytochrome p_{450} mixed-function oxidase system may be reflected by changes in D-glucaric acid excretion (9, 10). 6β-OHF excretion showed a wide range of increase (11). A patient with a very high induction (3.8 μmol/day) had complete suppression when isoniazid was substituted, and we agree with Yamada and Iwai (17) that isoniazid has a partial or totally suppressive effect in some patients. Nevertheless, this index and plasma

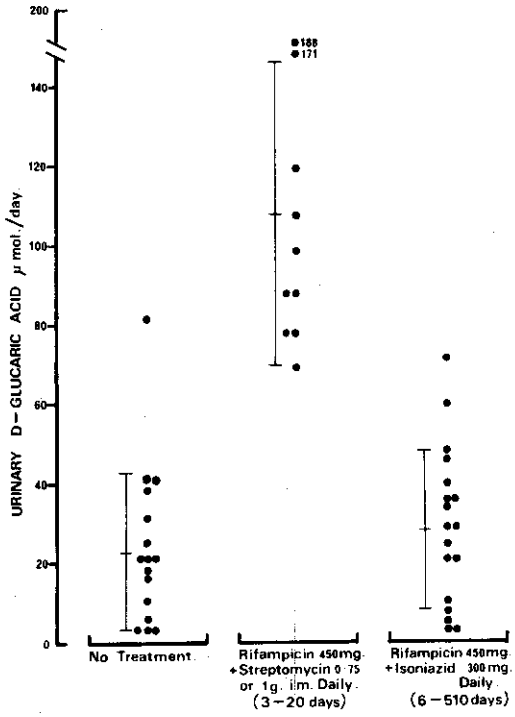

FIG. 1. *Rise in urinary D-glucaric acid excretion during rifampin-streptomycin treatment ($P < 0.001$) compared with controls and a rifampin-isoniazid group. i.m., Intramuscularly.*

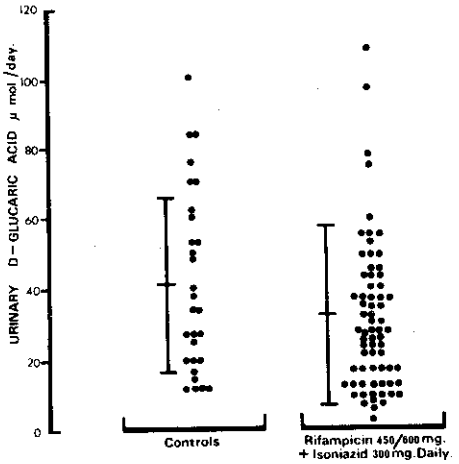

FIG. 2. *Urinary D-glucaric acid excretion unchanged during rifampin and isoniazid therapy. Vertical bars denote mean ± SD.*

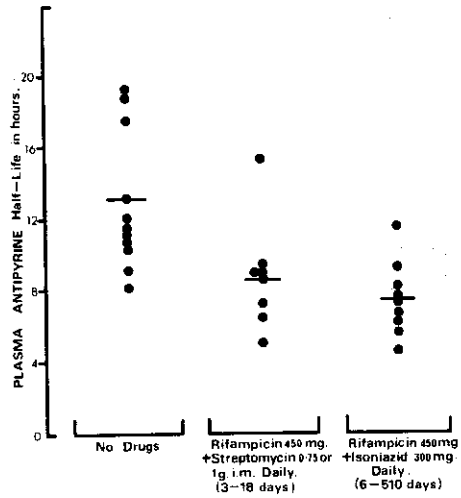

FIG. 3. *Decline in plasma antipyrine half-life during rifampin therapy (with streptomycin, $P < 0.005$; with isoniazid, $P < 0.001$). i.m., Intramuscularly.*

antipyrine half-life were the sensitive tests of persisting hepatic enzyme induction in this setting. From our results we clearly cannot extrapolate from one index and assume induction of other endogenous substrates or drugs. Each has to be looked at separately.

It was shown recently by Brodie et al. (4) that rifampin alone may cause a decline in plasma 25-hydroxycholecalciferol (25-OHD), although we had earlier suggested that this was not a contributing factor to late rickets or osteomalacia found in an Asian population receiving antituberculous therapy (6). In our 83 patients the criteria for admission for suspected osteomalacia included serum calcium of <2.25 mmol/liter and/or alkaline phosphatase of >14 King Armstrong units/100 ml or clinical symptoms of bone pain and tenderness suggestive of osteomalacia. Seven of eight patients suspected of osteomalacia were investigated in a metabolic ward; two underwent metabolic balance studies in the classic manner (1, 6), using copper thiocyanate for correction of fecal calcium recovery. Four Indian patients were confirmed to have the disease from the presence of Looser's fractures on X ray or iliac crest bone biopsy criteria (P. Byers, personal communication). One patient who was not admitted had unequivocal serum chemistry of osteomalacia which became normal on 900 U of vitamin D_2 per day. Thus, 5 of 52 Indian patients had osteomalacia during an 18-month course of rifampin therapy, but all of these patients were strict vegetarians with vitamin D intake of <40 IU/day. Treatment with 900 U of vitamin D per day produced complete healing of their bone disease. Only one European of 32 required investigation because of hypocalcemia. She had cirrhosis of the liver and her vitamin D intake was <40 IU/day. During metabolic balance studies two Indian patients with osteomalacia showed significantly positive calcium retention of 7.5 and 15 mmol/day while receiving rifampin and isoniazid therapy. Balance studies were performed in midsummer when their 25-OHD levels were 12.5 and 25 nmol/liter (5 and 10 ng/ml, respectively).

Serum calcium levels in 17 Asians and Europeans before treatment and after 6 months were 2.305 ± 0.145 and 2.330 ± 0.104 mmol/liter ($P > 0.1$). Thus, we have been unable to show an effect resembling anticonvulsant hypocalcemia (14). Similarly, the just under 10% incidence of osteomalacia in the Indian group (5 of 52) is well within the expected incidence of a control population in the United Kingdom (5, 7). However, the time of exposure to rifampin is much shorter than that to anticonvulsants and the presence of isoniazid might prevent a fall in plasma 25-OHD previously reported with rifampin alone (4). The main factor in the Indian population is nutritional vitamin D deficiency and lack of sunshine. If a small effect by rifampin has occurred, it is adequately overcome by 900 U of vitamin D_2 per day. It would seem unlikely to affect 1,25-dihydroxycholecalciferol activity as both metabolic balance patients showed significantly increased intestinal calcium absorption with low to normal plasma levels of 25-OHD. No European patient was observed to develop osteomalacia due to rifampin therapy, and we have now followed 60 patients to the end of their treatment.

We conclude that enzyme induction with rifampin is significantly different from that with anticonvulsant drugs and is variably suppressed by isoniazid.

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