# Calcium metabolism during rifampicin and isoniazid therapy for tuberculosis[1]

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**Summary:** Calcium metabolism was studied in 83 patients during eighteen months' rifampicin and isoniazid therapy for tuberculosis by measurements including calcium, alkaline phosphatase and 25-hydroxycholecalciferol (25-HCC). Five out of 52 Indian patients in the series were found to have osteomalacia, a prevalence probably no higher than in the Asian population in the UK at large. Moreover, osteomalacia responded to physiological supplementation with vitamin D. One European out of 31 had osteomalacia due to low vitamin D intake. Serum calcium was compared in 17 patients before and after six months of antituberculous chemotherapy but no significant difference was detected ($P > 0.1$). Two Indian patients were in positive calcium balance with low to normal plasma 25-HCC levels, indicating that an effect on 1,25 dihydroxyvitamin D activity during therapy was unlikely. It is concluded that rifampicin when combined with isoniazid has no significant effect on calcium metabolism over an eighteen-month treatment period.

## Introduction

The long-term effects of anticonvulsant therapy on calcium and vitamin D metabolism are widely appreciated. One of us (MAE) suggested that rifampicin might be contributing to the onset of late rickets or osteomalacia in Asian patients receiving antituberculous treatment. Rifampicin has powerful hepatic microsomal-inducing properties (Remmer *et al.* 1973, Perry *et al.* 1978) and, given alone over short intervals to normal volunteers, has been reported to cause a decline in plasma 25-HCC (Brodie *et al.* 1980). Isoniazid, however, has general hepatic microsomal enzyme inhibiting effects (Brennan *et al.* 1970, Raisfeld *et al.* 1973) which can suppress other indirect biochemical indices of rifampicin enzyme induction such as urinary D-glucaric acid (Perry 1981). Thus such a combination of drugs may have little ultimate effect on calcium metabolism and in a recent report we did not think that antituberculous chemotherapy had contributed over and above nutritional vitamin D deficiency to osteomalacia in the Asian group (Stamp *et al.* 1980).

The purpose of this paper is to report our findings in detail and to emphasize that if confusion is not to arise as to the aetiology of osteomalacia in Asians, pretreatment screening is essential before therapy is begun for tuberculosis or other diseases.

## Methods

Eighty-three patients (52 Asian and 31 European) were studied between the spring of 1975 and 1977 at three-month intervals before (17 cases), during and after treatment with rifampicin 450 or 600 mg daily and isoniazid 300 mg daily. The age range was 14 to 76 years with a mean of 39.7 years; there were 45 females and 38 males.

Serum calcium, phosphorus and alkaline phosphatase were measured by a Technicon SMA 12 analyser, and calcium was compared in 17 patients before and after six months'

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chemotherapy. Differences in serum albumin in the same individual during this period were small and thus a correction for serum calcium was not made. The criteria for admission for suspected osteomalacia included serum calcium <2.25 mmol/l and/or alkaline phosphatase >14 King-Armstrong units/100 ml, or clinical symptoms of bone pain and tenderness suggestive of osteomalacia. Seven patients were investigated in a metabolic ward, and 2 of these underwent metabolic balance studies in the classic manner (Dent & Smith 1969, Albright & Reifenstein 1948) using copper thiocyanate for correction of faecal calcium recovery. Antituberculous therapy was continued during balance studies; 25-HCC levels in these 2 patients were measured by the method of Haddad & Chyu (1971).

If osteomalacia was confirmed in any patient, vitamin $D_2$ 900 units/day was given orally throughout the period of chemotherapy.

## Results

Seven out of 8 Indian patients suspected of having osteomalacia were investigated in a metabolic ward, and the disease was confirmed in 4 from the presence of Looser's fractures on X-ray or iliac crest bone biopsy criteria (Dr P Byers). One patient who was not admitted had unequivocal serum chemistry of osteomalacia. Thus 5 out of 52 Indian patients had osteomalacia during the course of combined rifampicin and isoniazid antituberculous therapy, but all these patients were strict vegetarians with vitamin D intakes <40 iu/day. Treatment with 900 units of vitamin $D_2$/day produced complete healing of their bone disease. Only one European out of 31 required investigation because of hypocalcaemia. Osteomalacia was confirmed on iliac crest bone biopsy. The patient was a heavy drinker, cirrhosis of the liver was confirmed on biopsy and she had a vitamin D intake <40 iu/day. These findings are summarized in Table 1.

*Table 1. Incidence of osteomalacia among 52 Indians and 31 Europeans during 18 months' rifampicin/isoniazid treatment*

| | Osteomalacia | | |
|---|---|---|---|
| Patients | Suspected | Confirmed | Comment |
| European | 2 | 1 | (1 died) |
| Indian | 8 | 5 | ≐10% |

*Table 2. Serum calcium before and after 6 months' rifampicin/isoniazid treatment in 17 patients*

| | Serum calcium (mmol/l) | |
|---|---|---|
| Patients | Spring | Autumn |
| Asian and European | 2.305 ± 0.104 | 2.330 ± 0.104 |

$P > 0.1$

Of the 2 Indian osteomalacic patients who underwent metabolic balance studies, the first showed a significant positive calcium retention of 300 mg (7.5 mmol) per day (Figure 1). This was due to remineralization of bone during the summer when it is presumed his 25-HCC level of 5 ng/ml (12.5 nmol/l) had risen from even lower levels prior to the balance study. The second patient (Figure 2) was already receiving vitamin D, and a more striking calcium retention of 600 mg (15 mmol) per day was seen when her 25-HCC level was 10 ng/ml (25 nmol/l).

Serum calcium results in 17 tuberculous patients are shown in Table 2. No significant difference was detected during the six-month period of chemotherapy; the mean level of serum calcium was actually slightly higher after six months, which was consistent with an expected rise in the autumn (Gupta *et al.* 1974).

## Discussion

We have been unable to show an effect resembling anticonvulsant hypocalcaemia (Richens & Rowe 1970) after six months' combined rifampicin and isoniazid treatment. The incidence of

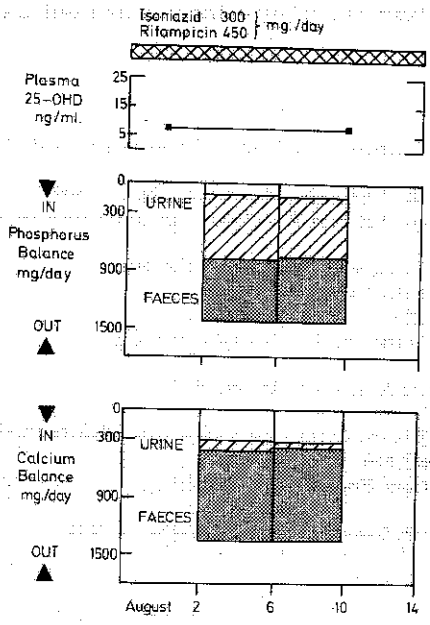


Figure 1. Calcium balance study in a patient with osteomalacia during antituberculous therapy. Note positive calcium retention in mid-summer (unshaded area) with 25-HCC levels at lower level of normal (normal > 4 ng/ml)

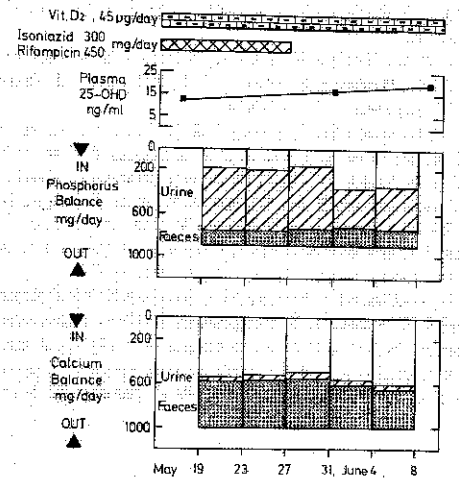


Figure 2. Positive calcium balance in a patient with osteomalacia at end of chemotherapy while receiving vitamin D. The implication is that 1,25 dihydroxycholecalciferol activity is unaffected during rifampicin treatment when 25-HCC levels are normal

osteomalacia of just under 10% in the Indian group (5 out of 52) identified during eighteen months of antituberculous treatment is well within the expected incidence of purely nutritional osteomalacia in this population in the United Kingdom (Forde *et al.* 1972, Clarke *et al.* 1972). However, the duration of exposure to rifampicin was much shorter than in therapy with anticonvulsants and, furthermore, the presence of isoniazid might prevent the fall in plasma 25-HCC previously reported with rifampicin alone (Brodie *et al.* 1980). The main factor causing osteomalacia in the Indian population continues to be their nutritional vitamin D deficiency and lack of sunshine contributing to low circulating 25-HCC levels (Gupta *et al.* 1974). If rifampicin did have some small effect, it has been adequately overcome by 900 units of vitamin $D_2$/day. This is unlike anticonvulsant osteomalacia which is resistant to treatment with vitamin D in the 1600–1800 units dose range (Dent *et al.* 1970). In two patients not included in this study, intravenous vitamin $D_2$ 1600 units given on alternate days for ten days restored calcium and phosphorus levels to within the normal range (unpublished); this provides further evidence against the likelihood of vitamin D resistance during rifampicin treatment. Rifampicin would seem unlikely to affect 1,25 dihydroxycholecalciferol activity, as both patients who underwent metabolic balance studies showed significantly increased intestinal calcium absorption with low to normal plasma levels of 25-HCC (Figures 1 & 2). In addition, remineralization of bone, judged by calcium retention, was proceeding normally in the presence of rifampicin and isoniazid.

Osteomalacia in the European population is generally rare and if rifampicin had a significant clinical effect one might have expected to see examples in our population. The one patient with confirmed osteomalacia had both cirrhosis and low vitamin D intake. We have now followed a total of 60 European patients to the end of their treatment without encountering a further example of osteomalacia.

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