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A study of drug interactions in leprosy—1. Effect of simultaneous administration of prothionamide on metabolic disposition of rifampicin and dapsone

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Summary A study has been undertaken to examine the potential effects of prothionamide (PTH) on the pharmacokinetics of rifampicin (RMP) and dapsone (DDS) in 15 untreated leprosy patients. A daily administration of RMP and DDS for 7 continuous days followed by that of RMP, DDS and PTH for 7 more days formed the drug schedule. RMP and DDS levels were estimated in timed blood samples collected on days 7 and 14. Twenty-four hour urinary excretions of the 2 drugs were also determined on day 7 and 14 of drug administration. The results showed a lack of any significant effect of PTH on pharmacokinetics of RMP and DDS.

Introduction

Drug interaction is one of several important factors that modify drug responses in man. A number of clinically important interactions have been documented.[1] Multidrug therapy is currently recommended for all highly bacillated (BL/LL) leprosy patients with a view to prevent or reduce the problems of bacterial resistance and bacterial persistence as have been found with use of DDS alone.[2, 3] Such a treatment might mean that leprosy patients will run a risk of drug interactions whether these are pharmacokinetic or pharmacodynamic in nature. While there are a few reports pertaining to pharmacodynamic interactions resulting in increased occurrence of hepatitis in patients treated with rifampicin (RMP), ethionamide (ETH), dapsone (DDS) and clofazimine (CLF) in combinations of any 2 or 3 drugs for a long period,[4–6] there is no reference to pharmacokinetic interactions between these drugs. It has been reported that addition of RMP to DDS results in an increased clearance of the latter. The present investigation was undertaken to see if a third drug like prothionamide (PTH) would result in any effect on blood levels and excretion of RMP and DDS.

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Materials and methods

Fifteen uncomplicated lepromatous (BL/LL) leprosy patients were included in this study. None of the patients had had any drugs during the past 4 weeks. All of them were admitted to the ward for supervised drug administration. They were given RMP 600 mg and DDS 100 mg daily for 7 consecutive days on empty stomachs. Venous blood was collected in oxalate vials, 3 h, 5 h, 7 h, 12 h and 24 h after patients had taken the seventh dose.

Plasma was separated immediately. Drug assays were made either immediately or the plasma aliquots were frozen at $-80°C$ till assay was done. Twenty-four hour urine specimens were collected on day 7. From day 8 onwards these patients were administered PTH 500 mg daily in addition to combined administration of RMP and DDS as before. On day 14, timed blood and urine specimens were collected as on day 7.

The protocol of 14 days comprising two equal halves of 7 days was chosen so that the findings of this study will have a better practical application, since the patients on multidrug therapy are given RMP daily for the initial 14 days along with DDS and PTH. Moreover, the self-induction of RMP gets to a steady state in 7 days and any significant change in pharmacokinetics of RMP on completion of 14 days can be attributed to PTH.

Plasma RMP levels were determined by microbiological assay[7] using *Staphylococcus aureus*. Urinary RMP was determined by amyl alcohol extraction method.[8] Urinary excretion of creatinine was evaluated by alkaline picrate method.[9] Plasma DDS levels were determined after 3 h, 5 h and 24 h, by a micro adaptation of the spectrophotometric method of Simpson[10] cited by Shepard *et al.*[11] Urinary DDS was measured by the colourimetric method of Ellard *et al.*[12]

The plasma $t^{\frac{1}{2}}$ for DDS was calculated from regression lines representing the logarithmic decay of the concentration of DDS with time.

Plasma half-life ($t^{\frac{1}{2}}$) for RMP was calculated in a similar way. Area under concentration-time linear gradient curve (AUC) for RMP was calculated for the period 0–12 h and expressed as $\mu g\ ml^{-1}$ h. Urinary excretion of the drugs was expressed as the ratio of microgram of DDS or RMP to milligram of creatinine. Statistical significance of the findings was evaluated by paired t test.

Results

It was found that the values for plasma DDS did not show any statistically significant alteration with additional administration of PTH, although mean 3 h DDS levels were slightly higher following PTH intake. Twenty-four hour urinary excretion of DDS also did not show any significant variation. The plasma half-life ($t^{\frac{1}{2}}$) for DDS was $18 \pm 2{\cdot}1$ h before and $19 \pm 2{\cdot}1$ h with PTH (Table 1).

The plasma RMP values too, did not present any significant variation with addition of PTH (Table 2). A marginal increase in plasma $t^{\frac{1}{2}}$ for RMP was found

Table 1

Regimen	Plasma DDS level mg/dl			Plasma $t^{\frac{1}{2}}$ h	24 h urinary DDS	
	3 h	5 h	24 h		mg	D:C
RMP+DDS (15)	0·170±0·020* (0·141–0·204)†	0·150±0·010 (0·128–0·168)	0·086±0·010 (0·063–0·096)	18±2·1 (13·2–20·5)	67·9±13·6	73·1±12·9
RMP+DDS+PTH (15)	0·186±0·020 (0·151–0·206)	0·160±0·020 (0·130–0·185)	0·089±0·015 (0·071–0·110)	19±2·1 (15·6–21·5)	70·4±11·5	72·9±11·8

Paired t test: not significant.
* ±SD
† Range.
‡ DDS: creatinine ratio, μg/mg.

Table 2

Regimen	Plasma RMP μg ml^{-1}					Plasma $t^{\frac{1}{2}}$ h	AUC 0–12 h μg ml^{-1} h	RMP in urine	
	3 h	5 h	7 h	12 h	24 h			mg	R:C
RMP+DDS (15)	9·42±0·59*	6·08±0·73	4·09±0·85	2·84±0·70	0·40±0·10	3·2±0·31	58·6±6·3	92·6±21·5	84·7±21·7
RMP+DDS+PTH (15)	8·98±0·63	6·4±0·58	4·5±0·74	3·1±0·7	0·42±0·15	3·7±0·38	60·3±5·2	106·4±24·4	94·1±16·6

paired t test: not significant.
*±SD
** RMP: creatinine ratio, μg/mg.

subsequent to the addition of PTH. There was no change in values for AUC 0–12 h when PTH was added. Urinary excretion pattern for RMP too remained the same subsequent to PTH administration.

Discussion

Most of the drugs used in multidrug therapy of leprosy are antituberculosis drugs. There are a number of reports on interactions between these drugs. Para-amino salicylic acid (PAS) is found to cause decreased RMP levels in plasma after simultaneous oral administration of the two.[13] This has been attributed to PAS' impeding gastrointestinal absorption of RMP, due to an alteration of the physico-chemical properties of RMP by PAS granules or by a decrease in the gastric emptying rate combined with more rapid intestinal transit. No significant effect on serum concentration or half-life of RMP or Isoniazid was found after simultaneous administration of the 2 drugs.[13]

The microbiological assay employed in this study was sensitive enough to detect RMP levels down to 0·05 μg ml^{-1}. Although the microbiological assay for RMP suffers from interference from its metabolite desacetyl RMP, it was felt adequate to measure total RMP as this metabolite is also biologically active.

Rifampicin is known to induce its own metabolism in addition to that of a number of drugs. This fact was kept in mind while drawing the protocol for the present study. During continuous administration of rifampicin, the half-life gradually decreases as a result of enzyme induction until a steady state is reached.[14] The maximum induction of rifampicin metabolism is probably attained by day 7 on daily treatment.[15] In the present study a slight increase in the plasma $t^{\frac{1}{2}}$ for RMP was found subsequent to the addition of PTH during the second half of the study. This insignificant rise could then be attributed to self-induction of RMP rather than PTH.

A decrease in blood and tissue levels of DDS during concurrent RMP administration has been reported.[16] The increased plasma DDS clearance in patients receiving RMP concurrently was suggested to be due to an enzymic induction.[17] It has been observed[18] that RMP had a transient mobilizing effect on DDS depot in the body, resulting in an increased excretion of DDS in urine. In another study[19] it has been observed that this DDS clearing phenomenon did not vary significantly in between acetylator phenotypes. Low plasma DDS levels comparable to values reported elsewhere have been found in the present study.

The findings of the present study suggest that PTH does not have any effect on pharmacokinetics of either RMP or DDS. Further studies are being planned to examine the possible effects of DDS and RMP on pharmacokinetics of PTH.

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