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# Plasma levels of ethionamide and prothionamide in a volunteer following intravenous and oral dosages

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*Summary* Available evidence which may aid a decision concerning which of the thioamides, ethionamide or prothionamide should be recommended for use in the treatment of lepromatous leprosy is inconclusive. The drugs possess similar antimycobacterial activities, but earlier work has suggested that after oral dosage ethionamide may give rise to higher blood levels than prothionamide. We report on investigations designed to examine whether this finding is as a result of different systemic availabilities, by comparing blood levels following intravenous and oral administrations. We conclude that the drugs' pharmacokinetics are very similar, each having high bioavailabilities, and that other factors such as cost may be more important determinants as to which thioamide should be used.

## Introduction

The antituberculosis drugs ethionamide (2-ethyl-thioisonicotinamide, ETH, Trescatyl) and prothionamide (2-propyl-thioisonicotinamide, PTH, Trevintix) have been in clinical use for some 20 years, mainly as components of retreatment regimens for patients relapsing with drug-resistant *Mycobacterium tuberculosis*. Experimental evidence has shown that both ETH and PTH possess similar powerful antileprosy activity when tested in the mouse footpad model.[1–3] These findings, together with the results from some small scale clinical trials of monotherapy with ethionamide or prothionamide suggested a future role for the two thioamides in the combined chemotherapy of lepromatous leprosy.[4–6] The World Health Organization advises that all lepromatous leprosy patients should be treated with a combination of three bactericidal drugs,[7] and currently recommends rifampicin, dapsone and clofazimine be used. However, many light skinned patients are unable to tolerate the skin pigmentation caused by clofazimine. For these patients it is suggested that clofazimine be replaced by

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250–375 mg/day of either ETH or PTH, but no guidance was given as to which of the two thioamides was to be preferred. The available evidence which may aid an informed decision concerning which thioamide should be recommended is inconclusive. Experimental studies have failed to demonstrate any differences in the inhibitory and bactericidal activities of ETH and PTH against *M. leprae*,[2,8] or between their sulphoxide metabolites which also possesses substantial antimycobacterial activities.[9,10] Prothionamide was originally introduced in an attempt to reduce the incidences of dose-dependant gastric side-effects associated with ETH. Although there is evidence that at larger doses ETH is less well tolerated than PTH,[11] recent findings suggest that at daily doses of 125–250 mg the regularity with which the two drugs are self-administered by leprosy patients is similar.[12]

In previous investigations we have attempted to determine if there were any pharmacokinetic differences between the two thioamides of potential clinical significance. In order to compare the rates of elimination of ETH and PTH, and the extent of their conversion to the antimycobacterial sulphoxide metabolites, we devised sensitive high performance liquid chromatographic (HPLC) methods to specifically measure the two thioamides and the sulphoxides in plasma and urine.[13,14] Single dose studies showed that the half-lives for the elimination of both ETH and PTH following oral dosage were about 2 h, but that the plasma concentrations of PTH from 1 h onwards were only about half those of ETH.[13] Later investigations indicated that the observed differences were not due to greater conversion of PTH to its sulphoxide metabolite; indeed the plasma levels of PTH sulphoxide were also less than those of the corresponding ETH metabolite.[14] Nor was there evidence of significant faecal elimination of unmetabolized drugs, suggesting that the absorption of both thioamides from the gut was probably good. We postulated that the differences in the plasma concentrations of ETH and PTH may have been due to differences in tissue distribution and/or protein binding. An alternative possibility is that PTH may have been cleared more extensively on the first pass through the liver. Estimates of distribution volumes and of pre-systemic clearance can only be made by comparing intravenous and oral administration. Since there are no reported studies of the intravenous dosage of either of the thioamides we describe the results of a study to compare the systemic bioavailabilities of ETH and PTH, in the same volunteer who took part in the earlier investigations.

## Materials and methods

### CHEMICAL

Ethionamide and prothionamide were donated by May and Baker (Dagenham, UK) for use as analytical standards. 2-Methyl-thioisonicotinamide was a gift from Dr N Rist. Ethionamide and prothionamide sulphoxides were prepared by

oxidation of the parent thioamides as described previously.[14] Stock solutions (1 mg $ml^{-1}$) of the thioamides in ethanol, and of the sulphoxides in chloroform were prepared and stored at 4°C.

### DRUG DOSAGES AND COLLECTION OF PLASMA SAMPLES

The study was divided in two parts. In the first part an oral dose of 500 mg PTH (Trevintix, May and Baker) was swallowed as crushed tablets with a glass of milk. Sixty minutes later 25 mg ETH (Trecator Perfusion, Theraplix, Paris, France) (2·5 mg $ml^{-1}$) was given by intravenous infusion over 10 min. In the second part of the study, conducted 1 week later, the formulations of the drugs were reversed; 500 mg ETH (Trecator, May and Baker) was administered orally, followed 1 h later by an intravenous infusion of 25 mg PTH (Trevintix Perfusion, Theraplix). Heparinized blood (7 ml) was collected at 30, 60, 70, 80, 90, 105, 120, 150, 240, 300 and 360 min after ingestion of the oral doses, the plasma spun down and the samples immediately frozen and stored at −20°C until analysis. On both occasions the volunteer (GAE) was administered the drugs supine, after an overnight fast.

### ANALYTICAL METHODS

As anticipated, the plasma levels of the intravenously and orally administered thioamides differed greatly because of the different size of the dose employed. Thawed plasma samples were therefore divided into two aliquots, the larger one (2·5 ml) for measurement of the intravenously administered thioamide and the smaller (between 0·2 and 0·7 ml) for determining the higher levels of the ingested thioamide. Both aliquots were diluted to 3 ml with distilled water and extracted and analysed by HPLC using the method previously reported for the simultaneous determination of the thioamides and their sulphoxide metabolites in plasma.[14] In brief, the samples were extracted with 7 ml of chloroform after the addition of an appropriate amount of 2-methyl-thioisonicotinamide as the internal standard. After extracting the organic phase with 1 ml 0·1 M HCl and neutralizing, the compounds were back extracted into chloroform, and this extract dried down. HPLC analyses were performed with a Waters Associates Model M6000A pump, a Model 440 absorbance detector (set at 340 nm) and a U6K valve injector. The normal phase silica column (Hypersil, Shandon Southern) was eluted with chloroform/propan-2-ol/water (916:80:4) at a flow rate of 2·5 ml $min^{-1}$. Estimates of the concentrations of thioamides in plasma samples were made by reference to a series of calibration curves prepared as described previously.[13,14]

### STATISTICAL METHODS

The kinetics of the plasma concentrations were analysed by the ESTRIP curve

stripping procedure[15] and by iterative computer fitting of a biexponential equation of the form

$$C_t = Ae^{-\alpha t} + Be^{-\beta t},$$

using MLAB,[16] a programme for evaluating mathematical models and functions. Values for the half-lives for the absorption and elimination of the drugs were calculated from the rate constants obtained by these procedures. The ESTRIP programme also calculated the areas under the plasma time curve using the trapezoidal rule. Total areas under the plasma time curves (AUC) were obtained by extrapolation to time infinity.[17]

## Results

The kinetics of the elimination of ETH and PTH from the plasma after oral and intravenous administration is illustrated in Figure 1. The absorption of PTH following oral dosage appears to be very rapid. Thus, the peak plasma concentration occurred within 30 min of ingestion with the consequence that an accurate estimation of the half-life for the absorption could not be calculated. By contrast ETH peak plasma levels occurred after about 90 min. At this time the PTH concentration had fallen to about half the level reached at 30 min. This elimination pattern is very similar to that encountered in the same volunteer 5 years previously.[13] The rate of decline in plasma levels, calculated using the rate constants obtained by the ESTRIP procedure, was equivalent to half lives of $1{\cdot}85 \pm 0{\cdot}08$ h for ETH and $1{\cdot}78 \pm 0{\cdot}17$ h for PTH ($p > 0{\cdot}05$). The data for ETH was best fitted by the ESTRIP procedure assuming a lag period of 17·9 min and gave a calculated half-life for the absorption of ETH of $18{\cdot}5 \pm 2{\cdot}7$ min. Alternative estimates, calculated by the MLAB programme, gave values for the terminal half lives of ETH and PTH of $1{\cdot}60 \pm 0{\cdot}31$ h, and $1{\cdot}49 \pm 0{\cdot}13$ h, respectively, similar to those obtained with the ESTRIP procedure.

Following intravenous dosage, plasma levels of the thioamides declined biexponentially (Figure 1), with half-lives for the distribution phases (as calculated using ESTRIP) of 7·2 and 5·8 min for ETH and PTH, respectively. The terminal rates of elimination were equivalent to half-lives of $1{\cdot}77 \pm 0{\cdot}07$ h for ETH and $2{\cdot}06 \pm 0{\cdot}12$ h for PTH. These values for the terminal half-lives are not significantly different from the corresponding half-lives following oral administration. The corresponding estimates using the MLAB programme were 7·0 and 6·4 min for the distribution half-lives of ETH and PTH, respectively; and $2{\cdot}06 \pm 0{\cdot}34$ h for ETH, and $2{\cdot}18 \pm 0{\cdot}11$ for PTH, for the terminal half-lives.

The total areas under the plasma time curves (AUC), were 55 and 1215 $\mu$g ml$^{-1}$ min after intravenous and oral dosage with ETH, respectively. Those for PTH were 48 and 870 $\mu$g ml$^{-1}$ min$^{-1}$. Using these values, the systemic availabilities[17] of oral ETH and PTH were calculated to be 1·1 and 0·9,

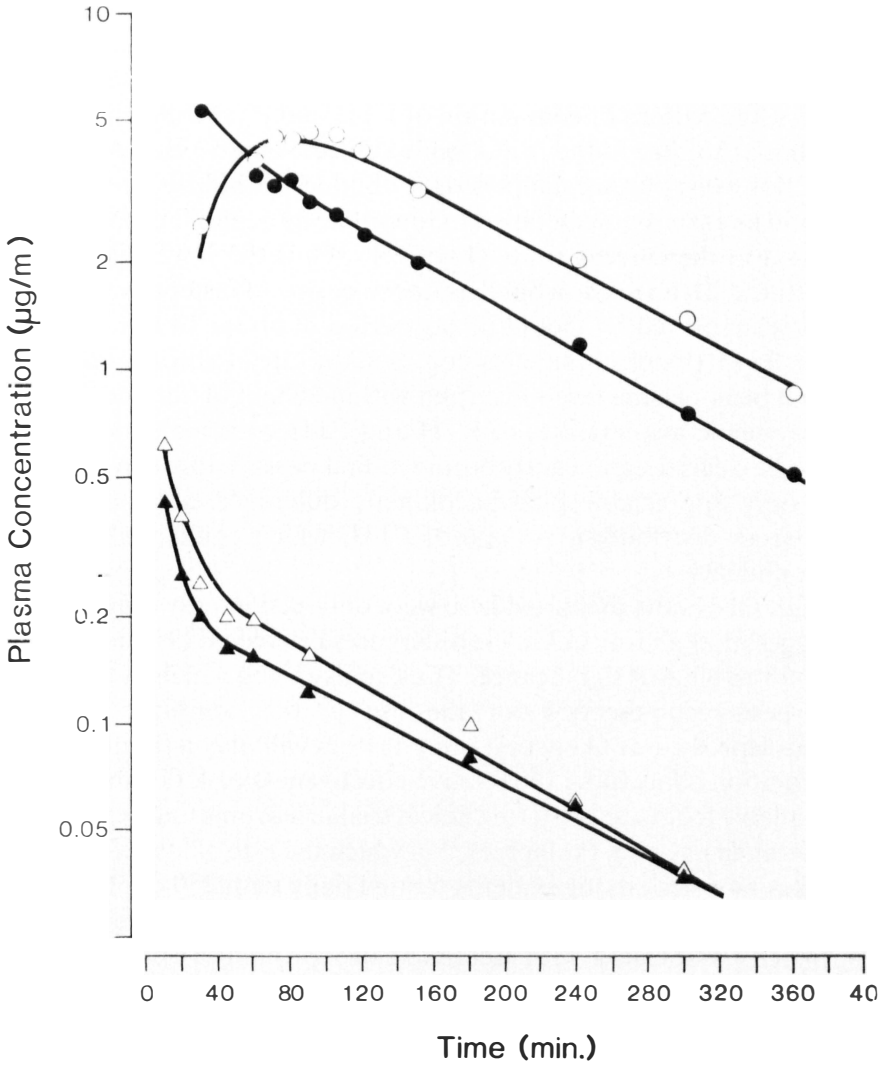


**Figure 1.** Plasma concentrations following oral dosage with 500 mg ethionamide (○) or prothionamide (●), and after intravenous administration of 25 mg ethionamide (△) or prothionamide (▲).

respectively. Thus it appears that both thioamides are essentially completely absorbed and are not subjected to any appreciable first pass metabolism. Volumes of distribution following intravenous administration, calculated from the formula $V = \text{dose}/B \times \text{AUC}$, where $B$ is the terminal rate constant, were 79 and 93 l for ETH and PTH, respectively.

## Discussion

The HPLC method for ETH and PTH devised by us previously is ideally suited to

measure plasma levels after combined dosage with both drugs. By using this approach it was hoped that some of the variation normally encountered when drugs are given separately, as in a cross-over study, would be reduced. Nevertheless, the pattern of elimination of ETH and PTH following oral dosage was very similar to that found in the same subject some 5 years previously.[13] In that study, however, plasma samples were obtained at hourly intervals from 1 h onwards, and as a consequence failed to reveal the more rapid absorption of PTH demonstrated in the current study (Figure 1). Thus the lower plasma levels of PTH from about 2 h onwards would appear to be due to faster absorption. Such a conclusion is supported by the initial lag period of about 18 min calculated for ETH by the ESTRIP programme. By contrast, the rate of absorption of PTH was so rapid that peak plasma levels occurred within 30 min of administration of the dose. The systemic availabilities of ETH and PTH were high and neither drug appeared to be cleared significantly during its first passage through the liver or gut wall. The only appreciable pharmacokinetic difference encountered was the higher apparent distribution volume of PTH, which could well be due to its greater lipophilicity.

Although the results presented here were obtained in only a single volunteer, they do suggest that pharmacokinetic differences between ETH and PTH are very slight and not of clinical significance. Thus, in assessing which of the thioamides might be best recommended for the use in the combined treatment of lepromatous leprosy, it is likely that other factors will play a far more important part. Information concerning the relative effectiveness of ETH and PTH should soon be available from a short-term clinical trial in lepromatous leprosy currently being undertaken in Cebu, Phillipines,[18] in which the rate of loss of viability of *M. leprae* in skin biopsies among patients treated daily with 250 or 500 mg doses of ETH or PTH is being compared. In view of reports of relatively high incidences of hepatic toxicity associated with treatment of lepromatous patients with daily ETH or PTH combined with daily or monthly rifampicin,[19–21] it is clearly important that liver function be monitored in future clinical trials of the thioamides in the combined chemotherapy of lepromatous leprosy. For the present moment, the major determinants as to which thioamide should be used should be relative cost and availability.

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