Metabolism and excretion of the quaternary ammonium compound thiazinamium methylsulfate (Multergan®) in man

II. Oral and rectal administration

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ABSTRACT

In this study it is shown that biotransformation of thiazinamium, when given orally, does not differ qualitatively from the pattern found after parenteral administration. However, quantitatively both the metabolism and excretion patterns are considerably different from those after intravenous injection.

The renal clearance accounted for 256 ± 136 ml.min⁻¹ (mean ± SD). This value is higher than glomerular filtration, which may be indicative of an active excretion process. Hepatic clearance (biotransformation and biliary excretion of unchanged cation) was 537 ± 495 ml.min⁻¹ (mean ± SD). Hepatic clearance was found to correlate negatively with bioavailability.

The ratio between unchanged drug and the only metabolite, the sulfoxide, in urine was about 1:0.9. This is substantially different from that found after parenteral administration (ca. 1:0.2), which may imply that a 'first-pass effect' occurs. It was estimated that ca. 50% of the absorbed amount was metabolized during the first liver passage.

The fate of thiazinamium after rectal administration in Witepsol H15 suppositories shows several similarities with that after oral administration. The ratio between unchanged drug and metabolite in urine in this case was ca. 1:0.8, indicating that also after rectal administration a 'first-pass effect' occurs, now to a degree of ca. 35%.

INTRODUCTION

In the accompanying paper, we report on the metabolism and excretion of the quaternary ammonium compound thiazinamium after intravenous and intramuscular administration in man (JONKMAN et al. 1982). As the drug is also used frequently by oral and, to a lesser extent, by rectal administration, we decided to investigate if there is any difference in metabolism and excretion after parenteral and non-parenteral administration. Because our previous study showed that the drug can easily be oxidized and that both unchanged drug and metabolite are extensively excreted in the bile, we decided to give special attention to a possible 'first-pass effect'.

MATERIALS AND METHOD

Qualitative study

Urine samples obtained at different time intervals after oral administration were analysed using the same materials and methods as described before (JONKMAN et al. 1982), with the exception that no experiments were done with 35S-labelled material.

Quantitative study

Urinary excretion after oral administration of a single dose of 300 mg. Ten patients suffering from quiescent generalized obstructive lung disease participated on a voluntary basis in this study. Some of the patients' characteristics are given in Table 1. (For further details see VAN BORK 1978.) No abnormalities in their circulation, blood composition, kidney function, or liver function were found upon clinical and laboratory analysis. The patients did not receive other medication; they fasted overnight. The tablet was ingested with about 200 ml of water. Urine was collected during 8 h after drug intake.

Coated tablets (Multergan forte®, Specia, Rhône-Poulenc, Paris, France) were used. Each tablet contained 300 mg (= 0.9494 × 10⁻³ mole) of thiazinamium base (= hydroxide) in the form of the methylsulfate salt. Chemical and biopharmaceutical properties of the tablets are given elsewhere (JONKMAN et al. 1977). All other materials and methods are identical to those described elsewhere (JONKMAN et al. 1977).

Urinary excretion after oral administration of repeated doses of 900 mg. In eight male volunteers (see Table 1) the metabolism and excretion were studied after giving a dose of 900 mg on seven different days. The doses were given with intervals of at least two days, to ensure the complete elimination of the previous dose. The dose was taken in the morning on an empty stomach with 200 ml of water. After 90 min a light meal was taken. Thereafter food intake and drinking was allowed, but standardized for each individual. Urine was collected during 24 h (excretion was shown to be complete during this period).

All other materials and methods were identical to those described above.

Urinary excretion after rectal administration of a dose of 150 mg. The patients were the same as mentioned in the paragraph Urinary and biliary excretion after intramuscular injection of a dose of 12.5 mg in part 1 of this study (JONKMAN et al. 1982). Details on the protocol and dosage form are given in a previous paper on the bioavailability after rectal administration of this drug (JONKMAN et al. 1979a). However, in the present study suppositories with a lipophilic base (Witepsol H15) were used, because only this base ensured systemic availability of the drug.

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Urine was collected during 24 h. The results of patient H.H. are omitted because of insufficient sampling.

RESULTS AND DISCUSSION

Qualitative study

Analysis of urine samples, obtained at different times after drug administration showed essentially the same results as obtained after parenteral administration. In addition to thiazinamium (Th) only one metabolite, thiazinamium sulfoxide (ThSO) could be detected.

Quantitative study

Urinary excretion after oral administration of a single dose of 300 mg. Figure 1 shows the renal excretion rate and the cumulative renal excretion of Th and ThSO in patient A.V. Table 1 presents the amounts of Th and ThSO excreted during the eight hours of the experiment in all ten patients.

In only four patients (F.K., J.A.M., D.M. and S.W.) the urinary excretion was found to be complete or could be determined by extrapolation. In the experiment in all ten patients, drug which became systemically available was excreted as unchanged Th and 44.1 ± 11.1% (SD) as ThSO.

Renal clearance (Clr) was calculated by means of the following equation:

\[ \frac{dQ}{dt} = Cl_r \cdot c_p \]

where: \( \frac{dQ}{dt} \) = renal excretion rate (the amount of drug eliminated in a certain period by renal excretion (e.g. ng.min\(^{-1}\)); \( Cl_r \) = renal clearance; that part of the total body clearance (= Cl\(_{bol}\)) that occurs by renal excretion (ml.min\(^{-1}\)); \( c_p \) = plasma concentration (ng.ml\(^{-1}\)).

For these calculations plasma concentration data of the bioavailability study (JONKMAN 1977) were used. The values obtained are given in Table 1, together with the figures for the total plasma clearance as they were found in these patients after receiving an intramuscular dose of 25.0 mg (calculated from the values of the volumes of distribution and the elimination rate constants).

All patients, except A.O., had a clearance value for Th which is higher than the average creatinine clearance of about 130 ml.min\(^{-1}\) (WAGNER 1971). This means that in most patients active excretion (probably by tubular secretion) occurred.

The mean value for renal clearance was 256 ± 136 ml.min\(^{-1}\) (SD), whereas the total plasma clearance was found to be 780 ± 450 ml.min\(^{-1}\) (SD). So, renal clearance is lower, in some patients even considerably lower, than the total plasma clearance. Expressed as a percentage, renal clearance varied from 11 to 94% of the plasma clearance. So in some patients we are dealing with a high hepatic clearance. This includes both biliary excretion of the unchanged drug and disappearance of Th from the plasma by biotransformation to the sulfoxide. The values for the hepatic clearance can be calculated by subtracting the renal clearance from the total plasma clearance, under the assumption that no other elimination routes exist. A mean value of 537 ± 495 ml.min\(^{-1}\) (SD) was found.

(N.B. In some patients relatively high values for the hepatic clearance were found. Theoretically these high values can also be explained by intestinal first-pass metabolism. This factor, however, could not be determined in these experiments. In a study in dogs (JONKMAN et al. 1981) the pure hepatic first-pass effect was determined. The figures found in those experiments correlate well with the above mentioned data, but comparison is precarious as another species is involved.)

With regard to the renal excretion of the metabolite ThSO, Figure 1 shows that this process started at a lower rate than the excretion of the unchanged drug, but soon the excretion rates were almost identical. The average quantity of ThSO found in the urine after oral administration expressed as a percentage of the bioavailable drug was considerably higher than after parenteral administration: 32.2 ± 20.3% (SD). This results in a quite different ratio between Th and ThSO in urine, namely 1:0.94, whereas after parenteral administration a ratio of approximately 1:0.2 was found (JONKMAN et al. 1982).

From Table 1 it becomes apparent that two correlations exist. Firstly, patients with a high hepatic clearance of Th (e.g. J.A.M., D.M. and O.V.) have excreted a relatively large amount of ThSO in urine. The calculated hepatic clearance in these patients is above 820 ml.min\(^{-1}\), and the ratio between Th and ThSO in urine is above 1:2.42.

On the other hand the table also shows that patients with a lower hepatic clearance (e.g. E.D., A.V. and K.W.) excreted only a small quantity of ThSO in urine, with ratios between 1:0.14 and 1:0.61.

Secondly, Table 1 shows that in patients with a relatively high hepatic clearance (> 820 ml.min\(^{-1}\)) a low bioavailability was estimated. When the liver plasma flow is assumed to be about 1000 ml.min\(^{-1}\) (being about two-third of the liver blood flow of 1500 ml.min\(^{-1}\); see ROWLAND 1972), this means that in these patients ca. 80% of the drug is eliminated from the plasma by the liver. On the other hand in patients with a low hepatic clearance a better bioavailability was seen.

The latter two findings, together with the observation that after oral administration a higher percentage of drug was excreted in the form of the metabolite, suggest that the liver plays a predominant role in the bioavailability and the fate of Th in man. The quantitative difference in biotransformation found after oral and parenteral administration and the relation between hepatic clearance and the