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# BIOAVAILABILITY AFTER RECTAL ADMINISTRATION OF THIAZINAMIUM METHYLSULPHATE IN DIFFERENT VEHICULA

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## SUMMARY

The bioavailability in humans of the quaternary ammonium compound thiazinamium methylsulphate (Multergan) was studied using plasma concentration measurements after the application of the drug in a lipophilic (Witepsol H-15) and a hydrophilic (a polyethylene glycol mixture) suppository base.

The best results were obtained with Witepsol H-15. The peak in the plasma concentration–time curve appeared about 60 min after administration, indicating that the rate of absorption is faster than that observed after oral administration. After the maximum, the curve declined rather rapidly, and usually dropped to zero or almost zero concentration in 7 h.

The bioavailability obtained with Witepsol H-15 suppositories was about 6% of the dose, which is of the same order of magnitude as after oral administration. Interindividual variation was also similar to that obtained after oral administration.

After the application of the drug in the polyethylene glycol base, very low plasma concentrations were found and the bioavailability was almost negligible.

## INTRODUCTION

Rectal administration is not only used for local activity but also for several classes of drugs with a systemic action, e.g. analgetics, spasmolytic drugs and drugs against generalized obstructive lung diseases (e.g. theophylline derivatives). This route of administration is recommended when the oral route is precluded by vomiting, when the patient is unconscious, i.e. drugs that are likely to cause gastric irritation, and whenever one wants to obtain a rapid action by means of a non-invasive method. Also in cases of degradation of the medicament in the gastrointestinal tract, the rectal route is preferred above the oral one.

Several textbooks on therapeutics describe that after rectal administration drugs will enter – at least to the main part – the general blood flow without an initial passage through the liver, provided that the suppository does not reach the higher parts of the rectum (e.g. Fingl and Woodbury, 1975; Huizinga, 1975; see also Bucher, 1948; Hennig, 1959; Greenleaf and Hadgraft, 1960; Ritschel, 1973; Jacquot et al., 1977).

This can be explained by the fact that the inferior and middle rectal veins (in contrast to the superior ones) are not in direct connection to the portal system. If complete first liver passage could be avoided by applying a drug by the rectal route, this way of drug administration would be beneficial – besides the above mentioned reasons – for those drugs that are in the large part metabolized by the liver or excreted in the bile (i.e. drugs that are subjected to a 'first pass effect').

Thiazinamium methylsulphate (Multergan; Specia/Rhône Poulenc, Paris) is a phenothiazine derivative with a quaternary ammonium group in the side chain of the molecule (Fig. 1). The drug is used in some types of generalized obstructive lung disease because it causes bronchodilatation, probably as a result of substantial anticholinergic and antihistaminic properties (Ducrot and Decourt, 1950a, b; Booy-Noord et al., 1957, 1970; Sluiter and De Vries, 1974; Van Bork et al., 1977; Bouhuys and Ortega, 1976; Van Bork, 1978).

Because we (Jonkman, 1977; Jonkman et al., 1977) had found a rather limited bioavailability after oral administration (which could be attributed in part to an extensive 'first pass effect'), we decided to investigate to see if rectal application of this drug would result in a better systemic bioavailability.

The relative bioavailability of rectally administered thiazinamium methylsulphate as compared to intramuscular injection was investigated using two different kinds of suppositories, one with a lipophilic base and one with a hydrophilic base. This was done in order to obtain information about the better type of vehicle for suppositories containing thiazinamium methylsulphate. The optimum dosage form of these suppositories should meet two prerequisites: it must give good bioavailability and it must cause minimal local irritation. The latter factor is important because it is known from experience that suppositories containing thiazinamium methylsulphate in cocoa butter can cause substantial local irritation, often resulting in premature expulsion of the suppository. Although many drugs cause irritation of the rectal mucosa (Fingl and Woodbury, 1975), this phenomenon seems to be rather pronounced for thiazinamium methylsulphate, possibly due to the quaternary ammonium group which has surface-active properties.

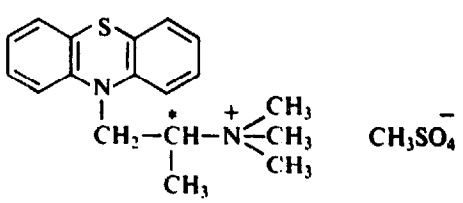


Fig. 1. Thiazinamium methylsulphate.

## MATERIALS AND METHODS

*Dosage forms*

For all experiments involving rectal administration of the drug, a dose of $0.4747 \times 10^{-3}$ M = 150 mg of thiazinamium base (hydroxide) was selected, which is equal to 194.6 mg of the methylsulphate

As a *lipophilic* (fatty) base Witepsol H-15 [1] (WH-15) was selected. Witepsol H-15 is a mixture of some mono-, di- and triglycerides of naturally occurring saturated fatty acids ($C_{12}$ to $C_{18}$), with a melting range of between 33.5 and 35.5°C and a congealing range of 32.5 to 34.5°C. The specific gravity of Witepsol H-15 at 20°C is from 0.950 to 0.980; it has an iodine number less than 3, a saponification value of 230 to 240 and an hydroxyl value of less than 15 (see the information bulletin Witepsol® für Suppositorien, 1967). Its melting behaviour both in vitro and in vivo was discussed by Ritschel (1973) who showed that a suppository of Witepsol H-15 without additional drug substances melts almost completely in the human rectum within 10 min.

Thiazinamium methylsulphate was passed through a sieve in order to obtain particles <150 μm in size. The suppositories were prepared by the fusion method, i.e. making a suspension of the powder (194.6 mg of thiazinamium methylsulphate per suppository) mixed with colloid silica (Aerosil; 2 mg per suppository). Afterwards the suspension was poured into 2-ml moulds at 34–35°C.

The content of drug substance in the suppositories was determined by means of an amphimetric titration and was found to be 100.3% (n = 3) of the stated amount (Jonkman, 1977).

The dissolution rate of the drug from the suppositories was determined as described by Cox and Breimer (1973) and de Blaey and Rutten-Kingma (1977). Within 30 min, 83% of the content of the suppositories appeared in the aqueous phase (Fig. 2). (N.B. Pure distilled water was used; buffering would be senseless because thiazinamium methylsulphate, being a quaternary ammonium compound, is completely ionized at all pH values.)

As a *hydrophilic* or polar base, a polyethylene glycol (PEG) mixture was selected [2]. The mixture consists of PEG 1500 and PEG 4000 in a ratio of 1 : 2. PEG 1500 is a blend of equal parts of PEG 300 and 1540 and it has the consistency of petrolatum. PEG 4000 is a white waxy solid. From a chemical point of view, polyethylene glycols are polymers of ethylene oxide with the generalized formula $HOCH_2(CH_2OCH_2)_nCH_2OH$, where n represents the average number of oxyethylene groups. The melting range of PEG 1500 is 38.0–41.0°C, and of PEG 4000 it is 53.0–56.0°C. The specific gravity of PEG 1500 at 20°C is 1.151, of PEG 4000 it is 1.204 (density g/ml). The melting range of this mixture was found to be 48–55°C.

The PEG suppositories were prepared as follows. The powder mixture of thiazinamium methylsulphate and colloidal silica was prepared as described above. The PEG was liquefied at 80°C and mixed with the powder; it was then poured at 50°C into 2-ml moulds.

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[1] Dynamit Nobel A.G./Chemische Werke Witten, Witten, G.F.R.

[2] Carbowax (Union Carbide Corporation, New York, U.S.A.)

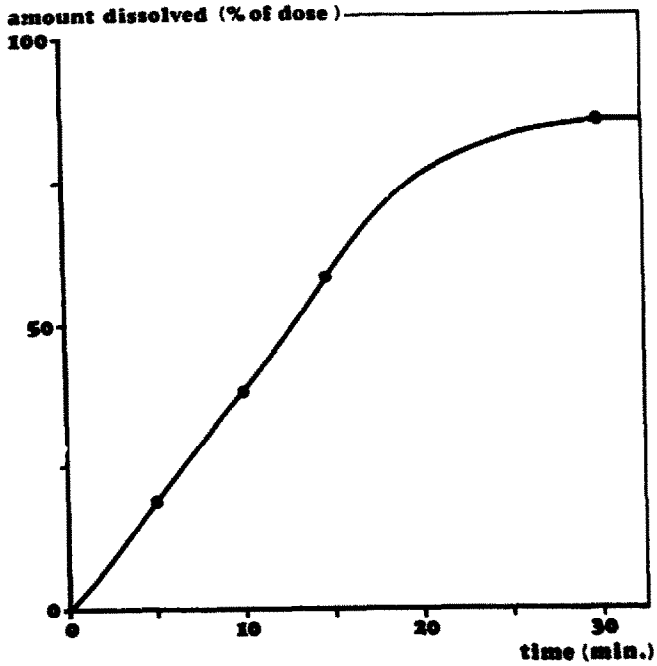


Fig. 2. Release of thiazinamium methylsulphate from a Witepsol H-15 suppository.

The content of the suppositories, determined by spectrophotometric analysis (Jonkman, 1977), was found to be 103.2% of the stated amount. (N.B. The dissolution rate of PEG suppositories was not determined according to the above method because the method is only applicable to lipophilic suppositories.)

The dosage form for intramuscular injection consisted of an aqueous solution containing 32.44 mg thiazinamium methylsulphate in 1.0 ml of a 0.45% sodium chloride solution to which an antioxidant (sodium metabisulphite, 1.25 mg/ml) and disodium-edetate (0.05 mg/ml) were added. The solutions were prepared and sterilized in the pharmacy of the Groningen University Hospital from the commercially available drug substance. Of this solution 0.5 ml was injected in the right thigh.

*Analytical methods*

The amount of thiazinamium cations in plasma and urine was determined as described earlier (Jonkman et al., 1975). The procedure is based on ion pair extraction of the compound with iodide as a counter ion. This is followed by gas chromatography using an alkali flame ionization detector.

*Protocol*

Seven male patients with generalized obstructive lung disease participated in this study. Each patient received both suppositories and an intramuscular injection (see below) with at least two days interval. The patients characteristics are given in Table 1. No abnormalities in their blood composition, kidney function, liver function or digestive tract were found. None of the patients used other drugs during the investigations or

TABLE I

PATIENT CHARACTERISTICS AND DOSE

| Patient | Age (years) | Body weight (kg) | Height (m) | Dose (mg/kg) |
|---|---|---|---|---|
| G.L. | 57 | 74 | 1.78 | 2.63 |
| P.H. | 62 | 86 | 1.74 | 2.26 |
| W.M. | 52 | 79 | 1.81 | 2.46 |
| H.H. | 63 | 67 | 1.76 | 2.90 |
| W.B. | 26 | 70 | 1.74 | 2.78 |
| M.F. | 71 | 72 | 1.76 | 2.70 |
| T.J. | 68 | 75 | 1.77 | 2.59 |
| Mean | 57 | 75 | 1.77 | 2.62 |
| S.D. | 15 | 6 | 0.02 | 0.21 |

during the preceding week. Patients fasted overnight. Control blood samples were drawn at the start of the experiment. After the administration of the drug, at 09.00 h, the patients stayed in bed for 1 h. Blood sampling took place after 3, 6, 10, 15, 20, 30, 45, 60, 75, 90, 105, 120, 150, 180, 210, 330 and 420 min. The samples (approx. 10 ml) were drawn from a permanent cannula [3] with a K-75a three-way stopcock [4] placed in the right cubital vein. The blood was collected in 15 ml glass tubes with screw caps [5], each containing one drop of heparin solution (5 mg = 500 U of heparin sodium per ml of distilled water). The samples were immediately stored in a refrigerator at 4°C, and then centrifuged within 2 h of collection for 20 min at 6000 × *g*. Next 4.0 ml of the plasma layer were transferred to a centrifuge tube of 50 ml capacity with Quickfit stopper and stored at −20°C until analysis was performed (within two months).

Immediately after administration, each patient was allowed to drink 200 ml of water. After 90 and 210 min the patients were given a light meal (rusks with sugar and a glass of orange lemonade). While the experiment was taking place the patients were allowed to drink some water if requested.

*Determination of the relative bioavailability*

The areas under the plasma concentration–time curve were determined by the cutting and weighing of a standard high-quality paper. The relative bioavailability versus an intramuscular injection of a dose of 12.5 mg – given in the right thigh – in the same patient was calculated by comparing the areas under the curve after correction for the dose. (Earlier investigations had proved that during the time of the experiment the bioavailability after intramuscular injection was 100% as compared to intravenous injection; Jonkman, 1977.)

[3] Indwelling catheter Braunule T with LOK, B. Braun, Melsungen, G.F.R.

[4] Pharmseal, Herstal, Belgium.

[5] Sovirel, Levallois-Perret, France.

RESULTS AND DISCUSSION

*(a) Investigations with Witepsol H-15 suppositories*

In Fig. 3 some typical examples are given of plasma concentration–time curves as were obtained after applying the drug in the WH-15 base. In general, plasma concentrations were found to be low. The values for $c_{max}$ varied from 54 to 290 ng/ml with a mean of 103 ± 89 (S.D.) (see Table 2).

This low absorption can be explained by the presence of the strongly polar quaternary ammonium group in the molecule, being ionized at all pH values. Absorption by passive diffusion, as postulated in the pH-partition hypothesis, is, for this reason, negligible. The only possible way of absorption for these ions seems to be 'ultrafiltration' through aqueous pores in the membrane (see also the exhaustive discussion in Jonkman et al., 1977).

It appeared that the rate of absorption showed considerable interindividual variation, but generally this process was rather fast. The values for $t_{max}$ varied from 15 to 120 min with a mean value of 63 ± 42 (S.D.) min (see Table 2). This suggests that thiazinamium cations are readily liberated from the WH-15 base in the rectum, which is in agreement with the 'in vitro' experiment.

In four patients the curve after reaching $c_{max}$ declined rather quickly, resulting in a concentration of almost zero at the end of the experiment (t = 420 min). In three other patients a more or less pronounced plateau level was found, which may indicate that absorption of the drug goes on for an extended period. Despite the fact that it is readily released from the base it seemed that absorption was not yet finished in these cases at the end of the experiment. This finding can probably be explained by the fact that the rectum has a motility which is more limited than the motility of the small intestines (Connell, 1961). So the 'ultrafiltration' process will go on during a rather long time.

From the plasma concentration–time curves during the time of the experiments a

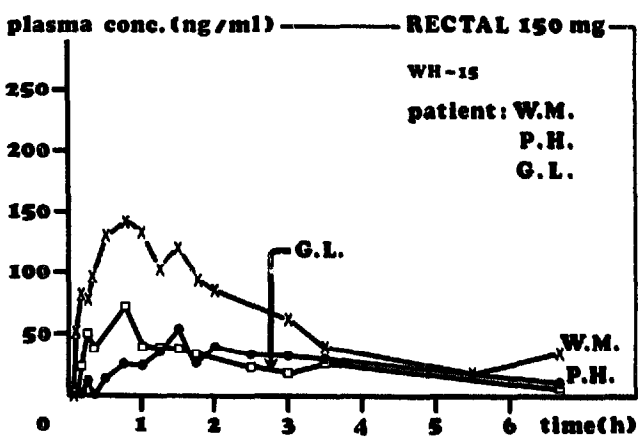


Fig. 3. Typical examples of individual plasma concentration–time curves obtained after rectal administration of a Witepsol H-15 suppository.

TABLE 2

ABSORPTION CHARACTERISTICS OF THIAZINAMIUM METHYLSULPHATE AFTER RECTAL ADMINISTRATION IN WITEPSOL H-15 AND PEG 1500/4000 (1:2) SUPPOSITORIES

| Patient | Bioavailability (% of dose) | | $c_{max}$ (ng/ml) | | $t_{max}$ (min) | |
|---|---|---|---|---|---|---|
| | WH-15 | PEG | WH-15 | PEG | WH-15 | PEG |
| G.L. | 6.3 | 0 | 72 | – | 45 | – |
| P.H. | 6.6 | 3.1 | 54 | 42 | 90 | 180 |
| W.M. | 11.0 | 0.4 | 142 | 19 | 45 | 20 |
| H.H. | 6.9 | 0.9 | 63 | 57 | 120 | 180 |
| W.B. | 0.7 | 0.1 | 45 | 8 | 105 | 15 |
| M.F. | 5.8 | 0.2 | 290 | 22 | 15 | 30 |
| T.J. | 3.4 | 1.0 | 53 | 19 | 20 | 15 |
| Mean | 5.8 | 0.8 | 103 | 24 | 63 | 73 |
| S.D. | 3.2 | 1.1 | 89 | 20 | 42 | 83 |

mean relative bioavailability, $F_{rel}$, of 5.8 ± 3.2 (S.D.)% of the dose was found. The estimated total relative bioavailability (obtained after extrapolation) was somewhat higher, namely 6.2 ± 3.4 (S.D.)% of the dose. These figures indicate that a quite large interindividual variation in bioavailability exists. This finding is in accordance with earlier observations that rectal absorption is often irregular (Wagner 1971; Fingl and Woodbury, 1975). Moreover, it has been stated that interindividual variation in bioavailability is generally large for drugs with poor absorption characteristics (Koch-Weser, 1974). The variation can also possibly be partly explained by the fact that a considerable 'first pass effect' had been found after rectal administration of thiazinamium methylsulphate (Jonkman, 1977), which is general enhances the variation in bioavailability (Wilson et al., 1976). As compared to the results obtained after oral administration of the drug (Jonkman et al., 1977), the absorption process after rectal application began earlier and seemed to take place at a higher rate, resulting in a more pronounced peak in the plasma concentration–time curve. The values for the relative bioavailability after rectal application of the drug in WH-15 are of the same order of magnitude as those following oral administration (after an oral dose of 300 mg $F_{rel}$ was found to be 3.6 ± 1.7 (S.D.)% and after 900 mg was 4.5 ± 3.4 (S.D.)% of the dose). This is rather surprising because there are no villi in the rectum and hence the surface of the membrane, and consequently the number of pores in it, is lower than in the small intestine. Moreover, the motility in the rectum is restricted. Variation of the bioavailability seems to occur to approximately the same extent after both routes of administration.

Concerning the *local irritation*, two patients (G.L. and H.H.) reported substantial local irritation resulting in defaecation (with loss of the suppository) after 20 and 45 min respectively. Two of the other patients reported slight but tolerable irritation between 10 and 20 min after application.

In comparison to the results we have obtained in an earlier study on oral adminis-tra-

tion (Jonkman et al., 1977) we can conclude that rectal application of this drug is only preferable over oral administration when a rapid onset of the action of the medicament is required (and injection is undesirable) or when oral administration results in too many adverse reactions.

As far as we know in the literature only one paper has been published dealing with the results of a similar study (Kerckhoffs and Huizinga, 1967). However, their results should be considered with criticism because their method of bioanalysis was probably inadequate (see also Jonkman, 1977).

*(b) Investigations with polyethylene glycol suppositories*

The plasma concentrations achieved after application of the PEG suppositories were extremely low. In one patient (G.L.) no drug substance at all could be detected in the plasma.

In the other patients no thiazinamium cations could be found in a number of samples. If any drug could be determined it was at irregular times and often close to the detection limit. Typical examples of plasma concentration–time curves are given in Fig. 4. These findings suggest that thiazinamium cations became available in the rectal fluid at a low rate and in small proportions, which would be in agreement with the general rule that water-soluble (hydrophilic) compounds are liberated slowly from a hydrophilic base like PEG. This may also be due to the fact that the dissolution time of PEG suppositories is long in comparison to the melting time of WH-15 suppositories; the former may lie in the range of 1 h or more (Hennig, 1959; Bevernage and Polderman, 1972; Kerckhoffs and Huizinga, 1967). Besides this low dissolution rate the solubility of PEG is also rather low, (PEG 1500: 1 in 1 of water; PEG 4000: 1 in 3 of water; Martindale, 1977) considering that only a few millilitres of mucous fluid occur in the rectum. (N.B. Although results of a similar study have been published (Kerckhoffs and Huizinga, 1967) comparison with our results would not be very sensible, for the reasons pointed out above.)

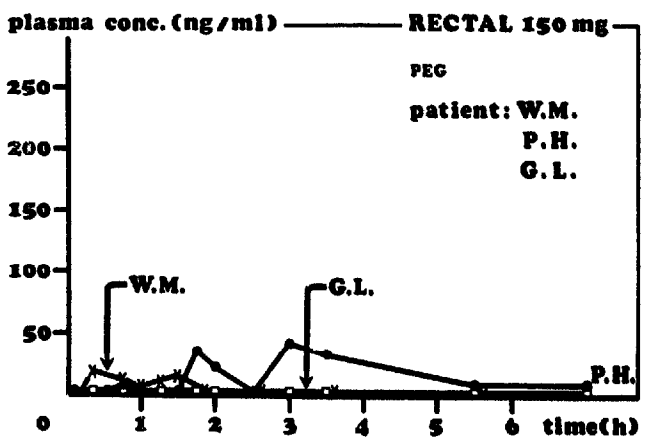


Fig. 4. Typical examples of individual plasma concentration–time curves after rectal administration of a polyethylene glycol suppository (PEG 1500/4000, ratio 1 : 2).

Apparently, if any absorption of thiazinamium cations from PEG suppositories does occur at all the elimination rate is almost the same or even higher than the absorption rate. Hence, a relative bioavailability, $F_{rel}$, of 0.8 ± 1.1 (S.D.) of the dose was calculated (Table 2), which is significantly lower than that obtained with WH-15 suppositories (paired $t$-test, $P < 0.01$).

In contrast to earlier literature observations on PEG suppositories on the subject (Wagner, 1971), PEG suppositories used in our study were generally well tolerated. Only two of the patients reported any notable local irritation, namely G.L. and H.H. (who both reported an unbearable irritation after application of the WH-15 suppositories!).

Attempts to improve bioavailability by changing the chemical and formulation form are now under investigation.

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