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# PHARMACOKINETICS OF MEPINDOLOL ADMINISTERED ALONE AND IN COMBINATION WITH HYDROCHLOROTHIAZIDE—A BIOEQUIVALENCE STUDY

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## ABSTRACT

The bioavailability and pharmacokinetics of 10 mg of mepindolol sulphate and of 25 mg of hydrochlorothiazide were compared in a cross-over design in five healthy volunteers after the administration of either the single drugs (Corindolan® and Esidrix®) or in combination (Tenesor®).

Maximum concentrations of mepindolol in the plasma of 25 ng ml$^{-1}$ were achieved 1·6 h after both treatments and the half-life of disposition was calculated to be 4–5 h, being somewhat longer after the combination tablet. The amount of hydrochlorothiazide renally eliminated up to 48 h after drug intake was about 60 per cent of the dose. The half-life of renal excretion was 3 h. The two formulations of mepindolol sulphate and hydrochlorothiazide proved to be bioequivalent with a tendency to better mepindolol bioavailability in the combination form.

KEY WORDS Mepindolol Hydrochlorothiazide β-Blocker/diuretic combination Bioequivalence

## INTRODUCTION

Tenesor® (registered trade mark of Schering) is a fixed combination of 5 mg of mepindolol sulphate and 12·5 mg of hydrochlorothiazide in a coated tablet. Both components are blood-pressure lowering agents with different mechanisms of action. Therefore, a combination is likely to exhibit synergistic antihypertensive effects, which has been proven for a number of β-blockers and diuretics.[1–4]

The aim of the present study, therefore, was to investigate whether the bioavailability of either of the two components mepindolol and hydrochlorothiazide is influenced by the presence of the other. Furthermore, it should be clarified whether there are any interactions on pharmacokinetics between the two drugs, which might be caused by the haemodynamic effects of the β-blocker

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or the diuretic. For example, the reduction in cardiac output, provoked by mepindolol, might influence the absorption or elimination of hydrochlorothiazide. Or the plasma volume reduced by the diuretic might influence the concentrations of the β-blocker in the plasma.

## EXPERIMENTAL DESIGN

Five healthy volunteers (two females and three males), who had given their written consent before, participated in the study. They were aged between 24 and 32 years (mean value 27 years) and weighed from 56 to 90 kg (mean value 69 kg). The doses administered were 10 mg of mepindolol sulphate and 25 mg of hydrochlorothiazide. They were given as two tablets of Corindolan®-5, one tablet of Esidrix® (trade mark of Ciba Geigy) and in the combination study as two tablets of Tenesor®, respectively. Drug intake took place in the morning after a light breakfast. The study was started with the combined preparation, followed by the β-blocker and the diuretic at weekly intervals.

Before and at various times up to 24 h after the first two treatments, blood samples were taken and the plasma obtained was frozen immediately. Urine was collected quantitatively in the time periods 0–2, 2–4, 4–6, 6–8, 8–12, 12–24, and 24–48 h after administration of esidrix® and Tenesor®. Having measured the total urinary volume, 20 ml of each fraction were kept frozen until analysis.

### *Determination of mepindolol and hydrochlorothiazide*

The concentration of mepindolol in plasma was measured by means of high-performance liquid chromatography (HPLC) with electrochemical detection, as has been described earlier.[5]

Hydrochlorothiazide concentrations in urine were determined by the method of Cooper *et al.*[6] In addition, 3-methyl hydrochlorothiazide was added as an internal standard (20 μg $ml^{-1}$). Extracts were analysed using a LiChrosorb RP-18 column and UV detection. The eluent consisted of 7·5 per cent (v/v) methanol in 0·01 M $NaH_2PO_4$ solution. At a flow rate of 2 ml $min^{-1}$ the retention times were 7·5 min for the drug and 15·6 min for the standard. The accuracy of the assay was calculated to be 3 per cent.

### *Pharmacokinetic analysis*

The time course of the concentration of mepindolol in the plasma and the renal excretion data of hydrochlorothiazide conformed to an open, linear, one-compartment model of drug disposition. The data were fitted by minimization of the squared sum of the absolute error according to the method of Poland and Woloszczak.[7] The area under the plasma concentration–time curve (AUC) was calculated according to the trapezoidal rule.

Statistical significance was evaluated by Student's *t*-test ($t_{\frac{1}{2}}$) or by the Wilcoxon test (AUC, maximum plasma drug concentration ($C_{max}$), absorption) for paired values.

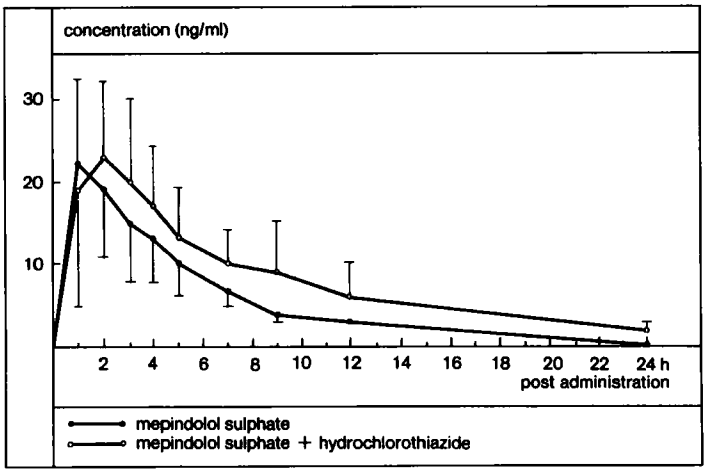


Figure 1. Plasma levels (mean ± S.D.) of mepindolol after oral administration of the drug alone (10 mg) and of a combination with hydrochlorothiazide (10 mg + 25 mg) to five healthy volunteers

## RESULTS

*Mepindolol*

The average plasma concentrations of mepindolol after administration of 10 mg of the drug alone and in combination with 25 mg of hydrochlorothiazide are shown in Figure 1. Mepindolol was absorbed with a half-life of 18 ± 6 min from Corindolan® (Table 1) and 17 ± 11 min from Tenesor®, achieving maximum concentrations of 23 ± 9 ng ml$^{-1}$ and 25 ± 12 ng ml$^{-1}$, respectively. The time to reach peak concentrations ($T_{max}$) was calculated to be 1·6 h in both cases. The half-life of disposition was somewhat longer after the combination tablet (4·7 ± 1·1 h) than after the single drug (3·5 ± 1·0 h). The difference, however, was statistically not significant ($p > 0{\cdot}05$). The AUC of Tenesor®-treated volunteers was 195 ± 90 ng h ml$^{-1}$ (median value 154·5 ng ml$^{-1}$), whereas after Corindolan® only 134 ± 42 ng h ml$^{-1}$ (median value 132 ng ml$^{-1}$) was calculated. The difference was statistically significant ($p < 0{\cdot}05$).

*Hydrochlorothiazide*

The mean urinary excretion of hydrochlorothiazide up to 48 h after the administration of either the diuretic alone or in combination with mepindolol was 15·2 ± 1·2 mg and 14·5 ± 2·6 mg, respectively, corresponding to 61 ± 5 per cent (median value 63 per cent) and 58 ± 11 per cent (median value 61 per cent) of the dose (Table 2). Figure 2 shows the time course of excretion. From these data almost identical half-lives of elimination were calculated: 3·2 ± 0·7 h for hydrochlorothiazide alone and 3·0 ± 0·4 h after the combination tablet.

Table 1. Pharmacokinetic parameters of mepindolol after oral administration of Corindolan® and Tenesor®

| Test subject | Half-life of absorption (min) | | Maximum concentration ($ng\,ml^{-1}$) | | $T_{max}$ (h) | | Half-life of disposition (h) | | AUC ($ng\,h\,ml^{-1}$) | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Corindolan | Tenesor | Corindolan | Tenesor | Corindolan | Tenesor | Corindolan | Tenesor | Corindolan | Tenesor |
| A | 18 | 3 | 30 | 42 | 1 | 1 | 2·6 | 5·4 | 156 | 348 |
| B | 11 | 29 | 34 | 33 | 1 | 3 | 3·3 | 3·0 | 193 | 200 |
| C | 3 | 14 | 21 | 14 | 1 | 1 | 2·6 | 5·1 | 105 | 132·5 |
| D | 13 | 27 | 18 | 17 | 1 | 2 | 4·6 | 5·6 | 132 | 154·5 |
| E | 44 | 12 | 11 | 19 | 4 | 1 | 4·4 | 4·5 | 86 | 139 |
| Mean ± S.D. | 18 ± 16 | 17 ± 11 | 23 ± 9 | 25 ± 12 | 1·6 ± 1·3 | 1·6 ± 0·9 | 3·5 ± 1·0 | 4·7 ± 1·1 | 134 ± 42 | 195 ± 90 |

Table 2. Pharmacokinetic parameters of hydrochlorothiazide (HCT) after oral administration of the diuretic—alone or in combination with mepindolol sulphate (25 mg + 10 mg)—to five healthy volunteers

| Test subject | Renal excretion (mg) | | Half-life of excretion (h) | | Absorption (% of dose) | |
|---|---|---|---|---|---|---|
| | HCT | Tenesor | HCT | Tenesor | HCT | Tenesor |
| A | 14·4 | 15·6 | 2·9 | 3·0 | 58 | 62 |
| B | 13·5 | 15·2 | 3·2 | 2·5 | 54 | 61 |
| C | 16·2 | 17·7 | 2·4 | 2·8 | 65 | 71 |
| D | 16·0 | 13·3 | 3·3 | 3·5 | 64 | 53 |
| E | 15·7 | 10·8 | 4·4 | 3·0 | 63 | 43 |
| Mean ± S.D. | 15·2 ± 1·2 | 14·5 ± 2·6 | 3·2 ± 0·7 | 3·0 ± 0·4 | 61 ± 5 | 58 ± 19 |

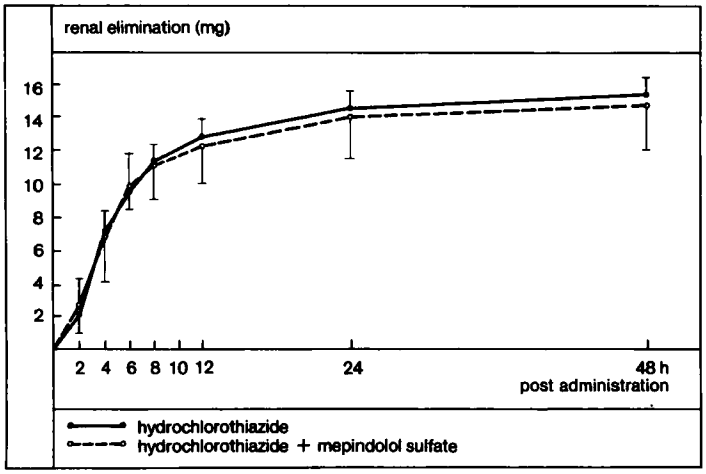


Figure 2. Renal excretion (mean ± S.D.) of hydrochlorothiazide after oral administration of the diuretic alone (25 mg) and after a combination with 10 mg of mepindolol sulphate to five volunteers

## DISCUSSION

The present report describes the plasma levels of the β-blocking agent mepindolol and the renal excretion of the diuretic hydrochlorothiazide either given as single drugs or in a combination tablet. From these data the bioequivalence of both drugs in the formulations tested was evaluated.

*Mepindolol*

For the half-lives of absorption and the maximum concentrations in the plasma—regarding either $T_{max}$ or $C_{max}$—nearly the same values were obtained. The half-lives of disposition and the AUC, however, were somewhat larger after the combination than after the single drug. The difference was statistically

significant in the case of the AUC. The area under the plasma concentration–time curve is defined as the ratio of dose/clearance. And so an increase in AUC must have been caused by a decrease in the clearance of mepindolol. On the administration of a diuretic a reduction in extracellular fluid volume can be expected. This effect might result in a different pattern of distribution for the coadministered β-blocking drug. Mepindolol now might be protected from biotransformation to a certain degree, therefore exhibiting longer plasma half-lives and a decreased clearance. The clearance, on the other hand, is affected by changes in the rate constant and the volume of distribution. Both variables are not significantly altered by the coadministration of hydrochlorothiazide. And so the resultant significant decrease in clearance might be due to a combination of two non-significant changes. From the data of Table 1 a tendency in this direction is to be recognized, but this effect should not be over-emphasized.

The half-life of absorption, the time of the maximum concentration in the plasma, and the half-life of disposition of mepindolol as reported in the present study are in agreement with the data after the administration of 20 mg of drug as had been investigated earlier.[5, 8]

*Hydrochlorothiazide*

There are a number of assay procedures described in the literature[9–11] for the determination of plasma or urine concentrations of hydrochlorothiazide. The method of Cooper *et al.*[6] is simple to handle, but due to lack of an internal standard the accuracy of the assay is not completely satisfactory. By the introduction of 3-methyl hydrochlorothiazide as an internal standard the coefficient of variation of the HPLC method could be lowered from 15 per cent to about 3 per cent.

Hydrochlorothiazide is a diuretic that is almost totally excreted via the kidneys in unmetabolized form.[12, 13] Therefore, the amount of renally eliminated drug is practically equivalent to the amount absorbed. Furthermore, the AUC of hydrochlorothiazide is not linearly correlated to the given dose,[14] so that bioavailability or bioequivalence studies should preferably be conducted by comparing the renal excretion and not the AUC of the drug. After the administration of 25 mg of hydrochlorothiazide either as Esidrix® or Tenesor® about 15 mg of unchanged drug were recovered in the urine. This is equivalent to about 60 per cent of dose. Similar values have been reported earlier.[15, 16] The half-life of excretion was identical in both studies and corresponded to that measured in the plasma as reported in the literature.[17]

From the pharmacokinetic data of mepindolol and hydrochlorothiazide evaluated after the administration of the combination tablet or the single drugs it can be concluded that the combined formulation is bioequivalent to Corindolan® and Esidrix®. This holds for the bioavailability as well as the absorption and elimination kinetics of both drugs, suggesting that there is no negative interaction between the β-blocker and the diuretic in terms of

absorption, metabolism and excretion. Similar results have been obtained with metoprolol[18] and sotalol[19] combined with hydrochlorothiazide. Again, no negative interference was observed.

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