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# Pharmacokinetic Profile of a Modified Release Formulation of Trimetazidine (TMZ MR 35 mg) in the Elderly and Patients with Renal Failure

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**ABSTRACT:**
*Objectives* – To study the effect of age and renal function on the pharmacokinetic profile of a modified release tablet of trimetazidine (TMZ MR 35 mg) administered twice daily.
*Methods* – Study 1: Twelve healthy elderly subjects ($CL_{creat}$ 72 ± 8 ml/min, 72 ± 4 years mean ± SD) and eight young volunteers ($CL_{creat}$ 134 ± 18 ml/min, 25 ± 8 years) received TMZ MR 35 mg b.i.d. (eight doses). Study 2: eight patients with severe renal failure ($CL_{creat.}$ 17 ± 5 ml/min, 54 ± 10 years), five patients with moderate renal failure ($CL_{creat.}$ 39 ± 6 ml/min, 54 ± 15 years) and eight volunteers ($CL_{creat.}$ 104 ± 17 ml/min, 53 ± 9 years) received TMZ MR 35 mg b.i.d. (patients: ten doses, volunteers: eight doses). Serial blood and urine samples were obtained following administration of the last dose in each study. TMZ plasma and urine concentrations were determined by gas chromatography (NPD-detector). The resulting data were analysed using standard non-compartmental pharmacokinetic methods.
*Results* – Study 1: Elimination half-life of TMZ was significantly longer and renal clearance significantly lower in the elderly subjects. Study 2: In patients with either moderate or severe renal failure, exposure ($AUC_{0–24}$) was significantly increased and renal clearance ($CL_R$) was significantly decreased. Significant correlations were observed between $CL_{creat}$ and $CL_R$ ($r$=0.94) and between $CL_{creat}$ and $AUC_{0–24}$ ($r$=−0.94).
*Conclusion* – With repeated administration of TMZ MR 35 mg b.i.d., a decrease in $CL_{creat}$ is directly related to a decrease in $CL_R$ and results in an increase in exposure to TMZ. Copyright © 2003 John Wiley & Sons, Ltd.

**Key words:** pharmacokinetics; trimetazidine; elderly; renal failure

## Introduction

A modified release tablet containing 35 mg of trimetazidine (TMZ MR 35 mg) has been developed in order to maintain a sustained 24 h coverage with only one tablet in the morning and one in the evening.

Trimetazidine (1-[2,3,4 trimethoxybenzyl]-piperazine dihydrochloride), the first known 3-ketoacyl coenzyme A thiolase inhibitor [1], is a metabolic agent with anti-ischaemic and anti-anginal properties. It inhibits long-chain fatty acid oxidation, shifting cardiac metabolism towards glucose oxidation. This results in an improved coupling of glycolysis with glucose oxidation, which has been shown to protect the ischaemic heart.

Taking into account that trimetazidine is mainly excreted unchanged in urine [2] and that the target population is mostly elderly, possible changes in the pharmacokinetic profile as a result of increasing age and deteriorating renal function were investigated.

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## Methods

*Study 1.* Twelve healthy elderly subjects (72 ± 4 years mean ± SD) with preserved renal function according to their age ($CL_{creat}$ 72 ± 8 ml/min) and eight young volunteers (25 ± 8 years, $CL_{creat}$ 134 ± 18 ml/min) received TMZ MR 35 mg b.i.d. (eight doses). The first tablet was given at 8:00 p.m. on the first day. Serial blood samples were obtained before each dose and following administration of the last dose at 1, 2, 3, 4, 5, 6, 7, 8, 10, 12, 14, 16, 20, 24, 30, 36, 40, 48 and 54 h. Urines were collected 0–12, 12–24 and 24–54 h after the last dose.

*Study 2.* Eight patients with severe renal failure ($CL_{creat}$ 34 ± 6 ml/min, 54 ± 15 years) and five patients with moderate renal failure ($CL_{creat}$ 39 ± 6 ml/min, 54 ± 15 years) received TMZ MR 35 mg b.i.d. (ten doses). Blood samples were taken before each dose and 2, 4, 6, 8, 10, 12, 14, 24, 36, 48, 60, 72 and 84 h after the last dose. Urines were collected 0–12, 12–24, 24–48, 48–72 and 72–84 h after the last dose.

Eight healthy volunteers ($CL_{creat}$ 104 ± 17 ml/min, 53 ± 9 years) received TMZ MR 35 mg b.i.d. (eight doses) and the schedule for sampling was the same as in study 1.

The two studies were carried out in accordance with the recommendations of the Declaration of Helsinki [3] with applicable regulation on Good Clinical Practice (ICH E6–Guideline for good clinical practice–1996). All subjects gave informed written consent before the study.

### *Analytical method*

Plasma and urine trimetazidine concentrations were determined by gas chromatography with a nitrogen-phosphorus selective detector (NPD). After the addition of an internal standard (S 201-1) and alcalinisation of plasma or urine aliquots, the extraction was performed with methylene chloride and the content in the organic phase was derivatised using heptafluorobutyric anhydride. The evaporated residue was redissolved in ethylacetate and injected into the gas chromatograph. The lower limits of quantification were 10.0 µg/l and 0.250 mg/l in plasma and in urine, respectively. The validation of the technique between the two laboratories which participated in the determination of concentrations was performed. The interlaboratory correlation was 0.97 for plasma samples and 0.96 for urine samples, obtained from treated healthy volunteers.

### *Pharmacokinetic analyses*

Pharmacokinetic analyses of the plasma and urine data were performed with standard non-compartmental methods. The parameters were determined under steady-state conditions. $C_{max}$, $C_{min}$ and $T_{max}$ were determined from the individual plasma concentration-time curve. $T_{75}$ $C_{max}$ was the time to reach a concentration equal to 75% of $C_{max}$. *K*el was estimated from linear least-squares regression of the terminal phase of the log plasma concentration time curve. AUC(0-t) was calculated with linear trapezoidal rule. The peak-trough fluctuation (PTF) was obtained by dividing the difference between $C_{max}$ and $C_{min}$ by $C_{max}$. Ae was the amount of unchanged drug excreted in the urine over 12 h for elderly subjects and over 24 h for patients with renal impairment. $CL_{RSS}$ was calculated by dividing the cumulative amount of unchanged drug by the AUC determined over the same time interval ($Ae_{12}/AUC_{0–12}$ or $Ae_{24}/AUC_{0–24}$).

### *Statistics*

Non-parametric parameters ($T_{max}$) were compared between the study groups using the Kruskal-Wallis test followed by the Mann-Whitney-*U* test for pairwise comparisons. Parametric parameters ($C_{max}$, AUC, $T_{1/2}$, $CL_{RSS}$) were compared between study groups by a one-way ANOVA using the factor of study group. Pairwise comparisons were made using the Scheffe's procedure. $C_{min}$ values were compared within each group using a one-way ANOVA for repeated measurement.

Rank correlation Spearman's test was used for relationships between creatinine clearance versus $T_{1/2}$, $CL_{RSS}$ and $AUC_{0–24}$.

## Results

### *Subjects*

The demographic data of study 1 are given in Table 1.

Table 1. Demographic characteristics of volunteers included in the study of pharmacokinetics of TMZ MR 35 mg in healthy elderly

| | *n* | Gender (m/f) | Age (year) | Weight (kg) | Height (cm) | Creatinine clearance (ml/min/1.73 $m^2$) |
|---|---|---|---|---|---|---|
| All subjects | 12 | 10/2 | 72.2 ± 4.20 | 80.2 ± 7.11 | 173 ± 7.90 | 71.8 ± 8.00 |
| Min/max | | | 67/79 | 64.4/88.7 | 154/184 | 58.6/85.3 |
| Control group | 8 | 6/2 | 24.8 ± 8.00 | 73.7 ± 7.60 | 178 ± 8.70 | 134 ± 18.4 |
| Min/max | | | 18/42 | 62.5/83.4 | 162/189 | 113.8/167.5 |

Values are mean ± SD.

Table 2. Demographic characteristics of volunteers included in the study of pharmacokinetics of TMZ MR 35 mg in patients with renal failure

| | *n* | Gender (m/f) | Age (year) | Weight (kg) | Height (cm) | Creatinine clearance (ml/min/1.73 $m^2$) |
|---|---|---|---|---|---|---|
| Severe renal failure | 8 | 5/3 | 54.1 ± 10.3 | 78.6 ± 12.6 | 173 ± 5.60 | 16.8 ± 4.67 |
| Minimum/maximum | | | 33/65 | 59/101 | 166/180 | 10/22 |
| Moderate renal failure | 5 | 4/1 | 53.6 ± 15.4 | 66.8 ± 9.18 | 163 ± 6.50 | 39.4 ± 6.41 |
| Minimum/maximum | | | 37/69 | 54/79 | 155/171 | 32/47 |
| Control group | 8 | 6/2 | 52.6 ± 9.23 | 76.5 ± 12.4 | 171 ± 6.45 | 104 ± 17.1 |
| Minimum/maximum | | | 34/64 | 53/94 | 164/181 | 81/130 |

Values are mean ± SD.

The demographic data of study 2 are given in Table 2.

Although the mean creatinine clearance of the severe renal failure group was within the interval 15–29 ml/min/1.73 $m^2$, three patients had a creatinine clearance ($Cl_{creat}$) below 15 ml/min (12, 12 and 10 ml/min). Only the subject with a creatinine clearance of 10 ml/min differed markedly from the mean of area under the plasma concentration-time curve from 0 to 24 h ($AUC_{0–24}$) of the group (13.24 μg/h/l). From an evaluation of the $C_{min}$ values, this subject had not reached the steady-state at the time of the pharmacokinetic evaluation. With regard to the demographic data, the control group was well matched with the group of patients with severe renal failure.

## *Pharmacokinetics*

In the elderly with preserved renal function according to the age, there were no significant variations in the individual peak concentrations, with the exception of one subject, who showed a relatively high maximum plasma concentration ($C_{max}$) compared with the other subjects. The pharmacokinetic parameters of elderly and young volunteers are given in Table 3. Compared with young volunteers, analysis of variance (log transformed) revealed that half-life of elimination ($T_{1/2}$), $AUC_{0–12}$ in the elderly were significantly higher, and that values for renal clearance at steady-state ($CL_{RSS}$) were significantly lower. Values for $C_{max}$ tended to be higher in elderly compared with young volunteers ($p$=0.05), without differences in time to reach the peak plasma concentration ($T_{max}$).

Pharmacokinetic parameters of patients with moderate or severe renal failure are reported in Table 4. Maximal concentration and exposure ($AUC_{0–24}$) were significantly increased in both groups compared with the control group. Renal clearance of trimetazidine was significantly decreased in both groups compared with the control group. The difference was also significant between moderate and severe renal failure for the three parameters. The half-life was significantly increased in patients with severe renal failure compared with patients with moderate renal failure and the control group.

## *Safety*

No severe adverse event was reported in either study. A number of minor adverse

Table 3. Pharmacokinetic parameters of TMZ MR 35 mg in elderly after repeated dosing compared to young healthy volunteers

| | *n* | Mean | SD | Minimum | Maximum |
|---|---|---|---|---|---|
| Elderly | | | | | |
| $C_{max}$ (μg/l) | 12 | 115 | 30.3 | 69.5 | 185 |
| $T_{max}$ (h) | 12 | — | — | 2.0 | 5.0 |
| $C_{min}$ (μg/l) | 12 | 67.6 | 23.8 | 27.0 | 123 |
| $T_{1/2}$ (h) | 12 | 11.7 | 2.33 | 7.40 | 15.2 |
| Kel ($h^{-1}$) | 12 | 0.0620 | 0.0137 | 0.0456 | 0.0937 |
| PTF (%) | 12 | 53.9 | 12.1 | 41.1 | 72.7 |
| $T_{75}C_{max}$ (h) | 12 | 7.34 | 1.87 | 4.1 | 10.3 |
| $AUC_{0-12}$ (μg/h/l) | 12 | 1104 | 292 | 701 | 1785 |
| $CL_{RSS}$ (l/h) | 12 | 15.69 | 3.87 | 9.50 | 21.2 |
| Control group | | | | | |
| $C_{max}$ (μg/l) | 8 | 91.2 | 13.1 | 63.9 | 104 |
| $T_{max}$ (h) | 8 | — | — | 2.0 | 6.0 |
| $C_{min}$ (μg/l) | 8 | 37.7 | 6.67 | 25.8 | 46.5 |
| $T_{1/2}$ (h) | 8 | 7.81 | 2.60 | 5.0 | 12.1 |
| Kel ($h^{-1}$) | 8 | 0.0969 | 0.0289 | 0.0573 | 0.139 |
| PTF (%) | 8 | 90.4 | 27.1 | 55.7 | 138 |
| $T_{75}C_{max}$ (h) | 8 | 4.0 | 1.99 | 1.5 | 7.1 |
| $AUC_{0-12}$ (μg/h/l) | 8 | 720 | 110 | 596 | 871 |
| $CL_{RSS}$ (l/h) | 8 | 25.2 | 4.89 | 18.1 | 33.5 |
| Statistical analysis on main pharmacokinetic parameters | | | | | *p* |
| $C_{max}$ (μg/l) | | | | | 0.05 |
| $T_{1/2}$ (h) | | | | | 0.003 |
| $AUC_{0-12}$ (μg/h/l) | | | | | 0.001 |
| $CL_{RSS}$ (l/h) | | | | | 0.001 |

Table 4. Pharmacokinetic parameters of TMZ MR 35 mg after repeated dosing (ten doses) in patients with renal failure, according to the renal function

| Group | $CL_{creat}$ (ml/min) | $C_{max}$ (μg/l) | $T_{max}$ (h) | $T_{1/2}$ (h) | $AUC_{0-24}$[a] (μg/h/l) | $Ae_{0-24}$[a] (mg) | $CL_{RSS}$ (l/h) |
|---|---|---|---|---|---|---|---|
| Control (I) | 104 | 113 | 3.30 | 10.3 | 1575 | 20.2 | 12.7 |
| *n*=8 | ± 17.1 | ± 26.6 | ± 1.20 | ± 1.61 | ± 326 | ± 7.76 | ± 3.30 |
| Moderate renal failure (II) | 39.4 | 251 | 4.00 | 13.8 | 4186 | 26.7 | 6.75 |
| *n*=5 | ± 6.41 | ± 82.7 | ± 2.00 | ± 2.13 | ± 1405 | ± 6.29 | ± 1.77 |
| Severe renal failure (III) | 16.8 | 396 | 5.30 | 24.2 | 7716 | 21.2 | 2.99 |
| *n*=8 | ± 4.67 | ± 107 | ± 2.40 | ± 7.17 | ± 2597 | ± 2.67 | ± 0.95 |
| Overall difference | | *p*=0.0001 | *p*=0.12 | *p*=0.0001 | *p*=0.0001 | *p*=0.16 | *p*=0.0001 |
| I–II | | $p<0.05$ | — | NS | $p<0.05$ | — | $p<0.05$ |
| I–III | | $p<0.05$ | — | $p<0.05$ | $p<0.05$ | — | $p<0.05$ |
| II–III | | $p<0.05$ | — | $p<0.05$ | $p<0.05$ | — | $p<0.05$ |

[a] $AUC_{0-24}$ denotes the area under the plasma concentration of trimetazidine versus time curve and $Ae_{0-24}$ the amount of trimetazidine excreted unchanged in urine from time 0 to 24 h following the last administration of one trimetazidine MR 35 mg tablet.

events were reported (mainly episodes of headache), but most of them were considered not to be related to the study drug.

## Discussion

Elimination of trimetazidine has been found to be predominantly renal with 79%–84% of adminis-

tered radioactivity appearing in the urine at 24 h of which at least 60% was due to unchanged trimetazidine [2]. Trimetazidine renal clearance was approximately 25.2 l/h i.e. 420 ml/min in subjects with normal renal function. Given the low plasma protein binding of trimetazidine (15%) [4] the renal clearance value which is 3.5 fold higher than the glomerular filtration rate suggests that trimetazidine is significantly secreted by the renal tubule. These observations account for the increase in trimetazidine exposure with the decrease in renal function. Accordingly, it is not surprising that renal dysfunction significantly affects the pharmacokinetics of trimetazidine.

A significant linear correlation ($p < 0.05$) was found between $CL_{creat}$ and $CL_{RSS}$ ($r$=0.943) (Figure 1), and between $CL_{creat}$ and $AUC_{0–24}$ ($r$=−0.936) (not shown) in the study of patients with renal failure. By contrast, there was a non-linear correlation between $CL_{creat}$ and half-life [half-life=192–185.$CL_{creat}$/(1.57+$CL_{creat}$)], showing a marked increase of trimetazidine half life for low creatinine clearance values (Figure 2).

TMZ MR 35 mg is intended for the treatment of diseases that have an increasing incidence with age, the pharmacokinetic data in elderly with preserved renal function are closer to those to be found in patients than those of young volunteers.

In the elderly (mean age 72 years), the exposure to TMZ (as assessed by AUC) is increased, approximately two fold. In severe renal failure (mean creatinine clearance 17 ml/min), the exposure is increased approximately five-fold compared with the control group of similar age. Nevertheless side effects appear not to be related to the exposure to TMZ MR 35 mg. Besides these pharmacokinetic studies performed on a limited number of patients, two other larger studies have been performed versus placebo. The first one was carried out in 223 patients with angina pectoris, mean age 58 years. During the 6 month study, 51.3% of the 117 patients treated with TMZ MR 35 mg b.i.d. exhibited adverse events and 54.7% in the 106 patients of the placebo group [5].

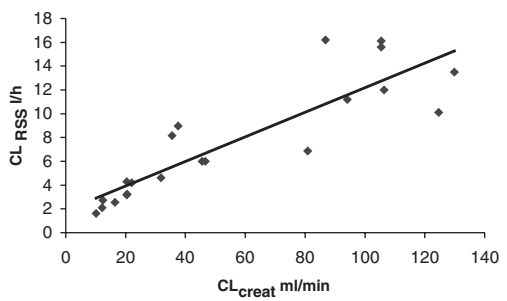


Figure 1. Relationship between creatinine clearance and trimetazidine renal clearance in patients with renal failure treated with TMZ MR 35 mg b.i.d.

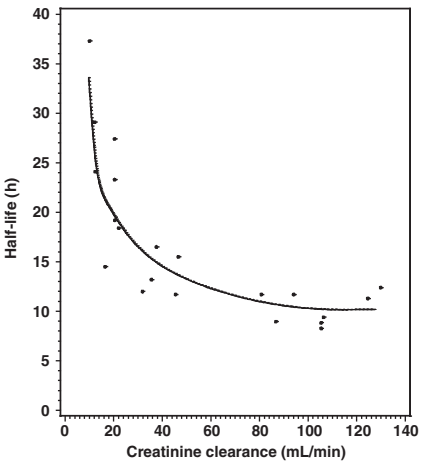


Figure 2. Relationship between creatinine clearance and trimetazidine half-life in patients with renal failure treated with TMZ MR 35 mg b.i.d. (---- spline through observed data)

The other study included 234 elderly patients (mean age 84 years, range 73–98; mean $CL_{creat}$ 45 ml/min, range 19–117) treated by TMZ MR 35 mg b.i.d. (119) or placebo (115) for 12 months. The increase in exposure to the study drug ranged from one to six fold, compared with the patients with coronary heart disease in the previous study. This increase in exposure did not involve any increase in the incidence of serious adverse effects, either quantitatively or qualitatively, compared with placebo, that might be attributed to the treatment [6].

With repeated administration of TMZ MR 35 mg b.i.d., a decrease in $CL_{creat}$ is directly related

to a decrease in $CL_R$ of trimetazidine and, as a consequence, an increase in exposure to trimetazidine. Despite this, the evidence from other studies suggests that trimetazidine has a wide safety margin and a decrease in dosage may not be necessary in patients with moderate or severe renal failure.

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