Pharmacokinetics of Cycloserine and Terizidone
A Comparative Study

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Abstract. The pharmacokinetics of Terizidone (TZ) in
comparison with cycloserine (CS) was compared. The trial
proved that blood concentration of TZ was higher at all
time intervals studied than the concentration reached in
blood after the same doses of CS; yet this increase was not
proportional to two molecules of CS contained in one molecule of TZ. The quantity
of TZ excreted with urine was also higher, but the difference, as compared with the
excreted CS, was not significant. The concentrations in the elderly patients were
higher, and excretion was slower than in the younger ones. The high concentration
of TZ in urine suggest the possibility of using this drug in treating genitalurinary
tuberculosis.

Key Words
Pharmacokinetics
Cycloserine
Terizidone

The success of antimicrobial therapy of tuberculosis depends to a con-
siderable degree on the good tolerance of the drugs administered. That is
why manufacturers are trying to develop preparations that would better
serve this purpose. One of them was given the name Terizidone (TZ) and
is manufactured by Bracco Industria Chimica S. p. A. from Milan. Essential-
yly, it is Schiff’s base of two molecules of D-cycloserine (CS) and one
molecule of terephthalic di-aldehyde.

The numerous clinical studies, conducted chiefly by Italian authors,
suggest that TZ is as effective as CS in treating tuberculosis. Patients are
reported to have tolerated TZ much better than CS. Therefore, we decid-
ed to study the pharmacokinetics of TZ in comparison with CS.
Material and Method

Pharmacokinetics of single oral doses of TZ and CS was studied in men aged 19–83, suffering from pulmonary tuberculosis. The patients were divided into three groups according to the magnitude of the dose administered; they received both TZ and CS in a single dose corresponding in the first group to 250 mg, in the second one to 500 mg and in the third one to 750 mg. In each group the patients were further subdivided according to their age into subgroup A (young patients) and subgroup B (elderly patients).

All patients were clinically examined thoroughly prior to the start of the trial. The following features were considered when comparing the homogeneity of the groups and subgroups: age, body weight, number of lung zones involved out of the total six, number of cavities present, erythrocyte sedimentation rate, hemoglobin value, leukocyte count, differential white blood cell count, glutamic-oxalacetic (GOT) and glutamic-pyruvic (GPT) transaminase values, values of urea in the blood and creatinine clearance. All the groups and subgroups of the patients under study were mutually comparable according to all the characteristics mentioned. The values obtained from examination of subgroup B were less favorable when compared with subgroups A. Transaminase values were significantly worse in patients from subgroup B who received a dose of 750 mg. One of the parameters concerning kidney function (filtration, absorption) was always significantly worse in subgroup B of all groups. However, the quantity of secreted urine hardly differed in the groups and subgroups compared.

There are small differences in the average TZ and CS doses per kg body weight between subgroups A and B, but they range within an order of tenths of a mg and do not influence the comparability of the groups and subgroups of patients.

The study was organized as a trial in which each patient served as his own control. On the day before launching the trial the patients were given no drugs. On the day of the trial they took a single prescribed dose of the drug on an empty stomach. Table I shows the time intervals following drug administration at which blood concentrations of the drug produced by the individual doses were studied. The order of the TZ and CS doses to be administered to patients of the different groups was fixed at random.

The blood and urine specimens were processed immediately after they had been collected; TZ and CS concentration in the blood and urine was determined by Jones’ method [4]. Bianchi’s data [1] about the absorption maximum and the constancy of the color reaction of the analyzed TZ were confirmed.

The absolute values of blood and urine concentrations of both drugs were compared and used for calculation by the open one-compartment model [3]. The following formula was used for calculating the pharmacokinetic parameters:

\[ c_t = \frac{D}{V_D} \cdot \frac{K_a}{K_a - K_e} \cdot (e^{-K_e t} - e^{-K_a t}), \]

where \( D \) = dose of the drug, \( V_D \) = distribution volume, \( K_a \) = constant of absorption, \( K_e \) = constant of elimination, \( c_t \) = drug concentration in the time \( t \) after
Table I. Plan of the trial

<table>
<thead>
<tr>
<th>Drug dosage of CS and TZ mg</th>
<th>Number of patients</th>
<th>Average age years</th>
<th>Subgroup</th>
<th>Number of patients</th>
<th>Average age years</th>
<th>Samples collected after the dosage, h</th>
<th>blood</th>
<th>urine</th>
</tr>
</thead>
<tbody>
<tr>
<td>250</td>
<td>10</td>
<td>47</td>
<td>A</td>
<td>5</td>
<td>29</td>
<td>2, 3, 6, 24, 30</td>
<td>0-6, 6-12, 12-18, 18-24, 24-30</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>B</td>
<td>5</td>
<td>64</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>500</td>
<td>15</td>
<td>49</td>
<td>A</td>
<td>7</td>
<td>29</td>
<td>1, 2, 3, 4, 6, 8, 12, 24, 30</td>
<td>0-6, 6-12, 12-18, 18-24, 24-30</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>B</td>
<td>8</td>
<td>67</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>750</td>
<td>10</td>
<td>47</td>
<td>A</td>
<td>5</td>
<td>27</td>
<td>2, 3, 6, 24, 30</td>
<td>0-6, 6-12, 12-18, 18-24, 24-30</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>B</td>
<td>5</td>
<td>67</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

dose D. The values of drug concentrations in the blood found 2 h after administration of the dose were used for calculating $K_a$ (absorption constant).

In the same way, the excretion of drugs and $K_u$ determined (the first-order rate constant for urinary excretion) was calculated from the value ascertained in all the urine portions investigated.

$T^{1/2}$ was calculated from the formula

$$t_{1/2} = \frac{1}{2} \frac{n}{K_e}$$

and $Cl_{tot}$ from the formula $Cl_{tot} = V_D \cdot K_e$.

Because it was so demanding, the calculation was carried out with the use of the D 21 DATASAAB automatic computer.

Results

(1) When testing the suitability of Jones' method for estimating TZ, we succeeded in determining TZ in solutions of different molar concentrations with an average deviation of 1.29% from the theoretical value. This deviation is within the limits of ±2%, given by Jones [4].

(2) The course of CS and TZ blood concentrations recorded after single oral doses of 250, 500, and 750 mg administered to the patients is plotted in figure 1.

After a dose of 500 mg the maximum concentration in the blood was achieved with both CS and TZ 3 h after their administration. On the oth-
Fig. 1. Course of blood concentrations of TZ and CS after doses of 250, 500, and 750 mg in male patients aged 19–83 years.

On the other hand, with doses of 250 and 750 mg, blood concentrations of CS reached their maximum after 2 h, and those of TZ after 3 h.

When comparing the course of the blood concentrations of both drugs, the concentration of TZ was found to be higher than that of CS at all time intervals and with all the doses under study. Only in the maximum reached after the 250-mg dose was there no difference between the two drugs. However, a statistically significant elevation of the blood concentration of TZ, as compared with that of CS, was recorded only with the 500-mg dose after the following intervals: 1 h (p<0.05), 6 h (p<0.05), 8 h (p<0.05), 9 h (p<0.05), and 30 h (p<0.01).

(3) Pronounced differences in course of CS and TZ blood concentrations in the subgroups were found between subgroups A (young patients) and B (elderly patients) after all doses of both drugs. The 500-mg dose again had a significant manifestation (fig. 2).

Blood concentrations of TZ were significantly increased in the elderly patients as compared with the young ones after the following time intervals: 8, 9, 12, and 30 h (p<0.05); 24 h (p<0.02).
Fig. 2. Course of blood concentrations of TZ and CS after a dose of 500 mg in male patients divided by age into subgroups A (young ones) and B (elderly ones).

(4) After 30 h following administration of the 250-mg dose the excreted quantity of TZ (97.6 mg, 39.0%/o) is practically the same as that of CS (96.3 mg, 38.5%/o). From the dose of 500 mg there were excreted within the same period 229.9 mg (46.0%/o) of TZ and only 191.7 mg (38.3%/o) of CS. The curve in respect to TZ admittedly had a steeper course, but a statistically significant difference as compared with CS, was recorded in only the third portion of urine (p<0.05), which contained 46.0 mg of TZ and 31.8 mg of CS. In the dose of 750 mg, the difference between TZ and CS are analogous but statistically insignificant. After this dose excretion within 30 h averaged 291.0 mg (38.8%/o) of CS and 287.0 mg (38.3%/o) of TZ (fig. 3).

(5) Results obtained from drug excretion investigated with urine in subgroups A and B gave values opposite those recorded in the blood. All three doses of both drugs were excreted more slowly by the elderly patients than by the young ones. The difference was not significant in the 250-mg dose. The urine excretion at the dose of 500 mg TZ and CS is demonstrated in figure 4.

With the 500-mg TZ dose, elderly patients excreted 197.9 mg (39.6%/o) of TZ after 30 h, while young patients excreted 272.6 mg (54.5%/o) of TZ.
Fig. 3. Excretion of TZ and CS with urine studied at 6-hour intervals up to 30 h after administration of doses of 250, 500, and 750 mg in male patients aged 19–83 years.

Fig. 4. Excretion of 500 mg dose of TZ and CS with urine in male patients divided by age into subgroup A (young ones) and B (elderly ones).
Table II. Mean values of pharmacokinetic parameters after a single administration of 250, 500, and 750 mg of cycloserine and Terizidone

<table>
<thead>
<tr>
<th>Parameter</th>
<th>250 mg CS</th>
<th>250 mg TZ</th>
<th>500 mg CS</th>
<th>500 mg TZ</th>
<th>750 mg CS</th>
<th>750 mg TZ</th>
</tr>
</thead>
<tbody>
<tr>
<td>$K_e$</td>
<td>0.028</td>
<td>0.022</td>
<td>0.047</td>
<td>0.035</td>
<td>0.033</td>
<td>0.028</td>
</tr>
<tr>
<td>$K_a$</td>
<td>1.599</td>
<td>1.364</td>
<td>1.469</td>
<td>1.385</td>
<td>1.944</td>
<td>1.173</td>
</tr>
<tr>
<td>$V_D$</td>
<td>114.969</td>
<td>112.637</td>
<td>176.543</td>
<td>175.051</td>
<td>255.832</td>
<td>245.602</td>
</tr>
<tr>
<td>$t_{1/2}$</td>
<td>25.099</td>
<td>33.101</td>
<td>15.785</td>
<td>20.928</td>
<td>21.757</td>
<td>24.820</td>
</tr>
<tr>
<td>$Cl_{tot}$</td>
<td>3.276</td>
<td>2.485</td>
<td>8.310</td>
<td>6.301</td>
<td>8.655</td>
<td>6.391</td>
</tr>
<tr>
<td>$K_u$</td>
<td>0.048</td>
<td>0.062</td>
<td>0.060</td>
<td>0.072</td>
<td>0.051</td>
<td>0.034</td>
</tr>
</tbody>
</table>

The difference approaches the limits of significance. The average amount of excreted CS after 30 h following administration of 500 mg dose equalled 144.5 mg (28.9%) in the elderly patients and 245.7 mg (49.1%) in the young ones. This difference is statistically significant ($p<0.02$).

The quantity of CS and TZ excreted after a dose of 750 mg is significantly lower in the elderly patients than in the young ones (CS, $p<0.01$; TZ, $p<0.05$).

(6) Table II gives mean values of the pharmacokinetic parameters calculated for absorption and excretion of the drugs in the individual groups, indicating statistical differences ascertained between CS and TZ.

The most favorable parameters were obtained after the 500-mg dose of both CS and TZ; it was absorbed more slowly than the 750-mg dose but more rapidly than it was excreted. The shortest $t_{1/2}$ was also ascertained in the 500-mg dose of both CS and TZ. The differences between the $K_e$ values are not great and fluctuate within a relatively small range. The 500-mg dose of both drugs exhibited the greatest $K_o$, which also appears from the slope of the straight line in figures 4 and 5 in which the main parameters of absorption and elimination are plotted.

No statistically significant difference was found between the $K_a$ of CS and that of TZ in any of the groups; $t_{1/2}$ of TZ was significantly greater than that of CS with doses of 250 and 500 mg.

(7) If two A and B age subgroups were compared in the CS and TZ
groups, the following results were obtained: after the 500-mg dose of CS and TZ, the difference in $K_a$, $K_e$ and $t_{1/2}$ was statistically significant. In the younger patients, both drugs were rapidly absorbed and disappeared from the serum more quickly than in the elderly patients. Excretion in urine was also quicker in the young ones. $Cl_{tot}$ differed significantly, in keeping with the results mentioned, in both drugs after the 500-mg dose. Higher values were also recorded in subgroup A.

Among the other parameters, $V_D$ differed significantly after 250 and 750 mg of TZ; it was greater in subgroup B. After the 250-mg dose a significantly longer half-time $t_{1/2}$ of TZ was found in subgroup B.

**Discussion**

A comparison was made of the pharmacokinetics of CS and TZ after graduated single doses. The purpose of the study was to assess whether the preparation actually formed by two molecules of CS has certain advantages over CS alone. The trial was arranged so as to allow a concrete comparison of the two drugs. The Czechoslovak drug Cycloserin SPOFA was used in tablet form. The study [7] completed before this trial demonstrated that the pharmacokinetics of CS in tablets did not differ from CS in capsules, and, therefore, the different drug forms in which CS and TZ were administered to the patients in the trial did not prevent an objective evaluation of the findings.
CS and TZ concentrations in the blood and urine varied a great deal individually. In order to eliminate this variation, we purposefully formed two age groups for each dosage, (elderly and younger patients). We found that the variation of values was smaller within the subgroups formed and, moreover, that it enabled a mutual statistical comparison between both age groups.

Our results confirmed in effect the information reported by Bonati et al. [2] and Mariani et al. [5] and are not contrary to the conclusions reached by Strata et al. [6].

When one compares the course of TZ blood concentrations with those of CS, it appears that TZ surpasses CS at all doses studied. However, this margin is not significant enough to correspond to two molecules of CS contained in TZ. A significant difference, approximating double the value and identical in both age subgroups, was found only 30 h after drug administration. It might be inferred from this that, in the organism, TZ is probably hydrolyzed slowly into CS. Therefore, a marked difference as compared with CS cannot be expected immediately after administration but only later. In contrast to CS, TZ remains in the blood longer.

Similarly to Strata et al. [6], we found that it was of no practical importance to further increase a single dose exceeding 500 mg, since doses above 500 mg no longer cause a proportional increase in the concentration of CS and TZ in the blood.

Excretion with the 250-mg dose is almost identical for both drugs; after the 750-mg dose the initial excretion of CS is faster, but after 24 h it is at the same level as that of TZ. Along the whole course of the curve, the concentration of TZ tested in the urine after 500 mg exceeds the concentration of CS obtained after the same dose.

The distribution volume would be expressed better by multiplying $V_D$ by $F$ (= the fraction of the dose absorbed). It was impossible to determine the value of $F$, because both drugs exist in the oral form only. From the values of absorption, $F$ seems to be dose-dependent, i.e. $F$ decrease with an increasing dose, whereas $V_D$ increases with an increasing dose.

It follows from the values of pharmacokinetic parameters that TZ depends more on graduation of the individual parameter values in relation to the size of the dose. On the other hand, the dose of 750-mg CS somewhat evades this dependence pattern. This phenomenon may be explained by our procedure adopted in the evaluation. For the sake of a good statistical comparability of the pharmacokinetic parameters when calculating the first point on the curve illustrating the blood concentration level, we
selected the value obtained after 2 h following administration of the dose – neither earlier nor later. $K_a$ was calculated from this point. This value did not always represent the attained maximum of blood concentrations. While the maximum was always reached at the second point for TZ, i.e. after 3 h following dosage, in CS this was so only after the 500-mg dose; otherwise the CS concentrations always exhibited their peak after 2 h. Therefore, the regression lines always included the peak concentration attained, with the exception of blood concentrations after 250 and 750 mg of CS. Thus, in the two cases mentioned, the point used for calculating $K_a$ was still situated on the ascending section of the curve.

In the younger patients the pharmacokinetic process was more elastic, even though no marked statistical differences were recorded. But in the elderly persons, the course of blood concentrations was obviously more gradual, and the half-time for excretion of both drugs (particularly TZ) was longer. Naturally, the longer persistence of the drugs in the blood of the patients in this age subgroup is also related to this. In the younger patients the dependence of graduation of the pharmacokinetic parameters on the size of dose was more conspicuous. The level of the blood concentrations attained was more influenced in the case of the elderly patients, while the velocity of excretion was more influenced in the younger ones. Certain significant differences were found between the state of the liver and kidney function in the elderly patients compared to the young ones. It may be assumed that these changes in the elderly patients have played a certain role in the pharmacokinetics of CS and TZ.

A single dose of 500 mg of both CS and TZ appeared to be more advantageous. TZ administered in this dose showed better pharmacokinetic parameters. This was also confirmed by the statistical evaluation. Particularly its concentration in the urine, as long as 30 h after administration, sufficiently acceded its minimum inhibitory concentration. From the therapeutic point of view, the dose of 500 mg of TZ would be very advantageous, especially when used twice daily.

**Conclusion**

Blood concentration of TZ was higher at all time intervals studied than the concentration attained in the blood after the same doses of CS, but this increase was not proportional to two molecules of CS contained in a molecule of TZ.
The excreted quantity of TZ with urine was also higher, but the differences, as compared with excreted CS, were not statistically significant.

Certain dependence of absorption and excretion of both drugs on the patients’ age was revealed. In patients with a higher age average the blood concentration of both drugs were higher and the excretion with urine was slower than in the younger patients.

From the pharmacokinetics point of view, the 500 mg dose of TZ was most advantageous.

High TZ concentrations in urine, which exceed the minimum inhibitory concentrations for as long as 30 h, indicate the possibility of using the drug in treating genitourinary tuberculosis.

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References


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