BIOAVAILABILITY OF TEMAZEPAM IN SOFT GELATIN CAPSULES

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1 Healthy volunteers received single doses of temazepam 30 mg in conventional gelatin capsules, suppositories or in solution. They experienced marked sedation and sleepiness. The onset of sleepiness was prompt after the administration of the solution; this latter showed the fastest absorption and gave the highest peak plasma levels. This observation led to the development of the soft gelatin capsule.

2 To assess bioavailability of the formulation, plasma levels of temazepam were determined in healthy volunteers after single oral administration of soft and hard capsules, and after seven consecutive night-time doses of the soft capsule. Absorption from the soft gelatin capsule was faster and produced earlier and higher peak plasma levels. There were no differences in relative availability.

3 The apparent half-life of temazepam after night-time administration was shorter than after morning administration, but no change was observed between the first and seventh night-time doses.

Introduction

BENZODIAZEPINES are usually effective at low doses (1-10 mg), and the sensitive and accurate analytical methods required to assess their kinetic properties became available only a few years ago, often after the introduction of the drugs into therapy. This may explain why sometimes some discrepancies exist between the clinical use of benzodiazepines and their pharmacokinetic properties.

From Table 1, it seems that, on the basis of their metabolic and kinetic characteristics, the most important benzodiazepines can be divided into three groups. The first includes diazepam and chlordiazepoxide and is characterized by a slow rate of elimination of the unchanged drug and/or of the pharmacological active metabolites formed during biotransformation. The benzodiazepines of the second group, oxazepam, temazepam and lorazepam, are characterized by a more rapid rate of elimination with mean biological half-lives of about 5, 8 and 12 h, respectively. They are directly conjugated with glucuronic acid and excreted in the urine without formation of active metabolites in clinically significant amounts.

The benzodiazepines of the third group, nitrazepam and flurazepam, are currently used as hypnotics. In fact, they seem to have some advantages over non-benzodiazepine hypnotics, mainly in terms of liability to abuse and danger of overdosage intoxication. Their pharmacokinetic

properties, however, do not fit so well with the aim of the medication. Nitrazepam is in fact slowly eliminated, with a half-life of about 30 h; flurazepam, however, is quickly metabolized and has a very short half-life, but its main metabolite, which has pharmacological activity similar to flurazepam, has a very slow rate of elimination with a half-life of 50-100 hours. Therefore, even if nitrazepam and flurazepam are taken once a day at bedtime, the drug or the active metabolites will accumulate in the body day-by-day leading to cumulative and persistent clinical effects even during daytime. Morning drowsiness is in fact the most common adverse effect observed with nitrazepam and flurazepam.

In clinical studies, temazepam has shown anxiolytic properties and has proved to be effective in the

Table 1 Biological half-lives of various benzodiazepines

Diazepam	20-50
N-desmethyldiazepam	20-80
Chlordiazepoxide	10-15
Demoxepam	30-60
Desoxydemoxepam	40-60
Oxazepam	3-8
Temazepam	5-10
Lorazepam	10-15
Nitrazepam	20-30
Flurazepam	1-2
N-desalkylflurazepam	50-100

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Figure 1 Mean plasma concentrations of temazepam after administration of 30 mg as solution (Δ , $n = 2$), capsules ($\square$) and suppositories ($\circ$, $n = 4$) to healthy volunteers.

treatment of insomnia in cases of neurosis and endogenous depression (Maggini *et al.*, 1969). The suggestion to develop a suitable pharmaceutical form of temazepam for induction of sleep came from studies aimed at evaluating the absorption of temazepam administered orally in normal hard gelatin capsules and the physiological availability of the drug administered in the form of suppositories. As a standard for this study of relative bioavailability, temazepam administered orally in solution was used (Fuccella *et al.*, 1972). Four healthy subjects were used for this study and the dose administered with all forms was 30 mg. As shown in Figure 1, when administered in capsules, temazepam was rapidly absorbed, peak plasma concentrations of the drug occurring on average 1 h after administration. After rectal administration of temazepam 30 mg as suppositories to the same subjects, absorption was slower. Peak levels were reached later (2-4 h after administration) and were about 50% lower than those observed after oral administration. After administration of the dose as solution, absorption was very rapid and peak levels, about 50% higher

than those observed after capsules, were reached at 20-40 minutes.

Oxazepam could not be detected in plasma following any of the routes of administration. In the urine temazepam was present only as glucuronide, and oxazepam recovered in 48 h urine was 3-8% of total benzodiazepines, all in the form of glucuronide (Fuccella *et al.*, 1972). During the study, some pharmacological effects were observed. The volunteers experienced sedation and sleepiness. Onset of the latter was very prompt (10-15 min) after administration of the solution. Sleepiness was marked after capsules and solution; the volunteers, after lying down on the bed, usually fell asleep and slept more or less deeply for 2-4 hours. After administration of suppositories, sedation was absent in the volunteer who had the slowest absorption and lower plasma concentrations. Two subjects had slight sedation and one showed signs of excitement, with euphoria, restlessness and hyperactivity.

On the basis of these data, the following conclusions were reached: In man temazepam is not metabolized to active compounds in clinically

Figure 2 Mean plasma concentrations of temazepam after oral administration of 10 (○) and 20 mg (□) as soft gelatin capsules and 10 mg as solution (Δ) to four healthy volunteers.

significant amounts. When temazepam is rapidly absorbed and rapidly reaches high plasma levels, an intense sedative effect arises.

Development of soft capsule

These facts, and the relatively short half-life of the compound in man, suggested the development of a solid pharmaceutical form — characterized by a fast rate of absorption — for the treatment of sleep disturbances. Soft gelatin capsules containing temazepam 10 mg were prepared and a preliminary study was carried out in four healthy volunteers (Carlo Erba, Internal Report). As shown in Figure 2, bioavailability of soft capsules was at least as good as bioavailability of solution, and peak levels of the drug were reached 20–40 min after administration. It was therefore decided to develop this pharmaceutical form. A study was designed to assess the relative bioavailability of hard and soft gelatin capsules of temazepam after single administration and the rate of elimination of temazepam after single and repeated night-time administration of soft capsules,

Figure 3 Plasma concentrations of temazepam after single morning administration of 20 mg in soft and hard gelatin capsules. Plasma levels between 20 and 120 min are reported in detail in the top right part of the figure.

that is, with a dosage schedule commonly employed with hypnotics which are taken once at night before going to sleep.

The study was carried out in six healthy male volunteers who, during the study, received no other drug and were carefully instructed to follow their usual dietary and living habits but to refrain from alcoholic beverages (Fuccella *et al.*, 1977).

In the first part of the study, in two sessions 7 d apart, each volunteer received two hard gelatin capsules each containing temazepam 10 mg (Levanxol®, Carlo Erba S.p.A.) and two Scherer soft gelatin capsules each containing temazepam 10 mg (Euhypnos®, Montedison Pharmaceuticals), according to a cross-over design. The capsules were administered in the morning on an empty stomach and a light meal was allowed after 4 hours. Before and at various times after administration, 5 ml venous blood was taken.

The second part of the study was carried out in the same subjects 1 week after completion of the first part. Each volunteer took two Scherer capsules of temazepam 10 mg at 23 00 h every night before going to bed, for 7 consecutive days. On the days after the first and the last dose (days 2 and 8 of the study), venous blood samples were taken 10, 12, 14, 16 and 18 h after the evening dose. Plasma concentrations of free temazepam were determined by gas chromatography (Belvedere *et al.*, 1972). As shown in Figure 3 and Table 2, absorption from soft capsules was faster than from hard capsules. Mean peak times (T_{max}) were 0.83 h and 1.44 h, respectively ($P < 0.05$ using Student's *t* test for paired data). Mean peak values (C_{max}) after administration of soft capsules were higher but the difference did not reach the 5% level of statistical significance. These data and the lack

Figure 4 Comparison of predicted and observed plasma concentrations between 10 and 8 h after the seventh night-time administration of temazepam 20 mg to six healthy subjects. Each symbol represents one subject. $r = 0.936$.

of significant differences in AUC, β and $T_{1/2}$, indicate that only velocity of absorption and disposition of the drug depended on the dosage form employed. During repeated night-time administration (Table 3) there was no significant difference between the apparent rate of elimination after the first and seventh doses. This suggests that the kinetics of temazepam did not change during repeated administration.

A further confirmation comes from the agreement

Table 2 Pharmacokinetic parameters after single oral administration in the morning of temazepam 20 mg as hard and soft gelatin capsules.

	<i>Temazepam hard gelatin capsules</i>	<i>Temazepam soft gelatin capsules</i>	<i>Significance level</i>
C_{max} (µg/ml)	0.668 (0.121)	0.892 (0.101)	NS
T_{max} (h)	1.44 (0.21)	0.83 (0.25)	$P < 0.05$
AUC (µg/ml × h)	3.842 (0.427)	3.866 (0.362)	NS
β (h ⁻¹)	0.0987 (0.0084)	0.0851 (0.0060)	NS
$T_{1/2}$ (h)	7.25 (0.56)	8.35 (0.61)	NS

Mean values in six subjects (s.e.m. in brackets).

Figure 5 Comparison of mean plasma concentrations of temazepam after single (O) and repeated night-time administrations (▲, first evening dose; △, seventh) of 20 mg to six healthy subjects. Mean plasma concentrations after single morning administration of temazepam 20 mg are shown for comparison.

between plasma levels observed after the seventh dose and those predicted with the superimposition principle (Figure 4). The correlation coefficient for linear regression of predicted versus observed concentrations was 0.93.

An interesting finding was the 30% difference in biological half-life of temazepam taken in the morning and at night-time. The significantly shorter half-life after night-time administration might be attributed to a circadian variation in the rate of elimination of the drug as suggested from the different slope of plasma level curves during night, after a single morning dose, and during the day, after single and repeated evening administration (Figure 5).

In conclusion, soft gelatin capsules of temazepam ensure a rapid and complete absorption of the drug and seem to be an appropriate pharmaceutical form

Table 3 Apparent rate of elimination of temazepam (β and $T_{1/2}$) after single and repeated administration of two 10-mg soft capsules in the evening.

	<i>First administration</i>	<i>Seventh administration</i>
β (h ⁻¹)	0.1428 (0.0188)	0.1234 (0.0119)
$T_{1/2}$ (h)	5.28 (0.61)	5.87 (0.56)

Mean values in six subjects (s.e.m. in brackets).

for treatment of sleep disturbances. On the other hand, the pharmacokinetic properties of the drug, particularly its short half-life and the lack of active metabolites of any clinical relevance, make it unlikely that performance during diurnal activity might be altered, as is the case with other benzodiazepines.

The studies on temazepam summarized in this paper have been carried out by the following principal investigators: G. Bolcioni, L.M. Fucella, E. Moro, V. Tamassia and G. Tosolini (Carlo Erba Research Institute, Milan) and L. Ferrario, P.L. Morselli and G. Tognoni (Istituto di Ricerche Farmacologiche Mario Negri, Milan, Italy). Tables 2 and 3 and figures 3, 4 and 5 first appeared in *Eur. J. clin. Pharmac.* **12**, 383-386 and are reproduced here by kind permission of Springer-Verlag.

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