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# Lack of pharmacokinetic interaction between vinpocetine and oxazepam

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The influence of multiple doses of vinpocetine (10 mg three times daily) on the steady state plasma concentrations of oxazepam (10 mg three times daily) was studied in 16 healthy subjects. The mean (± s.d.) AUC (ng $ml^{-1}$ $h^{-1}$) of oxazepam over 24 h during combined treatment was 4716 ± 2296 and for oxazepam treatment alone it was 4737 ± 2448 (95% confidence intervals for ratio of means = 95.4–103.7%). The degree of plasma protein binding of oxazepam was 98.11 ± 0.32% and was not affected by vinpocetine. Independent of vinpocetine treatment a significant diurnal change in the plasma binding of oxazepam was observed; the free drug fraction was 20% higher during the night than during the day. $C_{max}$ and AUC values based on total oxazepam in plasma were 10% lower during the night. The results indicate a lack of influence of vinpocetine on oxazepam kinetics. Diurnal changes in the plasma binding of oxazepam probably have no clinical consequences.

**Keywords** oxazepam vinpocetine interaction plasma protein binding diurnal variation

## Introduction

Vinpocetine (ethyl apovincaminate) is a synthetic eburnamenine derivative developed to dissociate the cerebral and peripheral effects of vincamine. Clinical studies have shown that vinpocetine is effective in the symptomatic treatment of cerebrovascular and cerebral degenerative diseases [1–5]. Part of its central action has been related to its indirect adenosine-like effect [6–9]. The currently recommended therapeutic dose is 10 mg three times daily.

Vinpocetine is absorbed rapidly after oral administration with a bioavailability of approximately 80%. The drug undergoes extensive metabolism, primarily by hydrolysis to apovincaminic acid, but also by oxidative metabolism followed by formation of conjugates [10, 11]. Vinpocetine exhibits extensive but saturable plasma protein binding [12].

The drug will be used in elderly patients who often receive other medication, especially psychopharmacological agents. Therefore, it is important to assess possible interactions with antidepressants [13] and benzodiazepines.

The benzodiazepine oxazepam is widely used as an anxiolytic. Its oral bioavailability is greater than 90% and it is eliminated almost exclusively as an ether glucuronide. The plasma binding of oxazepam ranges from 95–98% [14, 15].

The aim of the present study was to evaluate the effect of vinpocetine treatment on plasma concentrations of oxazepam during multiple dose administration in healthy subjects.

## Methods

### *Subjects*

Sixteen healthy, non-smoking male volunteers (aged 19–33 years; mean ± s.d.: 23.6 ± 4.1) with body weights within +10% and −15% of the normal range participated in the study. They were in good health as assessed by physical examination, ECG, medical history and routine laboratory tests. The study protocol and written informed consent forms were approved by a medical ethics committee.

### *Study design*

The study was carried out according to a single-blind, randomized two-way cross-over design with a washout interval of 2–3 weeks between treatment periods. Each treatment period involved multiple

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dosage with one 10 mg oxazepam tablet (Adumbran®, Thomae GmbH, Biberach, Germany) three times daily at 08.00 h, 16.00 h and 24.00 h for 11 days (days 1–11). Co-administration of one 10 mg vinpocetine tablet (Eusenium®, Thiemann Arzneimittel GmbH, Waltrop, Germany) or a visually identical placebo tablet three times daily was started on day 5. Each dose was taken with 200 ml of water. On days 4/5 and 11/12, the 08.00 h doses were given after a 10 h overnight fast, and meals were taken at least 2 h after drug administration. During the treatment periods the subjects were confined to the clinical research centre of Pharma Bio-Research.

Plasma oxazepam concentrations were measured in venous blood samples taken before and at hourly intervals over 24 h after the first dose on day 4 (before co-administration of vinpocetine or placebo) and on day 11 (during co-administration of vinpocetine or placebo). The samples at 8 h and 16 h after the morning dose were taken just before the 16.00 h and 24.00 h doses, respectively. Additional blood samples for the determination of the plasma binding of oxazepam were collected at 2, 10 and 18 h after the morning dose on days 4 and 11.

Plasma samples were stored frozen at −20°C until analysed. During the study periods, blood pressure, heart rate and temperature were measured daily in the morning and an ECG was recorded at 09:00 h on day 5.

*Drug analysis*

Oxazepam was assayed by reversed-phase h.p.l.c. with u.v. detection at 229 nm [16].

The lower limit of quantitation was 10 μg $l^{-1}$, using 250 μl of plasma.

The inter-day CV was 10.4% at 10 μg $l^{-1}$ and below 5% at 20 μg $l^{-1}$ and higher concentrations.

The plasma binding of oxazepam was determined by equilibrium dialysis [17]. The plasma samples (800 μl), collected at 2 h after each drug dose on days 4 and 11, were dialysed for 1.5 h at 37° C against an equal volume of phosphate buffer (pH 7.4).

The oxazepam concentration in the buffer compartment was measured by h.p.l.c..

*Data analysis*

Values of $C_{max}$, AUC and the extent of plasma binding of oxazepam were estimated for the three dosing intervals on days 4/5 and 11/12. AUC values were calculated using the linear trapezoidal rule.

Pharmacokinetic parameters were analysed for differences using ANOVA (analysis of variance) with treatment, period, sequence, and subject within sequence as factors. The influence of treatment (with or without co-administration of vinpocetine), study period, study day (day 4/5 compared to day 11/12 of each study period) and dosing interval were investigated. In evaluating the effect of vinpocetine the values of $C_{max}$ and extent of plasma binding (PPB) for the three dosing intervals were averaged and the AUC values were summed ($C_{max}$ (24), PPB (24), AUC (24)). Statistical analysis and ANOVA calculations were carried out using PC-SAS, version 6.03 (SAS Institute Inc., USA). To investigate the equivalence of both treatments the 95% shortest confidence intervals derived from ANOVA for the point estimates of the ratio of the $C_{max}$ (24), AUC (24) and PPB (24) values were calculated [18–20].

## Results

Sixteen subjects completed the study in accordance with the protocol.

No serious or severe adverse events were observed. However, tiredness and drowsiness of a mild to moderate intensity were reported frequently during both study periods and were considered to be related to the administration of oxazepam.

Mean plasma oxazepam concentrations during placebo and vinpocetine co-administration are shown in Figure 1 and derived pharmacokinetic parameters are listed in Table 1. The 95% confidence intervals of the data for vinpocetine co-treatment relative to placebo were within 80 to 120% for $C_{max}$ (24), AUC (24) and PPB (24).

ANOVA did not reveal any influence of vinpocetine treatment or study period on the degree of PPB (Table 1). PPB of oxazepam was 98.11 ± 0.32% (mean ± s.d. of all observations ($n$ = 192)). However, time influenced the extent of PPB significantly ($P < 0.0001$), independent of treatment and period. Multiple range testing showed that the unbound fraction of oxazepam was 20% higher ($P < 0.05$) during the night (02.00 h) compared with the day (10.00 h and 18.00 h).

Independent of the other effect factors in the ANOVA, time had a statistically significant influence on $C_{max}$ ($P < 0.001$), PPB ($P < 0.001$) and AUC ($P < 0.001$). Tukey's multiple range test on the parameters listed in Table 1 showed that $C_{max}$ and AUC values for the third dosing interval (24.00 h to 08.00 h) were significantly smaller ($P < 0.05$) than those obtained

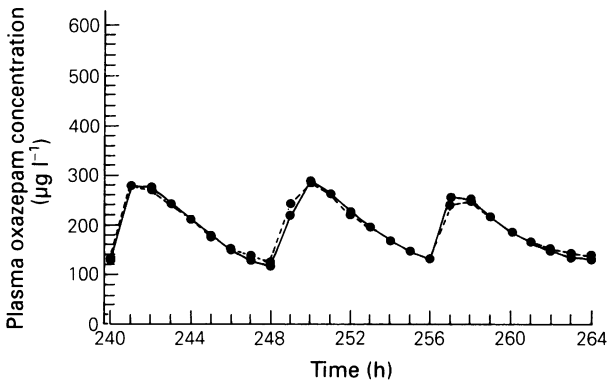


**Figure 1** Mean plasma concentrations of oxazepam during multiple dose administration (10 mg three times daily for 11 days) with 10 mg vinpocetine three times daily for 7 days starting on day 5 (A, —●—) and with placebo three times daily for 7 days starting on day 5 (B, · ·●· ·) ($n$ = 16).

**Table 1** Mean (± s.d.) pharmacokinetic parameters of oxazepam during multiple dose administration (10 mg three times daily) with co-administration of vinpocetine (treatment A) or placebo (treatment B)

| *Comparison of co-treatment with vinpocetine* vs *placebo* | | | | | *Comparison of dosing intervals within 24 h* | | |
|---|---|---|---|---|---|---|---|
| *Parameter* | *Treatment* | | | *95% shortest CI* (%)* | *08.00–16.00 h* | *16.00–24.00 h* | *24.00–08.00 h* |
| $C_{max}$ (24) (ng ml$^{-1}$) | A | 288 | (100) | 96.2–103.5 | 295 | 294 | 263 |
| | B | 288 | (112) | | (112) | (105.3) | (99) |
| AUC (24) (ng ml$^{-1}$ h) | A | 4716 | (2296) | 95.4–103.7 | 1600 | 1603 | 1469 |
| | B | 4737 | (2448) | | (790) | (776) | (712) |
| PPB† (24) (%) | A | 98 | (0.2) | 99.8–100.1 | 98.2 | 98.3 | 97.9 |
| | B | 98 | (0.2) | | (0.3) | (0.2) | (0.4) |

*CI = confidence interval calculated for the ratio of mean (A/B) expressed as % of mean of B.
†PPB = extent of plasma binding.

for the first and second dosing interval (08.00 h to 16.00 h and 16.00 h to 24.00 h, respectively).

## Discussion

The results suggest that an effect of vinpocetine on the kinetics of oxazepam is unlikely.

As a secondary observation we noted a significant diurnal change in the plasma binding of oxazepam associated with variation in $C_{max}$ and AUC values.

Diurnal fluctuations in total plasma drug concentrations associated with reciprocal variations in free drug fraction have been reported previously for diazepam and its metabolite *N*-desmethyldiazepam [17].

As a consequence of diurnal variations in the free drug fraction, circadian variation in clinical response may occur. Circadian variation in clinical response to diazepam has been occasionally observed [21, 22]. However, the fact that the higher free fraction may not be accompanied by a corresponding change in free drug concentration, and the wide margin of safety of benzodiazepines will probably protect most patients from clinical consequences.

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