The effect of erythromycin on the pharmacokinetics and pharmacodynamics of zopiclone

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1 The effect of erythromycin on the pharmacokinetics and pharmacodynamics of oral zopiclone, a non-benzodiazepine hypnotic, was investigated in a double-blind, cross-over study.
2 Ten healthy volunteers were given placebo or 500 mg erythromycin orally three times a day for 6 days followed by an oral dose of 7.5 mg zopiclone.
3 Erythromycin increased plasma zopiclone concentration by 4-fold at 0.5 h ($P < 0.05$) and by 2-fold at 1 h ($P < 0.05$). There were increases of 3- and 2-fold in the AUC(0,1h) and AUC(0,2h) values ($P < 0.05$). The total AUC of zopiclone increased by 80% ($P < 0.05$) but the peak concentration by only 40% ($P < 0.05$). The peak time of zopiclone concentration was reduced from 2 to 1 h ($P < 0.001$).
4 Significant pharmacodynamic differences between the treatments were observed from 0.5 h to 2 h with respect to saccadic latency and digit symbol substitution tests.
5 The interaction between erythromycin and zopiclone resulted mainly in accelerated absorption which may lead to a faster hypnotic effect in patients.

Keywords zopiclone erythromycin pharmacokinetic interactions psychomotor effects

Introduction

Zopiclone is chemically unrelated to the benzodiazepines, but has a similar pharmacological profile [1]. It has an established hypnotic efficacy, with short duration of action, and is thus a useful alternative to short-acting benzodiazepine hypnotics such as triazolam and midazolam. Zopiclone is metabolised extensively in the liver [1]. In healthy volunteers, gastric emptying facilitated by metoclopramide has been shown to increase plasma zopiclone concentrations [2].

The macrolide antibiotic erythromycin is a known inhibitor of oxidative drug metabolism [3]. It has been shown to increase peak concentrations and AUC values of triazolam and midazolam [4, 5]. Moreover, the psychomotor effects of midazolam were more profound and prolonged during erythromycin treatment [5]. Accordingly, because erythromycin increases gastric emptying [6] and inhibits drug metabolism, it might affect the pharmacokinetics of oral zopiclone by changing both its absorption and the extent of its metabolism. This study reports the effects of erythromycin on the pharmacokinetics and pharmacodynamics of oral zopiclone in healthy volunteers.

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Methods

Study design

The study protocol was approved by the Ethics Committee of the Department of Clinical Pharmacology, University of Helsinki. Ten healthy students (three men and seven women, aged 22 to 31 years, weighing 50 to 76 kg) volunteered for the study after giving their written informed consent. Before entering the study, the subjects were ascertained to be healthy by clinical examination. None of them was on con-

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tinuous medication, except three subjects using contraceptive steroids. The volunteers fasted 3 h before the administration of zopiclone and had a light standard meal 4 h afterwards. Neither alcohol, coffee, tea, cola nor tobacco was allowed during the test days.

A single dose of zopiclone (Imovane, 7.5 mg tablet, Rhone-Poulenc Rorer Ltd, Antony, France) was administered on the sixth day of treatment with 500 mg erythromycin base (Etromycin, 500 mg enterotablet, Orion Pharmaceutical Company Ltd, Helsinki, Finland) or matched placebo according to a double-blind, crossover design. The two treatment sequences were separated by an interval of 2 weeks. Erythromycin or placebo was given at 07.00 h, 15.00 h and 23.00 h on days 1 to 5. On the test day (day 6) erythromycin or placebo was given at 07.00 h, 13.00 h and 23.00 h and zopiclone was given at 15.00 h (i.e., 2 h after administration of erythromycin). All drugs were given orally, and zopiclone was ingested with 150 ml water.

Blood sampling and drug assay

Blood samples were taken before pretreatments and once during pretreatments on day 5. On the day of zopiclone administration (day 6), a forearm vein was cannulated with a plastic cannula and kept patent with an obturator. Blood (10 ml) was sampled immediately before the administration of zopiclone and 0.5, 1, 1.5, 2, 3, 4, 6, 17 and 24 h later. Plasma was separated within 30 min and stored at −20°C until zopiclone was assayed at Rhone-Poulenc Rorer (Paris) [7]. The coefficient of variation (CV%) of the assay was less than 6% (at a range of 5–500 ng ml⁻¹) and sensitivity was 5 ng ml⁻¹. Plasma erythromycin concentrations were measured in all blood samples by a modification of the h.p.l.c. method of Laakso et al. [8], using roxithromycin as internal standard. CV% was 12.1% (at 1.9 μg ml⁻¹) and sensitivity was 0.1 μg ml⁻¹.

Pharmacokinetic analysis

The area under the zopiclone plasma concentration-time curves from 0 to 1 h (AUC(0,1h)), 0 to 2 h (AUC(0,2h)) and from 0 to ∞ (AUC(0)) were calculated using the linear trapezoidal rule. Elimination half-lives (t₁/₂), peak zopiclone concentrations (Cₘₐₓ) and the times of peak concentrations (tₘₐₓ) were also estimated [9].

Psychomotor tests

The effects of zopiclone on psychomotor performance were assessed at the time of blood sampling by using a battery of tests. Saccadic eye movements were recorded and analysed with the Cardiff Saccade Generation and Analysis System [10, 11]. The value of each saccadic parameter at saccade angles of 5, 10, 20, 30, 35 and 40 was calculated by interpolation. Peak saccadic velocity (degrees/s) and latency (ms) at a saccadic angle of 35 degrees were used as primary results. The Maddox wing test was used to measure the coordination of extraocular muscles revealing exophoria or esophoria in diopters [12]. In the critical flicker fusion test (Leeds Flicker Fusion Tester), discrimination of fusion of flickering red light was measured at a distance of 1 m under standard conditions. Pupil diameter was standardized using special spectacles [13]. In the digit symbol substitution test the number of digits correctly substituted for with simple symbols in 3 min was recorded [14]. Subjective effects were recorded on visual analogue scales. The subjects expressed their responses on 17 horizontal 100-mm-long visual analogue scales [15]. Any undesired effects during the study were recorded together with the time at which the effect was noted, its severity and duration.

Statistical analysis

Results are expressed as mean values ± s.e. mean. Pharmacokinetic parameters between the groups were compared using the Wilcoxon matched-pairs test. The contributions of treatments and treatment sequences to overall pharmacodynamic variation were analysed at each testing period by repeated measures two-way (sequence x treatment) analysis of variance (ANOVA) followed by Student's t-test for paired data, and by the Wilcoxon matched-pairs test, when appropriate. All differences are given with 95% confidence intervals (95% CI) and a significant difference was accepted when P < 0.05.

Results

Plasma concentrations of zopiclone were increased during erythromycin treatment compared with the placebo phase (Figure 1). The AUC(0,1h) was 14 ± 4 (mean s.e. mean) compared with 41 ± 6 ng ml⁻¹ h during placebo and erythromycin phases, respectively

![Figure 1](attachment:image.png)
not administered intravenously, the least of absorption. The maximum plasma concentration of zopiclone was 53 ± 4 and 73 ± 5 ng ml⁻¹ (95% CI of the difference +6.9, +31.8; P = 0.013) during placebo and erythromycin phase respectively. The median (range) t<sub>max</sub> of zopiclone was decreased from 2 (1–4) to 1 (0.5–3) h (P = 0.024) and the t<sub>1/2,z</sub> prolonged from 4.8 ± 0.4 to 6.8 ± 0.7 h (95% CI of the difference +0.8, +3.3; P = 0.013) by erythromycin (Figure 1, Table 1).

The two-way ANOVA revealed a statistically significant difference between the treatments in the saccadic latency and in the digit-symbol substitution test. However, according to Student’s t-test, statistically significant differences in saccadic latency existed only at 0.5 (95% CI of the difference −38.7, −1.7; P = 0.038) and 1 h (95% CI of the difference −41.3, −1.7; P = 0.035) and for the digit-symbol substitution test at 0.5 (95% CI of the difference +1.7, +24.5; P = 0.052). 1 (95% CI of the difference +4.3, +20.3; P = 0.016) and 2 h (95% CI of the difference +1.0, +11.2; P = 0.045). The other psychomotor measurements showed no statistically significant differences between the treatments, (Figure 2, Table 2).

**Discussion**

The results indicate that erythromycin alters the pharmacokinetics of zopiclone, with effects on both absorption and elimination. The increased C<sub>max</sub> and shorter t<sub>max</sub> suggest a marked acceleration in the absorption of zopiclone.

Erythromycin has motilin-agonistic properties and accelerates gastric emptying [6]. This may explain, at least in part, the higher initial concentrations and decreased t<sub>max</sub> of zopiclone. Because zopiclone was not administered intravenously, it is not known whether the increased AUC values resulted from an increase in oral bioavailability or from a decrease in plasma clearance of zopiclone, or both. However, the prolonged elimination half-life of zopiclone during erythromycin treatment is indicative of a decreased plasma clearance of zopiclone.

Compared with the marked pharmacokinetic interaction between erythromycin and midazolam [5], erythromycin affected the pharmacokinetics of zopiclone to a lesser degree. The oral bioavailability of zopiclone is about 80% [1], whereas that of midazolam averages 44% [16]. Thus, the relatively high bioavailability of zopiclone precludes a large effect due to inhibition of first-pass metabolism.

Erythromycin appears to affect the biotransformation of those drugs which are metabolized by cytochrome P4503A isozymes [17]. Although zopiclone is eliminated mainly by oxidative hepatic metabolism, the isoforms of cytochrome P450 responsible have not been identified. The metabolism of zopiclone occurs by three major pathways [1]. Side-chain oxidation produces a pharmacologically less active N-oxide (11% of dose), and side-chain demethylation produces inactive N-desmethyl zopiclone (15%). These two metabolites are metabolized further before renal excretion. Ester hydrolysis involving oxidative de-carboxylation (50%) produces inactive metabolites which are, in part, eliminated as carbon dioxide via the lung [1].

The pharmacokinetic changes observed were reflected in some of the psychomotor test results. In parallel with its accelerated absorption during treatment with erythromycin, the effects of zopiclone on the digit-symbol substitution test and on saccadic latency were observed earlier and were more pronounced. However, in general, the pharmacokinetic interaction resulted in relatively small pharmacodynamic differences between the treatments. These differences are unlikely to be of major clinical significance in young adults. Since zopiclone is a relatively rapidly acting hypnotic, the five-fold increase in plasma concentration at 0.5 h and the two-fold increase at 1 h could result in a decreased sleep-onset time and increased efficacy. This is also suggested by the simultaneous changes in the digit-symbol substitution test and in saccadic latency.

**Table 1** Pharmacokinetic parameters of zopiclone after administration of 7.5 mg oral zopiclone following pretreatment with erythromycin (500 mg three times a day) or placebo for 6 days in 10 healthy volunteers

<table>
<thead>
<tr>
<th>Parameter</th>
<th>After placebo</th>
<th>After erythromycin</th>
<th>95% CI of difference</th>
<th>P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt; (ng ml⁻¹)</td>
<td>53 ± 4</td>
<td>73 ± 5</td>
<td>7–32</td>
<td>0.013</td>
</tr>
<tr>
<td>t&lt;sub&gt;max&lt;/sub&gt; (h)</td>
<td>2 (1–4)</td>
<td>1 (0.5–3)</td>
<td>12–42</td>
<td>0.024</td>
</tr>
<tr>
<td>AUC(0,1h) (ng ml⁻¹ h)</td>
<td>14 ± 4</td>
<td>41 ± 6</td>
<td>19–71</td>
<td>0.017</td>
</tr>
<tr>
<td>AUC(0,2h) (ng ml⁻¹ h)</td>
<td>54 ± 9</td>
<td>99 ± 10</td>
<td>166–343</td>
<td>0.005</td>
</tr>
<tr>
<td>AUC (ng ml⁻¹ h)</td>
<td>331 ± 40</td>
<td>585 ± 60</td>
<td>0.8–3.3</td>
<td>0.013</td>
</tr>
<tr>
<td>t&lt;sub&gt;1/2,z&lt;/sub&gt; (h)</td>
<td>4.8 ± 0.4</td>
<td>6.8 ± 0.7</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Data are mean values ± s.e. mean in 10 subjects; t<sub>max</sub> data are given as medians with range.

*Wilcoxon.
Figure 2  Results (mean ± s.e. mean) of critical flicker fusion (CFF) and digit-symbol substitution (DSS) tests, saccadic peak velocities and saccadic latencies as well as Maddox wing tests and visual analogue scales (VAS) after 7.5 mg oral zopiclone after pretreatment with oral erythromycin (500 mg three times a day) or placebo for 6 days in 10 healthy volunteers. Open circles—psychomotor effects of zopiclone after placebo; closed circles—psychomotor effects of zopiclone after erythromycin. *Denotes significant (P < 0.05) difference between the treatments.

Table 2 Effects of treatments and treatment sequences on psychomotor variables after administration of 7.5 mg of oral zopiclone after pretreatment with oral erythromycin (500 mg three times a day) or placebo for 6 days in 10 healthy volunteers as analyzed by two-way ANOVA for repeated measures. Values of F and statistical significance (P) are given

<table>
<thead>
<tr>
<th>Variable</th>
<th>Saccadic peak velocity</th>
<th>Saccadic latency</th>
<th>Digit-symbol substitution test</th>
<th>Critical flicker fusion test</th>
<th>Maddox wing test</th>
<th>Subjective drowsiness</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time (= t)</td>
<td>F 19.709</td>
<td>6.251</td>
<td>29.778</td>
<td>5.379</td>
<td>10.711</td>
<td>8.294</td>
</tr>
<tr>
<td></td>
<td>P &lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Treatment (= tr)</td>
<td>F 2.055</td>
<td>5.710</td>
<td>4.074</td>
<td>0.078</td>
<td>0.031</td>
<td>0.237</td>
</tr>
<tr>
<td></td>
<td>P 0.190</td>
<td>0.044</td>
<td>0.078</td>
<td>0.787</td>
<td>0.864</td>
<td>0.639</td>
</tr>
<tr>
<td>Sequence (= s)</td>
<td>F 0.178</td>
<td>0.270</td>
<td>0.288</td>
<td>0.223</td>
<td>2.085</td>
<td>0.008</td>
</tr>
<tr>
<td></td>
<td>P 0.684</td>
<td>0.617</td>
<td>0.606</td>
<td>0.649</td>
<td>0.187</td>
<td>0.932</td>
</tr>
<tr>
<td>t × tr</td>
<td>F 1.258</td>
<td>1.733</td>
<td>2.771</td>
<td>0.821</td>
<td>1.168</td>
<td>1.073</td>
</tr>
<tr>
<td></td>
<td>P 0.275</td>
<td>0.097</td>
<td>0.005</td>
<td>0.609</td>
<td>0.325</td>
<td>0.392</td>
</tr>
<tr>
<td>t × s</td>
<td>F 0.528</td>
<td>0.791</td>
<td>0.997</td>
<td>1.184</td>
<td>0.399</td>
<td>1.274</td>
</tr>
<tr>
<td></td>
<td>P 0.850</td>
<td>0.625</td>
<td>0.453</td>
<td>0.314</td>
<td>0.944</td>
<td>0.259</td>
</tr>
<tr>
<td>tr × s</td>
<td>F 3.258</td>
<td>0.236</td>
<td>8.443</td>
<td>2.342</td>
<td>0.420</td>
<td>0.014</td>
</tr>
<tr>
<td></td>
<td>P 0.109</td>
<td>0.640</td>
<td>0.020</td>
<td>0.164</td>
<td>0.535</td>
<td>0.908</td>
</tr>
<tr>
<td>t × tr × s</td>
<td>F 1.013</td>
<td>1.699</td>
<td>3.774</td>
<td>1.954</td>
<td>1.164</td>
<td>1.800</td>
</tr>
<tr>
<td></td>
<td>P 0.438</td>
<td>0.105</td>
<td>&lt;0.001</td>
<td>0.050</td>
<td>0.327</td>
<td>0.074</td>
</tr>
</tbody>
</table>
Compared with triazolam and midazolam, which are being used in many countries as short-acting hypnotics, zopiclone appears to be safer when used in combination with the macrolide antibiotic erythromycin. However, our results may not be applicable to older patients or to patients using other drugs affecting the central nervous system.

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References


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