Concentrations and effects of zopiclone are greatly reduced by rifampicin

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Aims The effects of rifampicin on the pharmacokinetics and pharmacodynamics of zopiclone, a non-benzodiazepine hypnotic, were studied.

Methods In a randomized, placebo-controlled cross-over study with two phases, eight young healthy volunteers took either 600 mg rifampicin or placebo once daily for 5 days. On the 6th day, 10 mg zopiclone was administered orally. Plasma zopiclone concentrations and effects of zopiclone were measured for 10 h.

Results The total area under the plasma zopiclone concentration–time curve after rifampicin was 18.0% (95% CI 13.5–22.5%) of that after placebo ($86.1 \pm 34.5 \text{ ng ml}^{-1} \text{ h}$ vs $473 \pm 114 \text{ ng ml}^{-1} \text{ h}$ (mean $\pm$ s.d.); $P < 0.001$). Rifampicin decreased the peak plasma concentration of zopiclone from $76.9 \pm 27.2 \text{ ng ml}^{-1}$ to $22.5 \pm 6.0 \text{ ng ml}^{-1}$ ($P < 0.001$) and the half-life from $3.8 \pm 0.6 \text{ h}$ to $2.3 \pm 0.9 \text{ h}$ ($P < 0.005$). A significant ($P < 0.02$) reduction in the effects of zopiclone was seen in three of the five psychomotor tests used (digit symbol substitution test, critical flicker fusion test and Maddox wing test) after rifampicin pretreatment.

Conclusions The strong interaction of rifampicin with zopiclone is due to enhanced metabolism of zopiclone. Zopiclone may show a reduced hypnotic effect when used concomitantly with rifampicin or other potent inducers of CYP3A4 such as phenytoin and carbamazepine.

Keywords: zopiclone, rifampicin, interaction, enzyme induction, pharmacokinetics

Introduction

Zopiclone is a short-acting, cyclopyrrolone hypnotic agent. After oral administration, zopiclone is rapidly absorbed and has a bioavailability of about 80% [1]. Zopiclone is metabolized extensively in the liver, but the CYP isoforms involved in its metabolism have not yet been identified. Only a few studies have addressed the interactions of zopiclone with other drugs [1], but two recent studies have shown that inhibitors of CYP3A4 can increase plasma zopiclone concentrations [2, 3].

Rifampicin, which is used e.g. in the treatment of tuberculosis, is a potent inducer of CYP3A4 and other CYP enzymes and, therefore, causes numerous drug interactions [4]. Recently, rifampicin pretreatment was shown to greatly reduce the plasma concentrations and effects of midazolam [5] and triazolam [6], two short-acting benzodiazepine hypnotics. On the other hand, there seem to be no data on the interaction between rifampicin and zopiclone. The aim of this study was therefore to investigate the effect of rifampicin on the pharmacokinetics and pharmacodynamics of zopiclone.

Methods

Subjects

Eight healthy volunteers (three women and five men; age range, 22 to 24 years; weight range, 55 to 84 kg) participated

in the study. All volunteers gave their written informed consent. They were ascertained to be healthy by a medical history, a physical examination and routine blood chemistry tests before entering the study. None of them had continuous medications, with the exception of three females who were using oral contraceptive steroids. These subjects were instructed to use in addition another method of contraception during the course of the study.

Study design

A randomized, placebo-controlled, cross-over study design in two phases was used. The phases were separated by a 4-week wash-out period. The subjects were given either 600 mg rifampicin (two 300 mg Rimapen capsules, Orion Pharmaceutical Company Ltd., Espoo, Finland) or matched placebo orally once daily at 20.00 h for 5 days. On day 6, 10 mg zopiclone (two Imovane 5 mg tablets, Rhone-Poulenc-Rorer Ltd, Antony, France) was administered orally with 150 ml water at 13.00 h, i.e. 17 h after the last dose of rifampicin. The volunteers fasted for 2 h before administration of zopiclone. A light standard meal was served 3 and 7 h after zopiclone intake. Alcohol, coffee, tea, cola and smoking were prohibited on the study days. The study protocol was approved by the Ethics Committee of the Department of Clinical Pharmacology, University of Helsinki, and the Finnish National Agency for Medicines.

Blood sampling and determination of plasma zopiclone

On day 6, a forearm vein was cannulated and timed blood samples were drawn just before zopiclone was administered

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and 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8 and 10 h later. The blood samples (10 ml each) were taken into tubes that contained ethylenediaminetetra-acetic acid (EDTA). Plasma was stored at -40°C until analysis. Plasma zopiclone concentrations were determined by high performance liquid chromatography [7, 8]. The limit of detection of the method was 3.0 ng ml^{-1} . The interday coefficient of variation was 6.6% at 9.5 ng ml^{-1} ($n=8$) and 2.4% at 53.0 ng ml^{-1} ($n=8$).

Pharmacokinetics of zopiclone

The pharmacokinetics of zopiclone were characterized by peak concentration in plasma (C_{max}), time to C_{max} (t_{max}), elimination half-life ($t_{1/2}$) and areas under the plasma concentration-time curve ($\text{AUC}(0,10\text{ h})$) and total AUC. The terminal log-linear phase of the plasma zopiclone concentration-time curve was identified visually for each subject. The elimination rate constant (k_{el}) was determined by a linear regression analysis, using the last three to nine points on the plot of the natural logarithm of the plasma concentration-time curve. The $t_{1/2}$ was calculated from the equation: $t_{1/2} = \ln 2 / k_{\text{el}}$. The AUC was calculated by the trapezoidal rule, with extrapolation to infinity by dividing the last measured concentration by k_{el} .

Pharmacodynamic measurements

The effects of zopiclone were characterized immediately after each blood sampling by five different psychomotor tests [5]. The volunteers had been trained to perform the tests before the study began. In the digit symbol substitution test (DSST), the number of digits correctly substituted in 3 min was recorded. A 100 mm long horizontal visual analogue scale (VAS) was used to measure subjective drowsiness. The discrimination of the fusion of a flickering red light was measured in the critical flicker fusion test (CFFT). The Maddox wing test was used to measure the co-ordination of extraocular muscles. Postural sway was measured by a swaymeter (Erikois-Elektroniikka Ltd, Orimattila, Finland) during the first 30 s with eyes open and thereafter 30 s with eyes closed. The mean speed of the mass centre of the subject (in mm min^{-1}) was used as a result. For each pharmacodynamic variable, the area under the effect against time curve from 0 to 10 h ($\text{AUC}(0,10\text{ h})$) was calculated by the trapezoidal rule.

Statistical analysis

Results are expressed as mean values $\pm$ s.d. or, in case of t_{max} , as median with range. 95% confidence intervals (CI) were calculated for selected endpoints. The pharmacokinetic variables of zopiclone and the $\text{AUC}(0,10\text{ h})$ for the pharmacodynamic variables between the two pretreatments were compared with a paired t -test (two-tailed). The Wilcoxon test was used for analysis of t_{max} . The data were analyzed with the statistical program Systat for Windows, version 5.0 (Systat, Evanston, USA). The level of statistical significance was $P < 0.05$.

Results

Pharmacokinetics

The mean total AUC of zopiclone after the rifampicin pretreatment was 18.0% (95% CI 13.5–22.5%) of that after the placebo pretreatment ($86.1 \pm 34.5\text{ ng ml}^{-1}\text{ h}$ vs $473 \pm 114\text{ ng ml}^{-1}\text{ h}$; $P < 0.001$) (Table 1, Figure 1). Rifampicin pretreatment decreased the peak plasma concentration of zopiclone from $76.9 \pm 27.2\text{ ng ml}^{-1}$ to $22.5 \pm 6.0\text{ ng ml}^{-1}$ ($P < 0.001$) and shortened the elimination half-life from $3.8 \pm 0.6\text{ h}$ to $2.3 \pm 0.9\text{ h}$ ($P < 0.005$).

Pharmacodynamics

In the DSST, CFFT and Maddox wing test, the effects of zopiclone were significantly smaller after the rifampicin pretreatment than after placebo ($P < 0.02$) (Table 2, Figure 2). Likewise, zopiclone seemed to cause less subjective drowsiness (as measured with VAS) after rifampicin pretreatment than after placebo, but the difference was not quite statistically significant ($P = 0.08$). The effect of zopiclone on postural sway was not affected by rifampicin.

Discussion

This study shows a considerable reduction in the plasma concentrations and effects of zopiclone even after short-term use of rifampicin. After 5-day pretreatment with rifampicin, the mean C_{max} of zopiclone was 31% and the mean total AUC 18% of that in the control phase. The fact that rifampicin shortened the mean $t_{1/2}$ of zopiclone by 40% suggests that rifampicin increased the systemic clearance of zopiclone. The t_{max} occurred significantly earlier following rifampicin pretreatment which reflects the increased rate of elimination of zopiclone: t_{max} occurs when the rate of elimination equals the rate of absorption and, therefore, an increase in the clearance of zopiclone causes the C_{max} to occur at an earlier time.

Of the five psychomotor tests used, the DSST, CFFT and Maddox wing test showed significantly reduced effects of zopiclone after rifampicin pretreatment. The finding that the

Figure 1 Plasma concentrations of zopiclone in eight healthy subjects (mean $\pm$ s.e. mean) after a 10 mg oral dose, following pretreatment with 600 mg rifampicin (●) or placebo (○) once daily for 5 days.

Table 1 The pharmacokinetic variables of zopiclone 10 mg (mean $\pm$ s.d. or median and range) in eight healthy subjects after pretreatment with placebo or rifampicin (600 mg day⁻¹) for 5 days.

Variable	Placebo phase (control)	Rifampicin phase	Mean difference between placebo and rifampicin (95% CI)
$C_{\max}$ (ng ml ⁻¹)	76.9 $\pm$ 27.2	22.5 $\pm$ 6.0*	54 (34–74)
% of control (95% CI)	100%	30.9% (22.4–39.4%)	
$t_{\max}$ (h)	3 (0.5–4)†	1.25 (0.5–3)†‡	
$t_{1/2}$ (h)	3.8 $\pm$ 0.6	2.3 $\pm$ 0.9*	1.5 (0.7–2.3)
% of control (95% CI)	100%	60.3% (41.0–79.7%)	
AUC(0,10 h) (ng ml ⁻¹ h)	370 $\pm$ 59.9	71.8 $\pm$ 25.4*	298 (260–336)
% of control (95% CI)	100%	19.1% (15.1–23.1%)	
Total AUC (ng ml ⁻¹ h)	473 $\pm$ 114	86.1 $\pm$ 34.5*	387 (308–466)
% of control (95% CI)	100%	18.0% (13.5–22.5%)	

*Significantly ($P < 0.005$) different from the placebo phase. †Median (range). ‡ $P < 0.05$ compared with the placebo phase.

Table 2 The results of pharmacodynamic tests after 10 mg zopiclone (mean $\pm$ s.d.) in eight healthy subjects following pretreatment with placebo or rifampicin (600 mg day⁻¹) for 5 days.

Test	Variable	Placebo phase	Rifampicin phase	Mean difference between placebo and rifampicin (95% CI)
DSST	AUC(0,10 h) (digits h)	1400 $\pm$ 163	1540 $\pm$ 171*	-139 (-178, -100)
VAS (drowsiness)	AUC(0,10 h) (mm h)	320 $\pm$ 105	272 $\pm$ 96†	48 (-6, 102)
CFFT	AUC(0,10 h) (Hz h)	209 $\pm$ 18	220 $\pm$ 19*	-11.3 (-17.6, -4.4)
Maddox wing	AUC(0,10 h) (diopters h)	57 $\pm$ 31	45 $\pm$ 32*	12.6 (2.6, 22.6)
Sway eyes open	AUC(0,10 h) (mm min ⁻¹ h)	3668 $\pm$ 1339	3449 $\pm$ 398	219 (-699, 1137)
Sway eyes closed	AUC(0,10 h) (mm min ⁻¹ h)	6222 $\pm$ 3912	5658 $\pm$ 1778	563 (-1628, 2756)

*Significantly ($P < 0.02$) different from the placebo phase. † $P = 0.08$.

Figure 2 Results of the digit symbol substitution test (DSST), Maddox wing test, critical flicker fusion test (CFFT) and the visual analogue scale (VAS) test for subjective drowsiness in eight healthy subjects (mean $\pm$ s.e.mean) after a 10 mg oral dose of zopiclone, following pretreatment with rifampicin (600 mg day⁻¹; solid circles) or placebo (open circles) once daily for 5 days.

pharmacodynamic interaction was less extensive than that seen with the pharmacokinetics is not unexpected since the intensity of a pharmacological response is proportional to the logarithm of the drug concentration. Since the effects of zopiclone are well known and the aim of this study was to characterize the interaction of rifampicin with zopiclone, a placebo was used for rifampicin but not for zopiclone. The rifampicin pretreatment alone had no effect on the psychomotor performance compared with the placebo when measured at baseline, before administration of zopiclone (Figure 2).

Rifampicin is a potent inducer of CYP3A4 in the liver and gut [9] and it also induces some other CYP isoforms. Rifampicin is known to induce the metabolism of several benzodiazepine hypnotics [10, 11], but the pharmacokinetics of midazolam [5] and triazolam [6] are affected most by rifampicin. Both midazolam and triazolam are substrates of CYP3A4 [12] and they undergo significant first-pass metabolism. The same 5-day pretreatment with rifampicin that was used in the present study decreased the AUC of midazolam by 96% and the $C_{\max}$ by 94% [5] and the AUC and $C_{\max}$ of triazolam by 95% and 88% [6], respectively.

Zopiclone is metabolized *via* three major pathways in human liver [1], but the contribution of different CYP isoforms to the metabolism of zopiclone is not known. However, drugs inhibiting CYP3A4 have been shown to affect the pharmacokinetics of zopiclone which suggests that this CYP isoform is involved in zopiclone metabolism; pretreatment with itraconazole or erythromycin increased the total AUC of zopiclone by about 70–80% [2, 3].

In contrast to midazolam and triazolam, the bioavailability of zopiclone is relatively high (about 80%) [13], which seems to make it less susceptible to drug interactions during first-pass metabolism. Concomitant use of itraconazole increased the AUC of oral midazolam and triazolam about 10- and 20-fold, respectively [14, 15], whereas the AUC of zopiclone was increased by less than 100% by itraconazole [3]. Similarly, rifampicin had a smaller effect on the pharmacokinetics of zopiclone than on those of midazolam and triazolam. These findings are in good accordance with the pharmacokinetic properties of these hypnotics.

Plasma concentrations and effects of oral midazolam were greatly reduced in patients taking carbamazepine or phenytoin [16]. In fact, the effects of rifampicin and these antiepileptic agents on the pharmacokinetics of midazolam were almost identical [5, 16]. Therefore, it is reasonable to assume that phenytoin and carbamazepine, both strong inducers of CYP3A4, are likely to decrease plasma concentrations and the effect of zopiclone to the same extent as rifampicin.

In conclusion, pretreatment with rifampicin considerably decreased the plasma concentrations of zopiclone. This was reflected in several psychomotor tests which showed reduced effects of zopiclone. Considering the magnitude of the observed interaction, zopiclone is likely to have a clearly reduced hypnotic effect when used concomitantly with rifampicin or other strong inducers of CYP3A4 such as phenytoin and carbamazepine.

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