Concentrations and effects of buspirone are considerably reduced by rifampicin

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Aims The effects of rifampicin on the pharmacokinetics and pharmacodynamics of buspirone, a non-benzodiazepine anxiolytic agent, were investigated.

Methods In a randomized, placebo-controlled cross-over study with two phases, 10 young healthy volunteers took either 600 mg rifampicin or matched placebo once daily for 5 days. On day 6, 30 mg buspirone was administered orally. Plasma buspirone concentrations and effects of buspirone were measured up to 10 h.

Results The total area under the plasma buspirone concentration-time curve after rifampicin was 10.4% (95% CI, 6.3–14.5%) of that after placebo ($1.64 \pm 0.35 \text{ ng ml}^{-1} \text{ h}$ vs $22.0 \pm 15.1 \text{ ng ml}^{-1} \text{ h}$ (mean $\pm$ s.d.); $P < 0.01$). Rifampicin decreased the peak plasma concentration of buspirone from $6.6 \pm 3.7 \text{ ng ml}^{-1}$ to $0.84 \pm 0.23 \text{ ng ml}^{-1}$ ($P < 0.01$) and the half-life from $2.8 \pm 0.7 \text{ h}$ to $1.3 \pm 0.5 \text{ h}$ ($P < 0.01$). A significant ($P < 0.05$) reduction in the effects of buspirone was observed in three of the six psychomotor tests employed (postural sway test with eyes closed, subjective drowsiness and overall drug effect) after rifampicin pretreatment.

Conclusions The strong interaction between rifampicin and buspirone is probably mostly due to enhanced CYP3A4-mediated first-pass metabolism of buspirone. Buspirone will most likely show a greatly reduced anxiolytic effect when used together with rifampicin or other potent inducers of CYP3A4 such as phenytoin and carbamazepine.

Keywords: buspirone, rifampicin, interaction, pharmacokinetics

Introduction

Buspirone is a non-benzodiazepine anxiolytic agent which belongs to the azapirone group [1]. Buspirone has the advantage over benzodiazepines that it causes less sedation and impairment of psychomotor performance [2–4]. After an oral dose, buspirone is almost completely absorbed, but it has a low bioavailability (about 4%) due to extensive first-pass metabolism [5]. The specific CYP enzymes responsible for buspirone metabolism are not known. However, itraconazole and erythromycin, both potent CYP3A4 inhibitors, showed a major interaction with buspirone, increasing its total AUC 19-fold and six-fold, respectively, suggesting that CYP3A4 plays a major role in buspirone biotransformation [6].

Rifampicin, an antibiotic drug used mostly in the treatment of tuberculosis, induces CYP3A4 in hepatocytes and small bowel enterocytes [7], thereby considerably decreasing the concentrations and effects of many drugs, especially CYP3A4 substrates with extensive first-pass metabolism such as midazolam and triazolam [8–10]. However, there seems to be no data on the interaction between rifampicin and buspirone. The aim of this study was therefore to investigate the effect of rifampicin on buspirone pharmacokinetics and pharmacodynamics.

Methods

Subjects

Ten healthy volunteers (five males and five females; age range, 18 to 26 years; weight range, 56 to 85 kg) participated in this study. The subjects were considered to be healthy on the basis of medical history, physical examination and routine laboratory tests before entering the study. Three subjects were regular smokers. One female used contraceptive steroids but no other subjects took concomitant medication. All subjects gave their written informed consent to participate in the study. The study was approved by The Ethics Committee of the Department of Clinical Pharmacology, University of Helsinki, Finland and The Finnish National Agency for Medicines.

Study design

A randomized, placebo-controlled, cross-over study design with two phases was used. The phases were separated by a 4-week wash-out period. The subjects took either 600 mg rifampicin (Rimapen, Orion Ltd, Espoo, Finland) or matched placebo orally once daily at 20.00 h for 5 days. On day 6, each subject was administered a single 30 mg oral dose of buspirone (three Buspar 10 mg tablets, Bristol-Myers Squibb, Espoo, Finland) at 13.00 h with 150 ml water. This dose of buspirone was used instead of the normal therapeutic single

dose (5–10 mg) to allow more accurate determination of plasma buspirone concentrations after rifampicin. The subjects fasted for 2 h before buspirone intake and had a standard meal 3 and 7 h afterwards. Consumption of alcohol, coffee, tea, or cola and smoking were prohibited on the study days.

Blood sampling and determination of plasma drug concentrations

On day 6, a forearm vein was cannulated and timed blood samples were drawn into EDTA (ethylenediaminetetraacetic acid) containing tubes before buspirone was administered and 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8 and 10 h later. Plasma was separated within 30 min and stored at -40°C until analysis. Plasma buspirone concentrations were determined by use of a capillary gas chromatographic method involving solid-phase extraction and nitrogen-phosphorus detection [11]. Zolpidem was used as an internal standard. The limit of quantification was 0.1 ng ml^{-1} . The between-day coefficient of variation was 9.4% at 0.26 ng ml^{-1} ($n=13$) and 3.2% at 2.3 ng ml^{-1} ($n=13$).

Pharmacokinetics of buspirone

The pharmacokinetics of buspirone were characterized by peak plasma concentration (C_{max}), time to peak concentration (t_{max}), elimination half-life ($t_{1/2}$) and areas under the plasma concentration–time curve [AUC(0, 10 h) and total AUC]. The terminal log–linear phase of the plasma buspirone concentration–time curve was visually identified for each subject. The elimination rate constant (k_{el}) was determined by a linear regression analysis, using the last 3 to 5 points on the log–linear part of the plasma concentration–time curve. The AUC was calculated by the trapezoidal rule, with extrapolation to infinity by dividing the last measured concentration by k_{el} .

Pharmacodynamic measurements

The pharmacodynamic effects of buspirone were measured immediately after each blood sampling by six psychomotor tests [9]. In the digit symbol substitution test (DSST), the number of digits correctly substituted in 2 min was calculated. The critical flicker fusion test (CFFT) measures the frequency (Hz) at which a flickering red light gives an impression of a constant light. The postural sway test measures the speed

(mm min^{-1}) of the subject's mass centre. This speed was recorded both with eyes open and eyes closed, using a special swaymeter (Erikois-Elektronikka Ltd, Orimattila, Finland). Subjective drowsiness and subjective overall drug effect were measured using 100 mm long horizontal visual analogue scales (VAS). Rifampicin pretreatment did not influence the baseline pharmacodynamic values. For each variable, the incremental (drowsiness, overall drug effect and postural sway) or decremental (DSST and CFFT) areas under the effect against time curve (i.e., the areas above or below baseline) from 0 to 4 h [AUC(0, 4 h)] and from 0 to 10 h [AUC(0, 10 h)] were calculated by the trapezoidal rule. The volunteers were asked about possible side-effects of buspirone 1, 2 and 3 h after buspirone administration.

Statistical analysis

Results are given as mean $\pm$ s.d. or, in the case of t_{max} , as median with range. 95% confidence intervals (CI) were calculated for selected variables. The pharmacokinetic variables of buspirone and the AUC(0,4 h) and AUC(0,10 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 level of statistical significance was $P<0.05$. The statistical program Systat for Windows, version 6.0.1 (SPSS Inc., Chicago, USA) was used for data analysis.

Results

Pharmacokinetics

The total AUC of buspirone in the rifampicin phase averaged 10.4% (95% CI, 6.3–14.5%) of that in the placebo phase ($1.64 \pm 0.35\text{ ng ml}^{-1}\text{ h}$ vs $22.0 \pm 15.1\text{ ng ml}^{-1}\text{ h}$; $P<0.01$) (Table 1, Figure 1). Rifampicin pretreatment decreased the C_{max} of buspirone by 83.7%, i.e. from $6.6 \pm 3.7\text{ ng ml}^{-1}$ to $0.84 \pm 0.23\text{ ng ml}^{-1}$ ($P<0.01$) and the $t_{1/2}$ from 2.8 h to 1.3 h ($P<0.01$). None of the subjects had a measurable plasma buspirone concentration at 6, 8 or 10 h in the rifampicin phase, while in the placebo phase the concentration could be determined up to 10 h in all subjects. In the subject who used contraceptive steroids, the pharmacokinetics of buspirone and the extent of the interaction were similar to those in the other subjects (Figure 2).

Table 1 The pharmacokinetic variables of buspirone 30 mg (mean $\pm$ s.d. or median with range) in 10 healthy volunteers after pretreatment with placebo or rifampicin (600 mg day^{-1}) for 5 days.

Variable	Placebo phase (control)	Rifampicin phase
C_{max} (ng ml^{-1})	6.6 ± 3.7	$0.84 \pm 0.23^*$
% of control (95% CI)	100%	16.3% (10.1–22.6%)
t_{max} (h)	1.5 (0.5–4) [†]	0.5 (0.5–2) ^{†*}
$t_{1/2}$ (h)	2.8 ± 0.7	$1.3 \pm 0.5^*$
% of control (95% CI)	100%	47.2% (40.8–53.6%)
AUC(0,10 h) ($\text{ng ml}^{-1}\text{ h}$)	20.6 ± 14.2	$1.48 \pm 0.28^*$
% of control (95% CI)	100%	10.0% (6.1–14.0%)
Total AUC ($\text{ng ml}^{-1}\text{ h}$)	22.0 ± 15.1	$1.64 \pm 0.35^*$
% of control (95% CI)	100%	10.4% (6.3–14.5%)

*Significantly ($P<0.01$) different from the placebo phase.

[†] Median (range).

Figure 1 Plasma concentrations of buspirone in 10 healthy subjects (mean $\pm$ s.e. mean) after a 30 mg oral dose, following pretreatment with 600 mg rifampicin (solid circles) or placebo (open circles) once daily for 5 days.

Pharmacodynamics

The effects of buspirone were significantly smaller after the rifampicin pretreatment than after placebo in the postural sway test with eyes closed ($P < 0.05$) and in the VAS tests for subjective drowsiness ($P < 0.01$) and overall drug effect ($P < 0.01$) (Figure 3, Table 2). Side-effects of buspirone were reported more often in the placebo phase (eight subjects) than in the rifampicin phase (two subjects) ($P < 0.05$ by the McNemar test). The most common side-effects were drowsiness, dizziness and nausea. The side-effects were mild and resolved spontaneously within 2 h in each case.

Discussion

In this study, a 5 day pretreatment with rifampicin produced a considerable reduction in the plasma concentrations and effects of buspirone compared with placebo. After rifampicin, the total AUC of buspirone averaged only about 10% of the corresponding value in the control phase. The effect of rifampicin on buspirone pharmacokinetics was consistent in each subject, although there was some interindividual variation in the extent of the interaction, as measured by the ratio of the total AUC of buspirone in the rifampicin phase to the AUC of buspirone in the placebo phase (range, 3.5% to 19%). However, the variability in buspirone C_{max} and total AUC was markedly decreased by rifampicin. Rifampicin also significantly shortened the half-life of buspirone, suggesting increased systemic clearance of buspirone.

Buspirone produces in general much less sedation and impairment of psychomotor performance than benzodiazepines [2–4]. Psychomotor performance was only slightly affected by 10 mg buspirone [6], while the 30 mg dose used in the present study seemed to cause distinct impairment of psychomotor performance, as demonstrated by the results of the psychomotor tests compared with the respective baseline values, obtained before buspirone administration. The results of the psychomotor tests after 30 mg buspirone were in good

Figure 2 The individual peak plasma concentration (C_{max}), elimination half-life ($t_{1/2}$) and total area under the plasma concentration-time curve (AUC) values after 30 mg oral buspirone in 10 healthy subjects, following pretreatment with 600 mg rifampicin or placebo once daily for 5 days. The broken line represents the subject who was using oral contraceptive steroids.

Figure 3 Results (mean) of the critical flicker fusion test (CFFT), postural sway test with eyes closed and visual analogue scale (VAS) tests for the subjective overall drug effect and subjective drowsiness in 10 healthy subjects after 30 mg oral buspirone, following pretreatment with 600 mg rifampicin (solid circles) or placebo (open circles) once daily for 5 days.

Table 2 The results of pharmacodynamic tests (presented as incremental or decremental AUC values) after 30 mg buspirone (mean $\pm$ s.d.) in 10 healthy volunteers following pretreatment with placebo or rifampicin (600 mg day⁻¹) for 5 days.

Test	Variable	Placebo phase	Rifampicin phase
DSST	AUC(0,4 h) (digits h)	25.6 $\pm$ 43.2	18.9 $\pm$ 36.7
	AUC(0,10 h) (digits h)	68.9 $\pm$ 126	60.0 $\pm$ 105
CFFT	AUC(0,4 h) (Hz h)	5.5 $\pm$ 3.9	2.3 $\pm$ 3.5†
	AUC(0,10 h) (Hz h)	14.5 $\pm$ 10.8	13.5 $\pm$ 9.3
VAS (drowsiness)	AUC(0,4 h) (mm h)	61.0 $\pm$ 31.9	10.6 $\pm$ 20.8*
	AUC(0,10 h) (mm h)	105 $\pm$ 83.8	27.2 $\pm$ 67.9†
VAS (drug effect)	AUC(0,4 h) (mm h)	69.6 $\pm$ 38.5	18.9 $\pm$ 24.4*
	AUC(0,10 h) (mm h)	71.6 $\pm$ 40.3	29.6 $\pm$ 44.2†
Sway eyes open	AUC(0,4 h) (mm min ⁻¹ h)	169 $\pm$ 278	39.3 $\pm$ 181
	AUC(0,10 h) (mm min ⁻¹ h)	404 $\pm$ 657	138 $\pm$ 404
Sway eyes closed	AUC(0,4 h) (mm min ⁻¹ h)	324 $\pm$ 319	-160 $\pm$ 340†
	AUC(0,10 h) (mm min ⁻¹ h)	417 $\pm$ 555	-331 $\pm$ 991

*Significantly ($P < 0.01$) different from the placebo phase.

†Significantly ($P < 0.05$) different from the placebo phase.

‡ $P = 0.08$.

agreement with the altered pharmacokinetics of buspirone; the body sway test (with eyes closed) and the VAS tests for subjective drowsiness and overall drug effect demonstrated significantly reduced effects of buspirone after rifampicin. In fact, some of the pharmacodynamic effects of 30 mg buspirone were practically abolished by rifampicin pretreatment.

Rifampicin is a potent inducer of CYP3A4 both in the liver and the gut wall [7], and it induces also some other CYP enzymes. In previous human studies, rifampicin has been shown to reduce considerably the plasma concentrations of CYP3A4 substrates undergoing extensive first-pass metabolism [9, 10, 12, 13]. For example, the same 5 day

pretreatment with rifampicin which was used in the present study reduced the total AUC of midazolam and triazolam by about 95% [9, 10].

Buspirone undergoes oxidative metabolism in the liver [14–16], but the specific CYP enzymes catalyzing its biotransformation in humans do not seem to have been identified. However, the extensive first-pass metabolism of buspirone, resulting in a bioavailability of less than 5% [5], as well as the fact that erythromycin and itraconazole greatly increased plasma buspirone concentrations [6] support the notion that CYP3A4 plays a major role in the presystemic metabolism of buspirone. Therefore, the interaction between rifampicin and buspirone probably resulted mostly from induction of CYP3A4-mediated first-pass metabolism of buspirone.

The role of gut wall in the presystemic metabolism of buspirone does not seem to have been studied. Considering the extensive expression of CYP3A4 in the duodenal wall [7, 17] and the fact that the $C_{\max}$ and total AUC of buspirone were affected much more than its $t_{1/2}$, the duodenal wall seems to be an important site of the rifampicin-buspirone interaction.

Apart from rifampicin, certain antiepileptic agents, such as carbamazepine and phenytoin, are also potent inducers of CYP3A4 and other CYP enzymes. For example, plasma concentrations and effects of oral midazolam were reduced in patients taking carbamazepine or phenytoin to the same extent as by rifampicin [18]. It is therefore reasonable to assume that plasma concentrations of buspirone will be considerably decreased also in patients taking these antiepileptic agents.

In conclusion, pretreatment with rifampicin greatly reduced plasma buspirone concentrations in healthy volunteers, probably by inducing its CYP3A4-mediated metabolism, especially that occurring during first-pass. This effect of rifampicin was reflected in several psychomotor tests which showed decreased pharmacodynamic effects of a single dose of 30 mg buspirone. These findings strongly suggest that concomitant therapy with rifampicin or other potent CYP3A4 inducers such as carbamazepine or phenytoin will greatly reduce the anxiolytic effects of buspirone.

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