DRUG DISPOSITION

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Clinical Pharmacokinetics and Pharmacodynamics of Buspirone, an Anxiolytic Drug

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Abstract

Buspirone is an anxiolytic drug given at a dosage of 15 mg/day. The mechanism of action of the drug is not well characterised, but it may exert its effect by acting on the dopaminergic system in the central nervous system or by binding to serotonin (5-hydroxytryptamine) receptors. Following a oral dose of buspirone 20mg, the drug is rapidly absorbed. The mean peak plasma concentration (C_{max}) is approximately 2.5 μg/L, and the time to reach the peak is under 1 hour. The absolute bioavailability of buspirone is approximately 4%.

Buspirone is extensively metabolised. One of the major metabolites of buspirone is 1-pyrimidinylpiperazine (1-PP), which may contribute to the pharmacological activity of buspirone.

Buspirone has a volume of distribution of 5.3 L/kg, a systemic clearance of about 1.7 L/h/kg, an elimination half-life of about 2.5 hours and the pharmacokinetics are linear over the dose range 10 to 40mg.

After multiple-dose administration of buspirone 10 mg/day for 9 days, there was no accumulation of either parent compound or metabolite (1-PP). Administration with food increased the C_{max} and area under the plasma concentration-time curve (AUC) of buspirone 2-fold.

After a single 20mg dose, the C_{max} and AUC increased 2-fold in patients with renal impairment as compared with healthy volunteers. The C_{max} and AUC were 15-fold higher for the same dose in patients with hepatic impairment compared with healthy individuals. The half-life of buspirone in patients with hepatic impairment was twice that in healthy individuals. The pharmacokinetics of buspirone were not affected by age or gender.

Coadministration of buspirone with verapamil, diltiazem, erythromycin and itraconazole substantially increased the plasma concentration of buspirone, whereas cimetidine and alprazolam had negligible effects. Rifampicin (rifampin) decreased the plasma concentrations of buspirone almost 10-fold.

Buspirone is an anxiolytic drug, structurally different from the benzodiazepines. Although it is as potent as the benzodiazepines as an anxiolytic drug, buspirone does not produce the sedation or motor impairment found with the benzodiazepines.[1] Chemically, buspirone is an azaspirodecanedione derivative (fig. 1). In its hydrochloride form it has a molecular weight of 422 and is highly soluble in water. Buspirone is a dibasic heterocyclic compound and has a pKa1 of 4.12 and a pKa2 of 7.32.[2]

Although the mechanism of action of buspirone has not been established, it has been shown that buspirone acts on the dopaminergic system in the central nervous system (CNS) and increases striatal concentrations of the dopamine metabolites homovanillic acid and dihydroxyphenylacetic acid.[3] Buspirone has also been shown to bind to serotonin (5-hydroxytryptamine; 5-HT) receptors in calf hippocampus.[4] Since 5-HT receptors in calf are similar to those in humans, buspirone may bind to 5-HT receptors in humans. The drug binds with high affinity to 5-HT_1, especially 5-HT_{1A}, and this type of activity is thought to be an important part of its mechanism of action. Berlin et al.[5] demonstrated that the psychostimulatory effect of buspirone may be caused by its active metabolite 1-pyrimidinylpiperazine (1-PP), an α_2-adrenoceptor antagonist, whose plasma concentration is substantially higher than that of buspirone at therapeutic doses. Buspirone may also have an indirect effect on the benzodiazepine γ-aminobutyrate (GABA)/chloride receptor complex.[6]

The recommended initial dosage of buspirone is 15 mg/day given as 2 doses.

1. Analytical Methods

Several analytical methods to measure buspirone and its metabolite 1-PP have been reported in the literature.[7-16] These methods include the use of gas chromatography,[12] gas chromatography-mass spectrometry,[11,14,15] high performance liq-

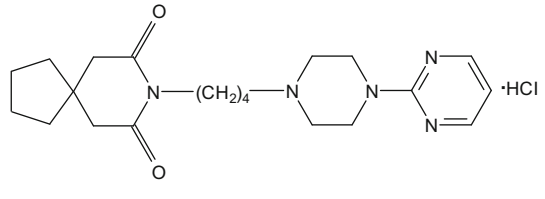

Fig. 1. The chemical structure of buspirone.

uid chromatography (HPLC)[7-10,13] and liquid chromatography coupled with mass spectrometry.[16] Some of the reported analytical methods can simultaneously measure buspirone and its 1-PP metabolite.[9-12,13]

2. Pharmacokinetics of Buspirone

2.1 Absorption

In a 2-way crossover study,[17] 8 healthy volunteers were given either [^{14}C]buspirone 1mg as a 10-minute intravenous infusion or [^{14}C]buspirone 20mg in solution orally. Blood samples were collected for 24 hours and the total radioactivity and buspirone concentrations (using radioimmunoassay) were measured in plasma, urine and faeces. Following oral administration the maximum plasma concentration (C_{max}) of buspirone was about 2.5 μg/L and the time to reach this concentration (t_{max}) was less than an hour (0.8 hours). The absolute bioavailability of buspirone is about 4%.

2.2 Metabolism

Buspirone is extensively metabolised, with less than 1% of the dose excreted unchanged. Studies on urinary metabolites indicated that the metabolism of buspirone takes place through hydroxylation on the spiro and pyrimidine rings and *N*-dealkylation of the butyl-substituted side chain.[18] Studies have also suggested that 1-PP is a major metabolite in plasma and may posses similar pharmacological activity to buspirone (1 to 20% as potent as buspirone).[19] Based on indirect evidence from drug interaction studies, cytochrome P450 (CYP) 3A4 may be involved in the metabolism of buspirone.

2.3 Distribution

The volume of distribution of the central compartment of buspirone is 5.3 L/kg. Plasma protein binding of buspirone is >95% and buspirone is bound to both albumin and $\alpha_{1\text{-acid glycoprotein}}$.[20]

2.4 Elimination

The systemic plasma clearance of buspirone is about 1.7 L/h/kg and the mean half-life ($t_{½}$) about 2.5 hours.[17]

2.5 Dose Proportionality

The pharmacokinetics of buspirone were found to be linear over the dose range 10 to 40mg when given orally to 24 healthy volunteers.[21]

2.6 Multiple Dose Administration

In a multiple-dose study,[22] buspirone was given orally to 12 healthy volunteers. Each volunteer received buspirone 10mg on day 1, and starting 36 hours after the first dose each volunteer received 10mg every 12 hours for 9 days. On the morning of day 10 the last dose of buspirone was administered. Blood samples were collected on days 1, 5 and 10 and the plasma concentrations of buspirone and its metabolite 1-PP were determined. The results of the study indicated that following multiple doses of buspirone for 10 days, there is no accumulation of buspirone or its metabolite in human plasma. However, it should be noted that the overall exposure (AUC) to 1-PP in human plasma was about 12 to 13 times higher than to buspirone.

2.7 Effect of Food

The effect of food on the pharmacokinetics of buspirone was evaluated in 8 healthy individuals in a 2-way crossover design study following an oral dose of buspirone 20mg.[23] Buspirone was administered 15 minutes after the meal following an overnight fast. The results of the study indicated that food increased the area under the concentration-time curve (AUC) and the Cmax of buspirone almost 2-fold, whereas there was negligible change in t_{max} and half-life between fed and fasting states.

Table I. Pharmacokinetic parameters (means ± standard deviation) of buspirone and its metabolite 1-pyrimidinylpiperazine in healthy individuals and patients with different degrees of renal impairment.[22] The creatinine clearance (ml/min/1.73m^2) values for each of these groups are as follows: healthy individuals, 98.2 ± 3.9; for patients with mild renal impairment, 58.0 ± 3.9 (range 40-75); moderate renal impairment 24.4 ± 1.3 (range 20-40); severe renal impairment 9.54 ± 1.9 (<20)

Pharmacokinetic parameter	Healthy		Mild impairment		Moderate impairment		Severe impairment	
	day 1	day 10	day 1	day 10	day 1	day 10	day 1	day 10
Buspirone								
C_{max} (μg/L)	1.01 ± 0.87	1.08 ± 0.80	2.48 ± 2.12	5.38 ± 5.40	1.81 ± 1.17	4.03 ± 3.97	1.83 ± 1.26	4.61 ± 3.52
AUC (μg/L • h)	2.89 ± 3.40	2.91 ± 3.37	6.63 ± 4.59	13.6 ± 15.1	4.64 ± 3.70	9.58 ± 11.60	4.09 ± 3.35	11.1 ± 10.1
$t_{½}$ (h)	3.18 ± 3.41	2.18 ± 1.26	12.61 ± 21.7	8.81 ± 10.3	4.34 ± 4.32	3.47 ± 2.45	2.74 ± 1.72	2.70 ± 1.68
1-Pyrimidinylpiperazine								
C_{max} (μg/L)	5.09 ± 1.49	7.63 ± 3.16	7.49 ± 0.72	11.50 ± 3.51	7.97 ± 2.53	15.0 ± 9.63	8.12 ± 2.18	13.5 ± 3.96
AUC (μg/L • h)	40.0 ± 22.5	39.7 ± 24.5	50.9 ± 22.2	58.9 ± 35.00	122.0 ± 109	114 ± 102	94.1 ± 48.4	96.9 ± 48.0
$t_{½}$ (h)	6.29 ± 3.30	5.52 ± 2.52	6.35 ± 1.71	11.4 ± 16.3	8.90 ± 6.49	9.60 ± 5.84	9.90 ± 3.70	10.2 ± 4.46

AUC = area under the plasma concentration-time curve; **C_{max}** = peak plasma drug concentration; **$t_{½}$** = half-life.

3. Pharmacokinetics of Buspirone in Special Populations

3.1 Renal Impairment

The pharmacokinetics of buspirone were investigated in 12 patients with mild to moderate renal impairment [creatinine clearance (CL_{CR}) <60 ml/min/1.73m^2] and in 12 healthy volunteers (CL_{CR} ≥60 ml/min/1.73m^2) following a single dose of buspirone 20mg.[24] Blood and urine samples from both healthy individuals and patients with renal impairment were collected for 48 hours (blood) and 54 hours (urine). Six anuric patients with chronic renal failure were also given doses of buspirone 20mg between dialysis and during dialysis. These patients required haemodialysis 3 times a week. The first dose (termed as between dialysis) was given 24 hours after the last dialysis of the week. Blood samples were collected for 48 hours. At 2 days after the first dose, each anuric patient underwent a 4-hour haemodialysis. At 2 days after this dialysis the anuric patients were given another oral dose of buspirone 20mg 2 hours before haemodialysis (termed as during dialysis). Venous blood samples were collected again for 48 hours.

The results of this study indicated that the C_{max} and AUC of buspirone in patients with renal impairment were almost 2 times higher than those of healthy individuals. The half-life of buspirone increased by almost 2 hours in patients with renal impairment as compared with healthy individuals. Negligible differences in the pharmacokinetic parameters of 1-PP were observed between healthy individuals and patients with renal impairment. In anuric patients between dialysis, the C_{max}, AUC and half-life of buspirone were comparable with those in renally impaired patients. The half-life and AUC of 1-PP were almost 3 times higher than those of healthy individuals or patients with renal impairment. In anuric patients during dialysis, the C_{max} and AUC of buspirone were 3- and 4-fold higher as compared with healthy individuals, whereas a comparable $t_{½}$ was observed between the 2 groups. However, in anuric patients during dialysis, AUC and half-life of 1-PP were 2- and 1.5-fold higher than those found in healthy individuals.

In a multiple-dose study,[22] buspirone was given orally to 12 healthy volunteers (CL_{CR} = 98.2 ml/min/1.73m^2), 6 patients with mild (CL_{CR} = 58.0 ml/min/1.73m^2), 5 patients with moderate (CL_{CR} = 24.4 ml/min/1.73m^2), and 6 patients with severe (CL_{CR} = 9.54 ml/min/1.73m^2) renal impairment. Each volunteer received 10mg of buspirone on day 1, and starting 36 hours after the first dose buspirone 10mg was given to each volunteer every 12 hours for 9 days. On the morning of day 10 the last dose of buspirone was administered. Blood samples were collected on days 1, 5 and 10 and plasma concentrations of buspirone and 1-PP were determined. Based on the AUC and C_{max} there was no

evidence of drug accumulation in healthy individuals between days 1 and 10. However, in all 3 groups of patients with renal impairment, at least a 2-fold increase in AUC and C_{max} was observed between days 1 and 10. For 1-PP, a slight increase in C_{max} was observed in both healthy and renally impaired patients on day 10 as compared with day 1, but the AUC in all 4 groups of volunteers was unchanged between days 1 and 10 (see table I).

On the basis of the high intra- and inter-individual variability in the pharmacokinetics of buspirone, it is difficult to make a recommendation for dosage adjustment in patients with renal failure.

3.2 Hepatic Impairment

Following a single oral dose of buspirone 20mg in 12 patients with cirrhosis and 12 healthy individuals, the mean AUC and C_{max} values were almost 15 times higher in the patients with hepatic impairment.[25] Although the t_{max} was comparable between the 2 groups, the mean $t_{½}$ in the patients with cirrhosis was double that of the healthy group.

In a multiple-dose study,[22] buspirone was given orally to 12 healthy volunteers and 6 patients with compensated cirrhosis and 6 patients with decompensated cirrhosis. Each volunteer received buspirone 10mg on day 1, and starting 36 hours after the first dose 10mg every 12 hours for 9 days. On the morning of day 10 the last dose of buspirone was administered. Blood samples were collected on days 1, 5 and 10 and plasma concentrations of buspirone and 1-PP were determined. Almost a 10-fold increase in the Cmax of buspirone was observed in patients with compensated and decompensated cirrhosis (table II). A 10- and 20-fold increase in the AUC of buspirone was observed in patients with compensated and decompensated cirrhosis, respectively. Both the single- and multiple-dose studies indicate that a reduction in buspirone dosage is necessary in patients with liver impairment.

3.3 Effect of Age and Gender

The pharmacokinetics of buspirone were investigated in 12 healthy elderly men and women (aged over 65 years).[26] The volunteers were given a single oral dose of buspirone 15mg followed by a 15mg dose every 8 hours for 5 days. The pharmacokinetic parameters (AUC, C_{max} and t_{max}) after the single and multiple doses were determined to be no different between young (31 to 40 years) and elderly participants. No gender difference was observed for AUC, C_{max} and t_{max}. However, the half-life of buspirone was 3 hours longer in females than in males irrespective of age. In this study[26] the mean half-life of buspirone was 11 hours in elderly men as compared with 7 hours in elderly

Table II. Pharmacokinetic parameters (means ± standard deviation) of buspirone and its metabolite 1-pyrimidinylpiperazine in healthy individuals and patients with hepatic impairment.[22] The patients in the compensated group were with varices (not bleeding), transient ascites (no complications) and normal or slightly abnormal laboratory tests (alkaline phosphatase, serum glutamic pyruvic transaminase, triglycerides, total bilirubin). The patients in the decompensated group were with varices (bleeding), complicated ascites, portal hypertension and laboratory abnormalities

Pharmacokinetic parameter	Healthy		Compensated		Decompensated	
	day 1	day 10	day 1	day 10	day 1	day 10
Buspirone						
C_{max} (μg/L)	1.01 ± 0.87	1.08 ± 0.80	4.61 ± 3.64	9.78 ± 15.7	11.7 ± 8.66	13.0 ± 8.51
AUC (μg/L • h)	2.89 ± 3.40	2.91 ± 3.37	15.4 ± 12.5	24.8 ± 33.5	70.2 ± 65.3	54.5 ± 36.2
$t_{½}$ (h)	3.18 ± 3.41	2.18 ± 1.26	11.1 ± 8.41	5.87 ± 4.51	4.70 ± 2.55	6.63 ± 2.66
1-Pyrimidinylpiperazine						
C_{max} (μg/L)	5.09 ± 1.49	7.63 ± 3.16	7.07 ± 3.28	8.67 ± 4.78	4.26 ± 1.59	8.44 ± 5.32
AUC (μg/L • h)	40.0 ± 22.5	39.7 ± 24.5	46.2 ± 36.9	48.4 ± 25.0	64.2 ± 53.2	64.1 ± 58.4
$t_{½}$ (h)	6.29 ± 3.30	5.52 ± 2.52	5.51 ± 2.48	9.62 ± 8.99	9.26 ± 5.92	9.17 ± 5.76

AUC = area under the plasma concentration-time curve; $\mathbf{C_{max}}$ = peak plasma drug concentration; $\mathbf{t_{½}}$ = half-life.

women. This was found to be statistically insignificant. The $t_{½}$ in young males and females was not reported. Because the half-life was estimated from the terminal portion of plasma concentrations *vs* time data, AUC may not be different in the 2 groups yet the half-life can be, to some extent, shorter or longer. This phenomena is not very unusual. Unfortunately, authors have not reported the half-life of buspirone in young males and females in this study.[26]

4. Drug Interactions

Buspirone undergoes extensive first-pass metabolism after oral administration. The specific CYP enzyme(s) involved in buspirone metabolism have not been established. However, based on the reported drug interactions, buspirone appears to be a substrate for CYP3A. Buspirone interactions with verapamil,[27] diltiazem,[27] erythromycin,[28] itraconazole,[28] diazepam,[29-31] cimetidine,[32] alcohol (ethanol),[29,33] rifampicin (rifampin),[34] alprazolam[35] and haloperidol[36] have been studied and are summarised in this section.

4.1 Verapamil or Diltiazem

Verapamil and diltiazem are inhibitors of CYP3A and have been reported to increase plasma concentrations of drugs such as triazolam and midazolam,[37-40] which are known substrates of CYP3A4.

Lamberg et al.[27] investigated the effects of these calcium channel blockers on the plasma concentrations of buspirone. In this study, 9 healthy individuals (8 men and 1 woman) received verapamil 80mg, diltiazem 60mg or placebo 3 times daily in a 3-way crossover fashion. On day 2 of each treatment period, at 1 hour after the fifth dose, they also received buspirone 10mg. The results of this study are presented in table III. When buspirone was administered with verapamil, the C_{max} and AUC of buspirone were both increased 3.4-fold, whereas the C_{max} and AUC of buspirone were increased 4.1- and 5.5-fold, respectively, in the presence of diltiazem. However, the apparent $t_{½\beta}$ values were not affected by the presence of either verapamil or diltiazem. It should be noted that there was a considerable interindividual variability in the reported interaction. Based on the results provided it appears that 1 male participant showed a much higher interaction compared with the other 7 males, and that the woman in the study was also taking oral contraceptives and exhibited the least interaction.[27]

The investigators also looked at the pharmacodynamic interaction by performing several psychomotor tests after each blood sample was taken, up to 8 hours after drug administration. The tests conducted were the Digit Symbol Substitution (DSST), Critical Flicker Fusion Test (CFFT), drowsiness as assessed by visual analogue scale (VAS) and Postural Sway tests. The authors reported that the subjective overall drug effects showed a minor impairment of psychomotor performance and a statistically significant difference between verapamil + buspirone and diltiazem + buspirone compared with buspirone given alone. There were no significant differences when verapamil + buspirone was compared with diltiazem + buspirone.[27]

An increased frequency of adverse effects was reported when buspirone was given in the presence of diltiazem. The investigators concluded that the clinical significance of the observed interaction is unclear, but recommended that caution be exercised when buspirone is coadministered with verapamil, diltiazem or other inhibitors of CYP3A4.

4.2 Erythromycin or Itraconazole

Kivisto et al.[28] investigated the effects of erythromycin and itraconazole, potent inhibitors of CYP3A4, on the plasma concentrations of buspirone. In this study 8 healthy females received erythromycin 500mg at 0700h, 1300h and 2100h, itraconazole 100mg at 0700h and 1300h or placebo at 0700h, 1300h and 2100h in a 3-way crossover fashion. On day 4 of each treatment period, 1 hour after the 1300 dose, they received buspirone 10mg. The results of the pharmacokinetic study are presented in table III.

The C_{max} and AUC of buspirone increased 5- to 6-fold in the presence of buspirone, whereas in the presence of itraconazole the mean C_{max} and AUC

Table III. Summary of changes in pharmacokinetic parameters of buspirone when coadministered with other drugs. Values are means ± standard deviation

	Buspirone dose (mg)	AUC_t (μg/L • h)	AUC_∞ (μg/L • h)	C_{max} (μg/L)	$t_{1/2}$ (h)	Reference
Verapamil + buspirone	10 sd	21.8 ± 18.7	24.3 ± 19.3	8.8 ± 7.9	2.6 ± 1.0	27
Buspirone		6.3 ± 2.3	6.9 ± 2.5	2.6 ± 1.0	2.4 ± 0.6	
Relative change		3.3	3.4	3.4	1.2	
Diltiazem + buspirone	10 sd	31.1 ± 14.2	36.8 ± 15.2	10.3 ± 3.5	3.3 ± 1.3	27
Buspirone		6.3 ± 2.3	6.9 ± 2.5	2.6 ± 1.0	2.4 ± 0.6	
Relative change		5.0	5.5	4.1	1.4	
Erythromycin + buspirone	10 sd	16.2 ± 9.6	19.5 ± 13.6	5.0 ± 2.3	2.6 ± 1.6	28
Buspirone		3.1 ± 3.3	3.3 ± 3.9	1.0± 0.99	1.5 ± 0.23	
Relative change		5.22	5.9	5.0	1.7	
Itraconazole + buspirone	10 sd	48.8 ± 16.3	63.2 ± 29.5	13.4 ± 3.9	2.7 ± 0.83	28
Buspirone		3.1 ± 3.3	3.3 ± 3.9	1.0± 0.99	1.5 ± 0.22	
Relative change		15.8	19.2	13.4	1.8	
Cimetidine + buspirone	15 tid	NA	8.9[a]	4.8 ± 3.0	9.5 ± 8.0	32
Buspirone			8.2	3.4 ± 1.5	24.9 ± 19.4	
Relative change			1.1	1.4	[b]	
Rifampicin (rifampin) + buspirone	30 sd	1.48 ± 0.28	1.64 ± 0.35	0.84 ± 0.23	1.3 ± 0.5	34
Buspirone		20.6 ± 14.2	22.0 ± 15.1	6.6 ± 3.7	2.8 ± 0.7	
Decrease		93%	93%	87%	54%	
Alprazolam + buspirone[c]	10 tid	NA	1.55 ± 1.4	0.61 ± 0.6	NA	35
Buspirone			1.20 ± 0.9	0.55 ± 0.4		
Relative change			1.29	1.2		
Grapefruit juice + buspirone	10 sd	NA	39.80 ± 9.6	8.40 ± 1.53	2.70 ± 0.18	41
Buspirone			4.30 ± 1.4	1.96 ± 0.74	1.80 ± 0.14	
Relative change			9.2	4.3	1.5	

a Geometric means.

b Half-life differences were stated as anomalous due to analytical limitations.

c Administration interval 0-8 hours steady state.

AUC_t = area under the plasma concentration-time curve from zero to time t; **AUC_∞** = area under the plasma concentration-time curve from zero to infinity; **C_{max}** = peak drug plasma concentration; **NA** = data not available; **sd** = single dose; **tid** = 3 times daily; **$t_{1/2}$** = half-life.

of buspirone increased 16- and 19-fold, respectively. However, apparent $t_{1/2}$ values were not affected by the presence of either erythromycin or itraconazole. Three participants were taking oral contraceptives, which would be expected to inhibit CYP3A4 additively with that caused by erythromycin or itraconazole. The investigators reported that, although the magnitude of inhibition was greater in these individuals, as a group the inhibition was not significantly greater than in those not taking oral contraceptives.

The pharmacodynamic interactions between buspirone and erythromycin or buspirone and itraconazole were studied using several tests after each blood sample up to 8 hours after drug administration. The tests conducted were DSST, CFFT, VAS and Postural Sway test. Psychomotor performance was impaired in the group taking buspirone with erythromycin or itraconazole, and an increased frequency of adverse effects were reported when buspirone was given with erythromycin or itraconazole. Kivisto et al.[28] recommend a reduced dosage of buspirone when it is administered with erythromycin or itraconazole.

4.3 Rifampicin (Rifampin)

Rifampicin is known to induce CYP3A4,[42] and therefore has the potential to decrease the concentrations of drugs that are substrates of CYP3A4. Consequently, Lamberg et al.[34] investigated the effect of rifampicin on buspirone pharmacokinetics.

In this study, 10 healthy individuals (5 men and 5 women) received rifampicin 600mg once daily or placebo at 2000 in a 2-way crossover fashion. On day 6 of each treatment period, at 1300 participants received buspirone 30mg (the higher dose was used to improve the determination of buspirone concentrations). The results of the pharmacokinetic study are presented in table III. The Cmax and AUC of buspirone decreased by 84 to 90%, and the half-life decreased from 2.8 to 1.3 hours, in the presence of rifampicin. None of the participants taking rifampicin had measurable buspirone concentrations at 6 hours and beyond. Women on oral contraceptives exhibited interactions similar to those in women not taking oral contraceptives.

The pharmacodynamic interaction was also studied by performing tests after each blood sample. The tests conducted were DSST, CFFT, VAS and Postural Sway test. The authors reported that the effects of buspirone were significantly smaller in the presence of rifampicin compared with when given with placebo; the same was true for the adverse effects reported in the study. The investigators concluded that buspirone plasma concentrations would be significantly decreased when the drug is given concomitantly with rifampicin or other inducers of CYP3A4, such as carbamazepine and phenytoin, and anxiolytic effects would be greatly reduced.

4.4 Alprazolam

Alprazolam[43,44] and buspirone are both eliminated via oxidative metabolism, and if coadministered there is the potential for competitive metabolism which could result in increased concentrations of both drugs. Therefore Buch et al.[35] investigated the effect of coadministration of alprazolam and buspirone on their pharmacokinetics. In this parallel design study with 2 groups of 12 healthy men, each was given alprazolam 1mg 3 times daily or placebo with buspirone 10mg 3 times daily for 7 days. On days 8 to 14 all participants received alprazolam 1mg and buspirone 10mg 3 times daily. Buspirone, alprazolam and their metabolites 1-PP and α-hydroxy-alprazolam were measured for samples taken between 0 and 8 hours. The pharmacokinetics of buspirone on days 7 (buspirone alone) and 14 (coadministered with alprazolam) are presented in table III. Coadministration of buspirone and alprazolam did not significantly affect the pharmacokinetics of either of these drugs, although their AUC and C_{max} were increased by about 10 to 29%, respectively. The metabolites of the drugs were not significantly affected. Thus the steady-state concentrations of buspirone and alprazolam are not affected when they are coadministered.

4.5 Cimetidine

Since simultaneous administration of cimetidine and many benzodiazepine anxiolytics has resulted in decreased clearance of the drugs,[45,46] Gammans et al.[32] investigated the effect of coadministration of cimetidine on the pharmacokinetics of buspirone. This study was of repeat design in 10 healthy men; all participants received all treatments in the same order. Each participant received buspirone 15mg 3 times daily for 7 days, with a washout period between days 8 and 14, then buspirone 20mg 3 times daily plus cimetidine 400mg at bedtime on days 14 to 21, and buspirone plus cimetidine 200mg 3 times daily plus an additional dose of cimetidine 400mg at bedtime on days 22 to 28. On days 8 and 29 buspirone and 1-PP were measured for samples taken between 0 and 32 hours after the last dose of buspirone. The results of this study for day 8 (buspirone alone) and day 29 (coadministered with cimetidine) are presented in table III.

Coadministration of buspirone and cimetidine did not significantly affect the pharmacokinetics of buspirone, but AUC and C_{max} were increased by about 10 to 40%, respectively. Although the mean half-life of buspirone was about 10 hours lower when coadministered with cimetidine, the authors report that this anomalous result may be due to concentrations in the terminal phase being close to the detectable limits. The AUC and C_{max} of 1-PP were about 12% and 33% greater, respectively, when buspirone was coadministered with cimetidine.

The pharmacodynamic interaction study was performed using 3 tests, a manual dexterity test, the Stroop colour-word interference test and a 5-question VAS test of mood. The authors reported that similar results were obtained for the 3 tests conducted and effects on cognitive or psychomotor performance were not noted. Thus the investigators concluded that clinically important interactions are unlikely when buspirone and cimetidine are coadministered.

4.6 Haloperidol

Goff et al.[47] reported that the coadministration of buspirone and haloperidol, a potent antipsychotic, increased the concentrations of haloperidol and its metabolite [reduced haloperidol (RH)] by 26% and 83%, respectively. This increase was seen in only 6 of the 19 patients with schizophrenia participating in the study. Since pharmacokinetic parameters were not evaluated in this study, Huang et al.[36] conducted a pharmacokinetic study to evaluate the interaction when these 2 drugs were coadministered. They concluded that coadministration of buspirone and haloperidol does not significantly alter the pharmacokinetics of haloperidol. However, they did not measure buspirone concentrations or evaluate pharmacodynamic parameters.

4.7 Alcohol (Ethanol)

Erwin et al.[29] studied the effect of buspirone 10mg and 20mg or diazepam 10mg on skilled performance and evoked response in the presence or absence of alcohol 0.8 g/kg in 24 healthy volunteers. 12 participants received the drug with an alcoholic beverage and another 12 with a placebo beverage. Numerous tasks were used to measure skilled performance.

The results indicated that both doses of buspirone had lesser effects than diazepam or alcohol. Buspirone had a short-acting sedative effect which adversely affected performance in tests requiring sustained arousal, and showed only slight additive interaction effects when given in the presence of alcohol. For evoked response, buspirone appeared to reverse the effect of alcohol. Based on plasma concentrations measured at 6 time-points within 24 hours after drug administration, the presence of alcohol did not affect the pharmacokinetics of buspirone.

Ciraulo et al.[33] measured the subjective (Tufts ARCI-MGB) and electroencephalographic (EEG) response in abstinent patients with alcoholism (n = 12) and healthy volunteers (n = 5) following buspirone 15mg or placebo. The results of the study indicated that buspirone has minimal liability for abuse in abstinent patients with alcoholism.

4.8 Grapefruit Juice

Lilja et al.[41] studied the effects of grapefruit juice (a CYP3A4 inhibitor) on the pharmacokinetics and pharmacodynamics of buspirone in this randomised 2-way crossover study with 4 male and 6 female (2 of whom were taking oral contraceptives) volunteers. The participants received either 200ml of double-strength grapefruit juice or 200ml of water 3 times daily for 2 days. On day 3, each took 1 tablet of buspirone 10mg with 200ml of grapefruit juice or water. Blood samples were collected until 12 hours after buspirone administration. Several pharmacodynamic tests (DSST, CFFT, VAS and Postural Sway test) were conducted after each blood sample up to 8 hours after the administration of buspirone.

The results of this study indicated that grapefruit juice increased the C_{max} and AUC of buspirone by 4.3- and 9.2-fold, respectively. Pharmacodynamically, only the VAS test for subjective overall drug effect was significantly greater ($p < 0.01$) when buspirone was given with grapefruit juice. Based on the pharmacokinetic and pharmacodynamic results, the authors suggested that concomitant administration of buspirone with grapefruit juice should be avoided.

4.9 Effect of Itraconazole or Rifampicin on an Active Metabolite

Kivisto et al.[48] investigated the effect of itraconazole (a CYP3A4 inhibitor) or rifampicin (a CYP3A4 inducer) on the pharmacokinetics of

1-PP, an active metabolite of buspirone. The studies were of placebo-controlled randomised crossover design in healthy individuals. In the first study, 6 participants were given oral itraconazole 200mg daily or placebo for 4 days. On day 4, buspirone 10mg was given orally. In the second study, another 6 participants received oral rifampicin 600mg or placebo for 5 days. On day 6, buspirone 30mg was given to the volunteers. Buspirone and 1-PP were measured in plasma. Itraconazole increased the AUC and C_{max} of buspirone 14.5- and 10.5-fold, respectively, whereas the mean AUC and C_{max} of 1-PP decreased by 50% and 57%, respectively. Rifampicin did not affect the AUC of 1-PP, but increased the C_{max} by 35%. Rifampicin reduced the mean AUC and C_{max} of buspirone by 91% and 85%, respectively.

This study confirms the previous observations by Lamberg et al.[34] that rifampicin decreases the C_{max} and AUC of buspirone. Overall, the results of the study indicate that itraconazole or rifampicin produce relatively minor changes in the plasma concentrations of 1-PP but produce substantial changes in the plasma concentrations of buspirone.

5. Conclusions

Buspirone appears to be an effective drug for the management of anxiety. Despite the fact that buspirone is comparable with benzodiazepines in anxiolytic potency, it does not produce the adverse effects of benzodiazepines. The pharmacokinetic data suggest that buspirone is rapidly and completely absorbed, extensively metabolised, has a high systemic clearance and a low absolute bioavailability. Buspirone appears to be metabolised by CYP3A4, and its interactions with other drugs that are either inducers or inhibitors of CYP3A4 have been documented.

The metabolite 1-PP may contribute to the effectiveness of buspirone. Renal or hepatic impairment alters the pharmacokinetics of buspirone and its metabolite 1-PP. Age and gender do not have any clinically significant effect on the pharmacokinetics of buspirone.

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References

1. Riblet LA, Eison SA, Eison MS, et al. Neuropharmacology of buspirone. Psychopharmacology 1984; 17 Suppl. 3: 69-78
2. Temple DL, Yevich JP, New JS. Buspirone: chemical profile of a new class of anxioselective agents. J Clin Psychiatry 1982; 43: 4-9
3. Cimino M, Ponzio F, Achilli G, et al. Dopaminergic effects of buspirone, a novel anxiolytic agent. Biochem Pharmacol 1983; 32: 1069-74
4. Glaser T, Traber J. Buspirone: action on serotonin receptors in calf hippocampus. Eur J Pharmacol 1983; 88: 137-8
5. Berlin I, Chalon S, Payan C, et al. Evaluation of the α_2-adrenoceptor blocking properties of buspirone and ipsapirone in healthy subjects: relationship with the plasma concentration of the common metabolite 1-(2-pyrimidinyl)piperazine. Br J Clin Pharmacol 1995; 39: 243-9
6. Oakley NR, Jones BJ. Buspirone enhances [^{3}H]flunitrazepam binding *in vivo*. Eur J Pharmacol 1983; 87: 499-500
7. Kristjansson F. Sensitive determination of buspirone in serum by solid phase extraction and two dimensional high performance liquid chromatography. J Chromatogr 1991; 566: 250-6
8. Tsai TH, Chen CF. Measurement and pharmacokinetic analysis of buspirone by means of brain microdialysis coupled to high performance liquid chromatography with electrochemical detection. J Chromatogr 1997; 762: 269-73
9. Bianchi G, Caccia S. Simultaneous determination of buspirone, gepirone, ipsapirone and their common metabolite 1-(2-pyrimidinyl)piperazine in rat plasma and brain by high performance liquid chromatography. J Chromatogr 1988; 431: 477-80
10. Odontiadis J, Franklin M. Simultaneous quantitation of buspirone and its major metabolite 1-(2-pyrimidinyl)piperazine in human plasma by high performance liquid chromatography with coulometric detection. J Pharm Biomed Anal 1996; 14: 347-51
11. Sciacca MA, Duncan GF, Shea JP, et al. Simultaneous quantitation of buspirone and 1-(2-pyrimidinyl)piperazine in human plasma and urine by capillary gas chromatography mass spectrometry. J Chromatogr 1988; 428: 265-74
12. Gaillard Y, Gay Montchamp JP, Ollagnier M. Simultaneous screening and quantitation of alpidem, zolpidem, buspirone and benzodiazepines by dual channel gas chromatography using electron capture and nitrogen phosphorus detection after solid phase extraction. J Chromatogr 1993; 622: 97-208
13. Betto P, Meneguz A, Ricciarello G, et al. Simultaneous high performance liquid chromatographic analysis of buspirone and its metabolite 1-(2 pyrimidinyl)-piperazine in plasma using electrochemical detection. J Chromatogr 1992; 575: 17-21
14. Kerns EH, Bullen WW, Gammans RE. Quantitative analysis of 1-(2-pyrimidinyl)piperazine in plasma by capillary gas chromatography mass spectrometry. J Chromatogr 1986; 377: 195-203
15. Gammans RE, Kerns EH, Bullen WW. Capillary gas chromatographic mass spectrometric determination of buspirone in plasma. J Chromatogr 1985; 345: 285-97

16. Goldthwaite Jr CA, Hsieh FY, Womble SW, et al. Liquid chromatography/chemical reaction interface mass spectrometry as an alternative to radioisotopes for quantitative drug metabolism studies. Anal Chem 1996; 68: 2996-3001
17. Mayol RF, Adamson DS, Gammans RE, et al. Pharmacokinetics and disposition of ^{14}C-buspirone HCl after intravenous and oral dosing in man [abstract]. Clin Pharmacol Ther 1985; 37: 210
18. Jajoo HK, Mayol RF, LaBudde JA, et al. Metabolism of the antianxiety drug buspirone in human subjects. Drug Metab Disp 1989; 17: 634-40
19. Gammans RE, Mayol RF, Eison ME. Concentration of buspirone and 1-pyrimidinylpiperazine, a metabolite in rat brain [abstract]. Fed Proc 1983; 42: 377
20. Bullen WW, Bivens DL, Gammans RE, et al. The binding of buspirone to human plasma proteins [abstract]. Fed Proc 1985; 44: 1123
21. Gammans RE, Mayol RF, Mackenthun AV, et al. The relationship between buspirone bioavailability and dose in healthy subjects. Biopharm Drug Disp 1985; 6: 139-45
22. Barbhaiya RH, Shukla UA, Pfeffer M, et al. Disposition kinetics of buspirone in patients with renal or hepatic impairment after administration of single and multiple doses. Eur J Clin Pharmacol 1994; 46: 41-7
23. Mayol RF, Gammans RE, Mackenthun AV, Sokya LF. The effect of food on the bioavailability of buspirone HCl [abstract]. Clin Res 1983; 31: 631A
24. Caccia S, Vigano GL, Mingardi G, et al. Clinical pharmacokinetics of oral buspirone in patients with impaired renal function. Clin Pharmacokinet 1988; 14: 171-7
25. Dalhoff K, Poulsen HE, Garred P, et al. Buspirone pharmacokinetics in patients with cirrhosis. Br J Clin Pharmacol 1987; 24: 547-50
26. Gammans RE, Mayol RF, LaBudde JA. Metabolism and disposition of buspirone. Am J Med 1986; 80 Suppl. 3B: 41-51
27. Lamberg TS, Kivisto KT, Neuvonen PJ. Effects of verapamil and diltiazem on the pharmacokinetics and pharmacodynamics of buspirone. Clin Pharmacol Ther 1998; 63: 640-5
28. Kivisto KT, Lamberg TS, Kantola T, et al. Plasma buspirone concentrations are greatly increased by erythromycin and itraconazole. Clin Pharmacol Ther 1997; 62: 348-54
29. Erwin CW, Linnoila M, Hartwell J, et al. Effects of buspirone and diazepam, alone and in combination with alcohol, on skilled performance and evoked potentials. J Clin Psychopharmacol 1986; 6: 199-209
30. Ashton CH, Rawlins MD, Tyrer SP. A double blind placebo controlled study of buspirone in diazepam withdrawal in chronic benzodiazepine users. Br J Psychiatry 1990; 157: 232-8
31. van Laar MW, Volkerts ER, van Willigenburg AP. Therapeutic effects and effects on actual driving performance of chronically administered buspirone and diazepam in anxious outpatients. J Clin Psychopharmacol 1992; 12: 86-95
32. Gammans RE, Pfeffer M, Westrick ML, et al. Lack of interaction between cimetidine and buspirone. Pharmacotherapy 1987; 7: 72-9
33. Ciraulo DA, Barnhill JG, Ciraulo AM, et al. Alterations in pharmacodynamics of anxiolytics in abstinent alcoholic men: subjective responses, abuse liability, and electroencephalographic effects of alprazolam, diazepam, and buspirone. J Clin Pharmacol 1997; 37: 64-73
34. Lamberg TS, Kivisto KT, Neuvonen PJ. Concentrations and effects of buspirone are considerably reduced by rifampicin. Br J Clin Pharmacol 1998; 45: 381-5
35. Buch AB, Van Harken DR, Seidehamel RJ, et al. A study of pharmacokinetic interaction between buspirone and alprazolam at steady state. J Clin Pharmacol 1993; 33: 1104-9
36. Huang HF, Jann MW, Wei FC, et al. Lack of pharmacokinetic interaction between buspirone and haloperidol in patients with schizophrenia. J Clin Pharmacol 1996; 36: 963-9
37. Olkkhola VA, Neuvonen PJ. Diltiazem enhances the effects of triazolam by inhibiting its metabolism. Clin Pharmacol Ther 1996; 59: 369-75
38. Backman JT, Olkkola KT, Aranko K, et al. Dose of midazolam should be reduced during diltiazem and verapamil treatments. Br J Clin Pharmacol 1994; 37: 221-5
39. Schlanz KD, Myre SA, Bottorff MB. Pharmacokinetic interactions with calcium channel antagonists: Part I. Clin Pharmacokinet 1991; 21: 344-56
40. Schlanz KD, Myre SA, Bottorff MB. Pharmacokinetic interactions with calcium channel antagonists: Part II. Clin Pharmacokinet 1991; 21: 448-60
41. Lilja JJ, Kivisto KT, Backman JT, et al. Grapefruit juice substantially increases plasma concentrations of buspirone. Clin Pharmacol Ther 1998; 64: 655-60
42. Kolars JC, Schmiedline-Ren P, Schuetz JD, et al. Identification of rifampicin-induced P450IIIA (CYP3A4) in human small bowel enterocytes. J Clin Invest 1992; 90: 1871-8
43. Dawson GW, Jue SG, Brogden RN. Alprazolam: a review of its pharmacodynamic properties and efficacy in the treatment of anxiety and depression. Drugs 1984; 11: 132-47
44. Sethy VH, Harris DW. Determination of biological activity of alprazolam, triazolam and their metabolites. J Pharm Pharmacol 1982; 34: 115-6
45. Desmond PV, Patwardhan RW, Schenkar S, et al. Cimetidine impairs elimination of chlordiazepoxide in man. Ann Intern Med 1980; 93: 266-8
46. Klotz U, Reimann I. Delayed clearance of diazepam due to cimetidine. N Engl J Med 1980; 302: 1012-4
47. Goff DC, Midha KK, Brotman AW, et al. An open trial of buspirone added to neuroleptics in schizophrenic patients. J Clin Psychopharmacol 1991; 11: 193-7
48. Kivisto KT, Lamberg TS, Neuvonen PJ. Interactions of buspirone with itraconazole and rifampicin: effects on the pharmacokinetics of the active 1-(2-pyrimidinyl)-piperazine metabolite of buspirone. Pharmacol Toxicol 1999; 84: 94-7

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