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Buspirone pharmacokinetics in patients with cirrhosis

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The pharmacokinetics of a single oral dose of buspirone (20 mg) were determined in 12 patients with cirrhosis and 12 normal subjects. The mean AUC of buspirone was 55 ± 38 s.d. ng ml^{-1} h in cirrhotics and 3.5 ± 2.4 s.d. ng ml^{-1} h in normals. The time until maximum concentration (t_{max}) attained was similar in the two groups (0.6 *vs* 0.7 h), but mean maximum concentration C_{max} was higher in patients (18.8 ± 16.3 s.d. ng ml^{-1}) than in normals (1.2 ± 0.8 s.d. ng ml^{-1}). Mean elimination half-life of buspirone was greater in cirrhotics, but this difference was marginally significant statistically (cirrhotics, 6.1 ± 3.5 s.d. h; normals 3.2 ± 1.5 s.d. h, $P = 0.05$). Eight of 12 patients and seven of 12 normal subjects had a second peak in the plasma concentrations of buspirone. In patients this occurred at 10.8 ± 7.4 s.d. h after the dose, and its mean concentration was 3.1 ± 6.6 ng ml^{-1}. In normal subjects the second peak occurred at 4.3 ± 2.1 h after the dose and its mean concentration was 0.5 ± 0.3 ng ml^{-1}. On the kinetic evidence buspirone should be used with caution in liver disease.

Keywords buspirone cirrhosis pharmacokinetics

Introduction

Buspirone hydrochloride, 8-(4-4-(2-pyrimidinyl))-1-piperazinyl(butyl)-8-azaspiro(4.5)decame-7.9-dione hydrochloride, is a new drug with anxiolytic activity (Temple *et al.*, 1982; Riblet *et al.*, 1982; Garattini *et al.*, 1982). On the basis of radiolabelled studies in normals (Mayol *et al.*, 1985), buspirone is absorbed completely after an oral dose, undergoes extensive presystemic metabolism, has a large apparent volume of distribution and a high plasma clearance. The two major metabolites (a 5-hydroxy derivative and a glucuronide) are eliminated in urine and faeces. The plasma half-life of the parent compound is about 2 h in normals, but the half-lives of the metabolites are over 8 h.

As a consequence of this, liver disease could change the metabolism of buspirone, to a clinically important degree, requiring changes in dose or dose intervals. The purpose of the present study was to investigate the kinetics of buspirone elimination in patients with cirrhosis.

Methods

Twelve male patients entered the study, eleven with biopsy-proven cirrhosis, eleven alcohol-induced and one xylene-induced (patient 445). Twelve healthy males without evidence of liver disease also were studied. The patients were admitted just prior to the study, none was encephalopathic and none had gastro-intestinal bleeding. Three had mild ascites. The patients were about twice as old as the controls, but there

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was no significant difference in body weight. Most patients were already receiving diuretics and Vitamin K, and six patients (nos. 432, 438, 445, 447, 449 and 451) received additional medication (see Table 1).

Galactose elimination capacity (GEC) (Tygstrup, 1966) and antipyrine clearance (Døssing *et al.*, 1982) were measured prior to administration of buspirone. An ECG was recorded and prothrombin index (0.85–1.15), albumin (532–813 μmol l^{-1}), alanine-aminotransferase (10–40 u l^{-1}), and alkaline phosphatases (50–275 u l^{-1}) were measured by routine laboratory methods before and 48 h after administration of buspirone (normal values given in parenthesis). Data are given in Table 1.

The study was approved by the local ethics committee and written informed consent was obtained. Patients and subjects were asked to report side effects.

Protocol

After an overnight fast each person took a single oral 20 mg dose of buspirone with 120 ml of water and continued to fast for 3 h. Blood samples were obtained before drug administration and 0.25, 0.5, 0.75, 1, 2, 3, 4, 6, 8, 11, 15, 24 and 36 h post dose through a cannula in a peripheral vein. Plasma was separated and stored at −20° C until analysis.

After hexane extraction, buspirone plasma concentrations were measured by a specific radioimmunoassay (Mayol *et al.*, 1981). Antibody

Table 1 Clinical and laboratory data in patients with liver cirrhosis and in healthy controls

Subject	*Weight (kg)*	*Age (years)*	*PP (ratio)*	*Albumin (μmol l^{-1})*	*ALAT (u l^{-1})*	*Alk Ph (u l^{-1})*	*GE*[a]	*AP-CL*[b]	*Other drugs*
Patient									
432	68	39	0.67	434	50	267	13.1	0.76	3
438	81	28	0.38	287	25	398	17.0	0.61	1
437	87	50	1.20	538	16	344	24.1	0.60	
439	74	61	0.65	331	20	478	21.4	0.52	
449	70	42	0.89	667	9	236	22.3	0.49	1
452	78	54	0.78	629	40	418	20.5	0.41	
451	96	41	1.62	684	95	316	30.0	0.39	1
431	115	45	1.05	719	58	315	30.4	0.30	
447	86	48	0.71	560	40	384	26.4	0.28	1
450	62	40	0.42	357	16	561	24.5	0.27	
445	65	45	0.59	553	14	366	20.8	0.24	2
446	79	50	0.66	602	39	399	23.5	0.17	
Mean	80	45	0.80	530	35	374	22.8	0.42	
s.d.	15	8	0.35	145	25	89	4.9	0.18	
Control									
433	72	23	0.84	670	16	112	32.1	1.72	
443	70	20	1.15	770	16	225	46.3	1.70	
444	70	21	0.81	598	17	188	38.1	1.63	
434	84	28	1.52	599	28	340	31.8	1.42	
436	62	26	0.88	639	15	206	36.5	1.15	
441	72	25	0.86	658	34	280	29.9	1.00	
440	65	27	0.97	726	20	245	38.9	0.92	
435	78	37	1.09	645	16	158	30.4	0.87	
442	73	24	0.60	698	13	214	27.8	0.74	
454	70	27	1.07	779	24	195	34.4	0.66	
448	83	36	1.11	688	19	124	29.2	0.55	
453	75	27	0.97	692	13	153	35.7	0.43	
Mean	73	27	0.99	680	19	203	34.3	1.07	
s.d.	6	5	0.23	58	6	65	5.2	0.46	

PP = prothrombin index (% of control value); ALAT = alanine-aminotransferase; Alk Ph = alkaline phosphatase; GE galactose elimination; AP-CL = antipyrine clearance.

[a] 10^{-3} mg min^{-1} kg^{-1} body weight.

[b] ml min^{-1} kg^{-1} body weight.

1 diazepam; 2 cimetidine; diazepam; 3 diazepam, phenobarbitone, disulfiram.

for the assay was produced in rabbits by injection of buspirone coupled to bovine serum albumin via a hemisuccinamide of the 5-amino pyramidinyl derivative. The lower limit of measurement was 0.06 ng ml^{-1}. The coefficient of variation for five repeated measurements was less than 9% in the concentration range 0.06–1.25 ng ml^{-1} plasma and somewhat higher for concentrations up to 10 ng ml^{-1} plasma.

Calculations

The elimination half-life ($t_{½}$) was estimated from the terminal part of the plasma drug concentration-time curve using regression analysis. In those cases where a second peak (defined as a concentration value higher than the previous value) was apparent, the elimination $t_{½}$ estimation was based upon the data points after the second peak. The area under the plasma concentration-time curve from 0 to the last time point t AUC(0,t) was calculated using the linear trapezoidal rule. AUC from t to infinity was extrapolated as $C(t)/k$, where k is the estimated elimination rate constant. The extrapolated area was 20% of total AUC in controls and 2% of total AUC in cirrhotics; the numeric values of the extrapolated areas were similar.

Differences between controls and cirrhotics were tested with the two-tail Student's t-test, P-values less than 0.05 were considered to be significant statistically.

Results

Individual and mean pharmacokinetic data are given in Table 2.

Table 2 Kinetic parameters of patients with liver cirrhosis and healthy controls after a single oral dose of 20 mg buspirone

Subject	C_{max} (ng ml^{-1})	t_{max} (h)	*AUC* (ng ml^{-1} h)	$t_{½}$ (h)	*Second peak* Time after dosing (h)	*Second peak* Concentration (ng ml^{-1})
Patient						
432	1.11	0.5	6.0	4.6	4	0.68
438	23.84	0.6	68.3	6.0	4	9.58
437	51.34	0.4	84.3	8.6	18	0.86
439	33.07	0.5	102.5	5.4	—	—
449	3.88	2.0	17.9	16.3	24	0.10
452	1.90	0.5	46.3	6.1	4	7.44
451	40.54	0.5	88.5	3.9	—	—
431	3.89	0.5	9.7	4.3	14	0.51
447	21.01	0.3	35.4	5.9	8	1.49
450	14.73	0.5	69.9	4.3	—	—
445	20.49	0.3	115.4	3.5	10	4.20
446	10.02	0.25	16.2	3.9	—	—
Mean	18.82*	0.6	54.7*	6.1†	10.8*	3.11*
s.d.	16.25	0.5	38.4	3.5	7.4	3.61
Control						
433	0.49	0.5	1.53	2.67	—	—
443	1.08	1	3.54	1.88	4	0.58
444	2.29	1	10.6	3.40	6	1.03
434	0.49	0.5	1.25	4.29	—	—
436	0.60	0.5	1.45	1.69	3	0.26
441	0.66	0.6	2.49	1.31	2	0.52
440	0.97	0.6	1.91	2.37	—	—
435	0.94	0.5	1.93	6.60	4	0.21
442	0.91	0.5	2.98	3.43	3.1	0.44
454	3.07	1	8.26	2.61	—	—
448	1.18	1	3.56	4.75	8	0.26
453	1.07	0.5	2.96	3.42	—	—
Mean	1.15	0.68	3.54	3.20	4.3	0.47
s.d.	0.77	0.24	2.40	1.48	2.1	0.28

*$P < 0.05$, t-test *vs* controls.
†$P = 0.05$ t-test *vs* controls.

The maximum plasma drug concentration was about 16 times higher in cirrhotics than in controls ($P < 0.01$) but occurred at the same time after drug administration in both groups ($P = 0.56$). The buspirone elimination half-life in cirrhotics was about twice that of the normal subjects ($P = 0.05$). Eight of the cirrhotics and seven of the controls had two peaks in the plasma drug concentration-time curve. The second peak appeared between 4 and 24 h after drug administration in the cirrhotics and between 2 and 8 h after drug administration in the controls. Concentrations of the second peak ranged from 0.10 ng ml^{-1} to 9.58 ng ml^{-1} in the cirrhotics and from 0.21 ng ml^{-1} to 1.03 ng ml^{-1} in the controls.

No significant or systematic changes were seen in the liver blood tests, or ECG during the trial. There was no significant correlation between buspirone AUC and liver blood tests, antipyrine clearance and galactose elimination.

Side effects

Eight of the 24 study participants (three subjects and five patients) reported adverse effects within 20–45 min after dosing. One control subject reported nausea and lack of concentration. The remaining seven subjects experienced one or more episodes of sedation, or both. All events were mild and disappeared within 0.5–4 h after onset, without any treatment.

Discussion

The primary results of this study were that, after a single oral dose of buspirone, both plasma drug concentrations and AUC were approximately 16 times higher in patients with cirrhosis than in healthy subjects.

The results of an oral tracer study in normal subjects (Mayol *et al.*, 1985) indicated complete gastrointestinal absorption, but only 1–10% of the dose reached the systemic circulation unmetabolized. It seems unlikely that the differences in AUC values are due to changes in absorptive capacity between normal subjects and patients with cirrhosis. A high degree of hepatic shunting and moderate decreased hepatic elimination is the most likely explanation of the 16-fold elevated buspirone peak concentration and the moderately decreased elimination half-life in patients with cirrhosis.

The large first pass effect implies that the normal liver has a high intrinsic buspirone metabolism capacity and that the extraction ratio is greater than 0.7. This would place buspirone in the flow-limited hepatic clearance class (Blaschke, 1977). Therefore, reduction in hepatic blood flow in patients with hepatic cirrhosis should contribute to the decreased elimination rate.

The secondary plasma drug peaks indicate some biliary excretion of intact buspirone, but excretion apparently is not influenced by the severity of the cirrhosis as evaluated by antipyrine clearance and galactose elimination. The absence of differences between patients and controls in secondary peaks would seem to exclude cholestasis as a factor in the changes in apparent buspirone clearance.

Buspirone AUC could not be correlated with liver function markers such as serum albumin levels, antipyrine clearance or galactose elimination rate, indicating a different effect of cirrhosis on the synthesis or metabolism of these substances.

On the kinetic evidence from this study buspirone should be used with caution in liver disease.

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