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Oral pharmacokinetics of pirenzepine in man following single and multiple doses

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Summary

The relative bioavailability of pirenzepine tablets (50 mg and two 25 mg) was assessed in 18 subjects in a single dose crossover study. The relative bioavailability of the tablet formulations, compared to a 50 mg oral reference solution given in the fasted state, was unity. The parameters of area under the curve, peak pirenzepine plasma concentration and time-to-peak demonstrated no significant difference for tablet formulations as compared to a 50 mg oral reference solution. After single oral dosing, the harmonic mean half-life of pirenzepine was 10.2 h. The mean renal clearance of 110 ± 12 ml/min approximated glomerular filtration rate. Twelve of the 18 subjects were administered the 50 mg tablet every 8 h for 6 days to assess the multiple dose pharmacokinetics of oral pirenzepine. Drug accumulation to steady state occurred within 4 half-lives as predicted from single dose data. The harmonic mean half-life of pirenzepine after multiple oral dosing was 12.4 h.

Introduction

During the last decade, the pharmacological treatment of peptic ulcer has been directed toward the selective inhibition of gastric acid secretion and enhancement of mucosal defense systems. H_2-receptor antagonists and antacids have become the cornerstone of therapy (Grossman, 1981). Although effective in the inhibition of acid secretion, the therapeutic use of conventional antimuscarinic drugs in duodenal ulcer disease has met with marginal success, primarily limited by well known side-effects. In contrast to the classic anti-muscarinic drugs, pirenzepine, a drug compound being studied in clinical trials for the treatment of duodenal ulcer, exhibits selectivity at a molecular level by distinguishing between subclasses of anti-muscarinic receptors (Hammer et al., 1980; Giachetti et al., 1982; MacIntosh, 1983). Animal pharmacology data have shown pirenzepine to be a potent inhibitor of gastric acid secretion, with minimal anti-muscarinic effects on other organs when compared to other anticholinergic compounds (Heathcote and Parry, 1980; Sewing et al.,

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1982). In equipotent doses, pirenzepine has a lower affinity for smooth muscle than either hyoscyamine or atropine (Jaup et al., 1980; Jaup et al., 1981; Jaup et al., 1982). In therapeutic doses, pirenzepine has fewer side-effects than conventional anti-muscarinic drugs (Jaup et al., 1980; Jaup et al., 1982; Dent et al., 1983), inhibiting gastric secretion at much lower doses than those required to inhibit salivation or smooth muscle contraction and produce tachycardia (Baron et al., 1980; Hammer et al., 1980). The addition of pirenzepine to an H_2-antagonist may provide a potentially powerful antisecretory combination, useful for patients who do not respond to conventional doses of an H_2-antagonist (Feldman, 1984). Pirenzepine may also exhibit gastric cytoprotective activity. This mechanism remains to be elucidated (Del Soldata et al., 1982; Konturek et al., 1982).

The pharmacokinetics of pirenzepine in man after single dose intravenous administration have been described (Hammer et al., 1977a, Hammer et al., 1979). The triexponential decline of plasma pirenzepine is characterized by two rapid phases with half-lives of approximately 5 and 40 min, and a slower terminal phase with a half-life of approximately 10 h. The pharmacokinetics of pirenzepine after multiple oral dosing have not been extensively described. The present studies were undertaken to develop a model consistent with the pharmacokinetics of pirenzepine in normal volunteers after single and multiple oral dosing, utilizing the therapeutic regimen chosen for U.S. clinical trials.

Materials and Methods

Eighteen healthy male volunteers between the ages of 22 and 29 years were selected for a single dose bioavailability study. Twelve of these volunteers then participated in the multiple dose pharmacokinetic study. Informed consent was obtained and clinical protocols were approved by the Institutional Review Board, using the principles set forth for human investigation (Federal Register, 1981).

Prior to enrollment in the study, a medical history was taken and physical examination (including ECG) performed. Subjects were accepted into the study if their clinical laboratory tests (blood and urine) were within normal limits.

No medications were taken by the subjects for 14 days prior to or during either investigation. No coffee, tea, cola or alcoholic beverages were consumed for 24 h prior to the start of each study or until specimen sampling was completed.

To determine the relative oral bioavailability of pirenzepine, a single 50 mg tablet (Gastrozepin, manufactured by Boehringer Ingelheim Pharmaceuticals, Ridgefield, CT), two 25 mg tablets (Gastrozepin, Dr. Karl Thomae GmbH, F.R.G.) and a 50 mg pirenzepine reference solution (Boehringer Ingelheim Pharmaceuticals) were given orally with 6 oz. of water, following a 10 h fast. Drug administration was single dose, open label crossover with at least one week washout between administration of each formulation.

Blood samples were collected prior to and 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10, 12, 24, 36 and 48 h after administration of each pirenzepine formulation. Urine samples following drug administration were collected at 4 h intervals for the first 12 h, followed by 12 h intervals up to 48 h.

To determine the multiple dose pharmacokinetics of pirenzepine, 50 mg tablets (Gastrozepin, Boehringer Ingelheim Pharmaceuticals) were administered at least 0.5 h prior to meals at 8 h intervals for 144 h (6 days) with 6 oz. of water. Blood samples were collected immediately before starting the dosage regimen, and 0.5, 1, 1.5, 2, 2.5, 3, 4 and 6 h after the first dose. Further blood samples were collected immediately before the second, fourth, fifth, seventh, eighth, tenth and twelfth doses (at 144 h) with intensive sampling at 144.5, 145, 145.5, 146, 146.5, 147, 148, 150, 152, 156, 168, 180, 192 and 204 h. On days 1 and 6 (intensive sampling periods) the subjects were fasted for at least 10 h prior to dosing in the same manner as in the single dose bioavailability study.

Blood samples (7 ml) were drawn using an evacuated heparinized tube and inverted at least five times for proper mixing of heparin and blood. Blood samples were centrifuged at 2000 rpm for at least 3 min to obtain plasma. The plasma and urine samples were immediately frozen and stored at approximately $-20°C$ until analyzed. Con-

centrations of pirenzepine in plasma and urine were quantitated by a sensitive and specific radioimmunoassay (Bozler, 1978; Homon et al., 1985).

The area under the plasma concentration-time curve ($AUC_{0 \rightarrow 48h}$) for each subject and each formulation were calculated by the trapezoidal rule in the single dose study. In 14 subjects, the plasma levels were below detectable limits by 48 h. For the remaining 4 subjects with detectable levels, the final plasma concentration was divided by the terminal phase rate to correct for the $AUC_{48h \rightarrow \infty}$. Renal clearance was determined by dividing the urinary excretion rate for pirenzepine during each collection interval by the plasma concentration at the interval midpoint. Pharmacokinetic parameters for multiple dosing were calculated using an iterative curve-fitting and simulation procedure (Hammer et al., 1977b) on a WANG 2200 computer. The data were weighted by a function representative of the random error of the radioimmunoassay. Multiple test statistics were performed utilizing a general linear models procedure with a Bonferroni simultaneous multiple determination to assure a joint significance level of 5% (Miller, 1981; SAS, 1982).

Results and Discussion

The relative oral bioavailability of the three pirenzepine formulations studied was found to be similar. There was no significant difference between area under the curve, peak, or peaktime following administration of the pirenzepine 50 mg tablet, the two 25 mg tablets, or the 50 mg solution. Mean area under the curve, mean peak concentration and mean time to peak for each formulation are summarized in Table 1. The power of detecting a 20% difference in this study between a manufactured formulation and the oral reference solution with $\alpha = 0.05$ was 0.8.

Total plasma clearance of pirenzepine is divided equally between renal and biliary mechanisms (Hammer et al., 1979). Due to the hydrophilic nature of pirenzepine, oral absorption is incomplete (Hammer et al., 1979), and mean cumulative amounts of pirenzepine recovered in the urine represented excretion of only 6–7% of the total dose administered. The fastest rate of excretion was in the 4–8 h interval corresponding to peak plasma levels. Mean renal clearance of pirenzepine (Table 2) was 110 ± 12 ml/min ($n = 18$). As reported previously (Hammer et al., 1979), the renal clearance of pirenzepine approximates the glomerular filtration rate. The harmonic mean terminal half-life was 10.2 h (range 8.7–15 h), in agreement with published intravenous data (Hammer et al., 1979). From intravenous studies, a peripheral tissue compartment, approximating 125 liters is considered to be a depot compartment contributing to the elimination half-life. The apparent volume of distribution of the central compartment corresponds to the extracellular space in man of approximately 14 liters (Hammer et al.,

TABLE 1

MEAN AREA UNDER THE CURVE, MEAN PEAK CONCENTRATION AND MEAN TIME-TO-PEAK FOR PIRENZEPINE IN PLASMA FOLLOWING SINGLE ORAL ADMINISTRATION OF 50 mg TREATMENTS

Parameter	Reference solution	2 × 25 mg tablets	% of oral reference solution	50 mg tablet	% of oral reference solution
Area under the curve 0 → 48 h (ng · h/ml)	477 (226) [a]	546 (194)	115	470 (120)	98
Peak concentration (ng/ml)	33 (18)	36 (4)	108	32 (12)	97
Time-to-peak (h)	4.2 (2.1)	4.3 (1.5)	102	4.5 (1.7)	107

[a] Mean of 18 subjects with standard deviations in parentheses.

TABLE 2

COMPILATION OF SINGLE AND MULTIPLE DOSE PHARMACOKINETIC PARAMETERS FOR PIRENZEPINE IN THE 18 SUBJECTS STUDIED

Single dose [a]							Multiple dosing [b]								
Subject identification	C_p^{max} (ng/ml)	t_{max} (h)	$AUC_{0\rightarrow\infty}$ (ng·h/ml)	β (h^{-1})	$t_{1/2}$ (h)	Cl^{c}_{renal} (ml/min)	C_p 8 h (ng/ml)	$C^{min\ d}_{P_{ss}}$ (ng/ml)	$C^{max}_{p\ day\ 6}$ (ng/ml)	t_{max} (h)	$AUC^{ss}_{0\rightarrow\tau}$ (ng·h/ml)	β (h^{-1})	$t_{1/2}$ (h)	AR [e] predicted	AR actual
1	51	1	656	0.064	10.8	112	26	93	80	1	548	0.050	13.9	1.9	3.6
2	22	6	426	0.079	8.7	86	18	34	50	1	385	0.044	15.8	1.6	1.9
3	39	4	521	0.079	8.7	109	14	28	55	2	378	0.059	11.7	1.6	2.0
4	28	4	474	0.055	12.7	100	19	50	77	6	550	0.055	12.6	2.3	2.6
5	21	5	298	0.073	9.5	129	30	29	47	1	330	0.055	12.6	1.7	1.0
6	35	1.5	587	0.046	15.0	96	26	54	87	4	626	0.038	18.2	2.7	2.1
7	35	6	505	0.075	9.2	112	19	37	54	0.5	336	0.060	11.5	1.7	1.9
8	56	4	598	0.069	10.0	120	19	32	39	8	283	0.063	11.0	1.8	1.7
9	17	6	285	0.060	11.5	118	13	37	46	2	336	0.069	10.0	2.1	2.8
10	17	4	365	0.059	11.6	103	15	30	32	0.5	224	0.045	15.4	2.1	2.0
11	24	8	453	0.079	8.7	103	27	52	76	1.5	534	0.069	10.0	1.6	1.9
12	28	5	470	0.079	8.7	134	47	42	47	4	328	0.066	10.5	1.6	0.9
13	35	6	501	0.067	10.4	97	–	–	–	–	–	–	–	–	–
14	23	5	373	0.081	8.6	110	–	–	–	–	–	–	–	–	–
15	35	5	514	0.075	9.2	126	–	–	–	–	–	–	–	–	–
16	21	5	312	0.060	11.5	107	–	–	–	–	–	–	–	–	
17	35	4	590	0.062	11.1	111	–	–	–	–	–	–	–	–	–
18	53	2.5	732	0.077	9.0	109	–	–	–	–	–	–	–	–	–
x ± S.D. (1–12)			470	0.068	10.2 [f]	110					405	0.056	12.4 [f]	1.9	2.0
			(115)	(0.011)		(14)					(127)	(0.010)		(0.3)	(0.7)
x ± S.D. (1–18)			481	0.069	10.1 [f]	110					–	–	–	–	
			(125)	(0.010)		(12)									

[a] 50 mg single oral dose.

[b] 50 mg every 8 h for 6 days.

[c] Uncorrected as protein binding was considered to be minimal.

[d] $C^{min}_{P_{ss}}$ min calculated from mean of data at 48, 56, 72, and 144 h.

[e] Accumulation ratio; predicted from single dose kinetics.

[f] Harmonic mean.

1979). Using the pharmacokinetic model of Hammer et al. (1979), an estimate of absolute bioavailability in this single dose study would be approximately 10–15%. If pirenzepine plasma clearance is equally divided between renal and biliary mechanisms, approximately 5–8% of the dose should be recovered in the urine. The urinary recovery of 6–7% of the total dose in this study is in agreement with previous investigators.

Although intravenous pharmacokinetic studies have suggested a 3-compartment model for pirenzepine (Hammer et al., 1979), following both single and multiple oral dosing the ability to discern this multi-compartmental characteristic of pirenzepine decreases. The plasma concentration–time curves for orally administered pirenzepine appear biexponential (Fig. 1), suggesting complete distribution within the time frame of absorption.

A comparison of plasma concentrations following single and multiple oral dosing of pirenzepine in 12 subjects (Table 2) showed linear accumulation kinetics for the 50 mg dose. Accumulation ratios obtained in the 12 subjects were consistent with the ratios predicted from the single dose study. The area under the curve ($AUC_{0\rightarrow\infty}$) following single dose was not significantly different from the area under the curve at steady-state for one dosing interval ($AUC_{0\rightarrow\tau}$). The percent coefficient of variation for $AUC_{0\rightarrow\infty}$, $AUC_{0\rightarrow\tau}$ and Cp_{min} was approximately 30% for the population regardless of the number of doses administered.

There was a statistically significant difference (paired t-test; $P < 0.05$) between the half-life following a single dose (harmonic mean $t_{1/2} = 10.2$ h) and the half-life following multiple dosing (harmonic mean $t_{1/2} = 12.4$ h), however, the clinical significance of this 2 h increase in pirenzepine half-life with multiple dosing is expected to be minimal. The effect on accumulation was negligible, explained in part by the decrease seen in area under the curve upon multiple dosing. There appeared to be a decrease in the oral absorption of pirenzepine with multiple dosing. Pirenzepine absorption is known to be reduced by food (Matzek et al., 1985). Pirenzepine did not, however, appear to delay gastric emptying in the twelve subjects studied as mean time-to-peak concentration following multiple dosing (2.6 ± 2 h) was less than the mean time-to-peak following a single dose (4.5 ± 2 h). It has been reported that oral administration of pirenzepine at therapeutic dosages does not inhibit gastrointestinal, interdigestive motility

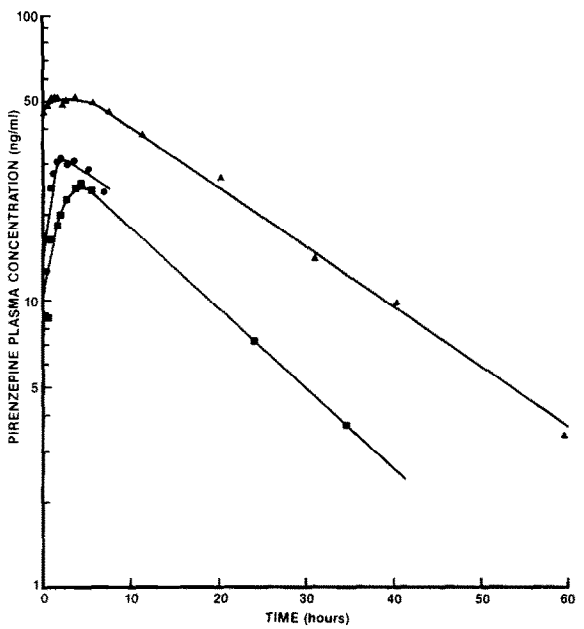

Fig 1. Pirenzepine mean plasma concentration–time profiles for 12 subjects following a single 50 mg oral dose (■) and 50 mg given every 8 h — first dose 0–8 h (●); and last dose 144–204 h (▲).

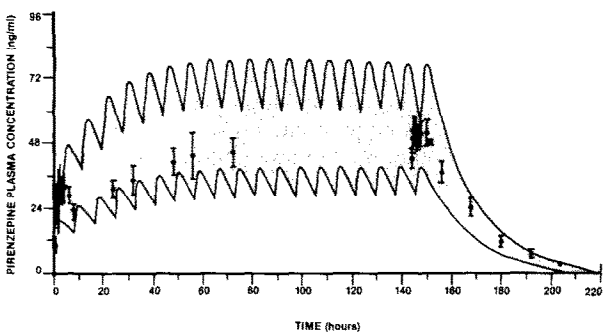

Fig. 2. Mean pirenzepine plasma concentration–time profile for 12 subjects showing the consistent accumulation to steady-state (Cp_{min} sampled on days 2, 3 and 4) after dosing every 8 h for 6 days. The overall coefficient of variation for the 12 subjects was approximately 30% (shaded region) for Cp_{min} and $AUC_{0\rightarrow\tau}$. (Means ± S.E.M.).

in man (Lederer et al., 1982), and has no effect on gastric emptying (Corinaldesi et al., 1982), although Stacher et al. (1982) found the gastric emptying rate after 50 mg of oral pirenzepine was on the mean 30% slower than after placebo. The clinical significance of delayed gastric emptying is not known, nor is the effect pirenzepine may have on its own absorption.

Greater than expected variability in the oral absorption of pirenzepine may account for the differences seen in Subjects 1 and 12 as compared to the studied population (Table 2). Subject 1 appeared to have absorbed a large fraction of the fourth and seventh doses, however, the Cp_{min} for this subject was comparable to the rest of the population by the sixth day of multiple dosing. Subject 12 absorbed a large fraction of the first dose such that there was no discernable accumulation. The variability in absorption appeared to have no adverse effect on the pharmacokinetic profile of these 2 subjects. By the sixth day of dosing, plasma levels from these 2 subjects were comparable to the other 10 subjects studied. Clinically, pirenzepine has been shown to be efficient in healing duodenal ulcers utilizing a regimen of 50 mg three times a day over a 28-day course of therapy (Laugier, 1982). For a hydrophilic drug with incomplete absorption pirenzepine exhibits remarkably consistent kinetics at steady state (Fig. 2) with linear accumulation over 4 half-lives (approximately 48 h) and a 30% coefficient of variation for absorption.

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