CIMETIDINE—A CLINICAL AND PHARMACOKINETIC STUDY

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- 1 The effect of six months therapy with cimetidine (800 mg or 1600 mg/day) and subsequent withdrawal was studied in 19 patients with duodenal ulceration.
- 2 The overall rates of healing were 63% and 79% of patients after 3 and after 6 months of treatment respectively. The longer course (6 months) or the higher dose (1600 mg) did not result in significantly increased rates of ulcer healing.
- 3 Abrupt withdrawal of cimetidine resulted in the recurrence of severe symptoms in 15 patients (79%).
- 4 Pharmacokinetic studies showed the mean elimination half-life of cimetidine to be 100 ± 25 min, the total body cimetidine clearance 652 ± 223 ml/min, the mean volume of distribution at steady state 65 ± 18 l and the overall bioavailability 78%.
- 5 Long term cimetidine treatment does not result in drug accumulation or changes in its pharmacokinetic profile.
- 6 Inter-individual differences in clinical and endoscopic response to cimetidine cannot be explained by pharmacokinetic differences.

Introduction

Cimetidine is widely prescribed for the treatment of duodenal ulcer. It relieves symptoms and accelerates ulcer healing (Bodemar & Walan, 1976; Gray, Smith, McKenzie, Crean & Gillespie, 1977).

The aims of our study were to determine the pharmacokinetic profile of cimetidine in patients with active duodenal ulcer and to investigate whether interindividual differences in pharmacokinetics contribute to a poor response to treatment.

Methods

Patients with radiologically proven chronic duodenal ulcer and severe symptoms not controlled by antacid were considered for selection. Patients were excluded if there were symptoms of pyloric stenosis, recent gastrointestinal bleeding or a history of surgery for peptic ulcer. Patients were also excluded if they had any other illness requiring concomitant drug therapy

or if they had abnormalities in routine biochemical or haematological investigations.

Active duodenal ulceration was confirmed by endoscopy on each patient. Informed written consent was obtained from each subject. The study was approved by the Area Ethical Committee.

Design

Treatment with cimetidine was randomly allocated in one of two doses, 800 mg or 1600 mg daily, in a double-blind design. Patients were treated continuously with cimetidine for 6 months, attending hospital every 2 weeks for 8 weeks and thereafter at monthly intervals. A supply of antacid tablets was also issued to all participants at the start of the study. At each visit a record was made of symptoms, antacid consumption, cigarette smoking, alcohol intake and weight. Unused tablets were counted and laboratory investigations repeated. Endoscopy was repeated

after 3 months and after 6 months treatment. Cimetidine was stopped after 6 months of therapy irrespective of symptoms or endoscopy appearances. Patients were thereafter seen at regular intervals.

Differences in clinical features between the two groups were analysed by unpaired *t*-tests. Differences in endoscopic evidence of healing were assessed by the Chi-square test.

Pharmacokinetic studies

Each patient participated in a single oral dose study on three separate occasions—before treatment, after 3 months and after 6 months of therapy and also in a single intravenous bolus study after cessation of the 6 month course of treatment. On each occasion venous blood samples were taken at intervals for 6 h after administration of the cimetidine dose. Samples were stored in lithium heparin tubes at -20°C . Whole blood cimetidine concentrations were measured by high pressure liquid chromatography (Randolph, Osborne, Walkenstein & Intoccia, 1977).

Pharmacokinetic analysis

Intravenous bolus administration Cimetidine blood concentration data proved to be best represented by a biexponential equation delineating a two compartment open model (see equation 1 below and Figure 1). The equation was fitted to the data using an iterative procedure employing a modification of the Gauss-Newton non-linear least squares technique (Hartley, 1961) using an IBM 370 digital computer.

$$C_1(t) = Ae^{-\alpha t} + Be^{-\beta t} \quad (\text{eq 1})$$

C_1 is the concentration of drug in compartment 1, i.e. blood concentration; α , β are fast and slow disposition rate constants, and A and B are constants such that $A + B = C_1$ at time zero. The precision of each parameter estimated was established by calculating its 'asymptotic' standard deviation (Boxenbaum, Riegelman & Elashoff, 1974) and hence the per cent coefficient of variation ($\text{CV} = \text{s.d.}/\text{parameter} \times 100$).

Each experiment was analysed according to three weighting schemes (Boxenbaum *et al.*, 1974; Wagner 1975) i.e., $W_i = 1$, $W_i = 1/Y_i$ and $W_i = 1/Y_i^2$. The final choice was then made on the basis of several criteria, such as the median % CV, plots of the observed concentration time points with the model predicted line drawn through the points, the standard deviations of the estimated parameters, and the consistency of the estimated parameters from subject to subject.

Oral administration Cimetidine blood concentration data could not be represented by a simple linear model, because absorption was often non-continuous,

giving rise to more than one peak concentration in several cases (Figure 2). Areas under the concentration time curves were estimated by interpolating the data by Spline and Akima methods (Fried & Zietz, 1973) before integrating between points.

The area beyond the last datum point was treated as an extension of the β phase slope, as in equation 1:

$$\int_T^{\infty} C_1 dt = \frac{C_1(T)}{\beta} \quad (\text{eq 2})$$

where $C_1(T)$ is the blood concentration at some time T after dosing when the absorption and primary distribution of the drug are negligible. Where β was not directly calculable from the orally administered cimetidine concentration time curve, the parameter was obtained from the intravenous kinetics curve.

A similar procedure was used to compensate for circulating drug present before the test dose was given. Hence:

$$\int_0^{\infty} C_1 dt = \text{AUC} + \frac{C_{1(T)} - C_{1(0)}}{\beta} \quad (\text{eq 3})$$

where AUC is the calculated area from time 0 to time T, at which times the concentrations of drug are $C_{1(0)}$ and $C_{1(T)}$ respectively.

The peak(s) of the interpolated curve was taken as the maximum concentration achieved, and the time taken to reach this peak recorded.

Results

Nineteen patients (16 men, 3 women) completed the study. The mean length of ulcer history was 10.8 years (range 1–24). Nine patients received 800 mg cimetidine daily and ten patients received 1600 mg daily. Comparison of the groups showed no important differences in sex ratio, age, length of history, cigarette consumption and alcohol consumption or initial endoscopy appearances. Compliance with therapy was satisfactory throughout.

No unexpected symptoms or signs attributable to cimetidine developed during the study. No abnormality was seen in routine biochemical or haematological testing apart from minor fluctuations in serum creatinine.

Ulcer symptoms and ulcer healing

Complete relief of ulcer pain was achieved within a few days of starting cimetidine in both groups. Only one patient continued to take occasional antacids.

Ulcer healing was defined as disappearance on endoscopy of all ulcers and erosions. Neither the higher dose (1600 mg) nor the longer treatment (6 months) produced a statistically significant improvement in

healing when compared to the shorter course or lower dose. After 3 months treatment complete ulcer healing had occurred in six patients in each group (63%). After 6 months of therapy complete healing had occurred in 15 patients (800 mg—6 patients, 1600 mg—9 patients). Two patients with ulcers healed at 3 months had developed asymptomatic ulcers at 6 months.

Follow up

Patients were followed up for a mean of six months (range 2–12) after stopping treatment. Fifteen patients (79%) suffered recurrence of severe symptoms (Table 1). The mean time interval between stopping cimetidine and symptomatic relapse was 9 weeks (range 1–21) and was similar in the two groups.

The patients who developed new ulcers while continuing on therapy (patients 03, 15—Table 1) suffered recurrence of severe symptoms within 48 h of stopping cimetidine.

Pharmacokinetic analysis

Complete data were obtained in 16 patients (Table 1). Analysis of variance of the area under the concentration-time curve per unit dose of cimetidine showed no significant differences between the two dosage groups, between patients who had healed and who had not, between the three oral dose studies or between patients who suffered rapid symptomatic relapse and those who did not (Table 2; Figures 1, 2).

The mean elimination half-life of cimetidine was 100 ± 25 min, the the total body cimetidine clearance

Table 1 Clinical and pharmacokinetic results in sixteen patients receiving cimetidine for duodenal ulcer

Patient	Daily dose (mg)	Endoscopy 3 months	Endoscopy 6 months	Symptom recurrence after cessation of treatment	AUC/100 mg cimetidine—oral mean of 3 ($\mu\text{M min}$)	AUC/100 mg cimetidine—intravenous bolus ($\mu\text{M min}$)	$T_{1/2}$ (min)	V_{dss} (l)	Total body clearance of cimetidine (ml min^{-1})
04	800	NH	H	Yes	691.0	592.4	62	41.0	670
07	800	H	H	Yes	527.3	715.2	92	50.5	556
09	800	H	H	Yes	403.8	571.2	97	74.5	695
15	800	H	NH	Yes	685.0	958.1	146	70.3	414
16	800	H	H	No	540.4	597.9	145	94.8	668
17	800	H	H	Yes	494.3	814.9	121	60.3	487
03	1600	H	NH	Yes	523.3	532.8	91	70.1	745
05	1600	NH	H	No	384.1	458.8	81	74.4	865
06	1600	H	H	No	483.0	314.1	72	94.4	1264
08	1600	H	H	Yes	548.0	642.4	122	70.3	618
10	1600	NH	H	Yes	467.3	866.0	96	49.4	472
11	1600	H	H	Yes	553.2	553.5	113	89.6	717
12	1600	H	H	Yes	450.9	473.8	66	53.0	839
13	1600	H	H	Yes	476.4	764.0	93	55.9	520
14	1600	NH	H	Yes	509.7	652.6	92	62.1	608
18	1600	NH	H	Yes	728.6	1368.1	119	36.3	290

H = healed, NH = not healed

Table 2 The mean ($\pm$ s.e. mean) area under the plasma concentration-time curve/100 mg cimetidine ($\mu\text{M min}$). Comparison of groups in relation to dosage, endoscopic healing and treatment periods.

	Oral 1 Pretreatment	Oral 2 3 months	Oral 3 6 months	Intravenous bolus	Bioavailability Mean oral % bolus
800 mg group	509 $\pm$ 49	727 $\pm$ 112	522 $\pm$ 46	708 $\pm$ 62	83
1600 mg group	509 $\pm$ 43	511 $\pm$ 47	518 $\pm$ 54	663 $\pm$ 93	77
Healed 3 and 6 months (n = 9)	458 $\pm$ 42	492 $\pm$ 41	535 $\pm$ 40	605 $\pm$ 51	77
Unhealed 3 months (n = 5)	538 $\pm$ 49	612 $\pm$ 104	517 $\pm$ 103	788 $\pm$ 159	84
Unhealed 6 months (n = 2)	707 $\pm$ 6	554 $\pm$ 128	551 $\pm$ 131	720 $\pm$ 213	84

Comparison of groups in relation to dosage, endoscopic healing and treatment periods.

Figure 1 Cimetidine plasma concentration-time curves after administration of 100 mg intravenous bolus. Δ Patient 08, $\circ$ patient 06 (All other patients lay between these limits).

Figure 2 Cimetidine plasma concentration-time curves after oral dosing with 200 and 400 mg (initial and 6 months values). Δ 400 mg time 0, $\blacktriangle$ 400 mg 6 months, $\circ$ 200 mg time 0, $\bullet$ 200 mg 6 months.

652 ± 223 ml/min, the mean volume of distribution at steady state 65 ± 18 l and the overall bioavailability 78%.

Discussion

This study is the first to correlate clinical and endoscopy findings with repeated pharmacokinetic studies in patients receiving cimetidine for duodenal ulceration.

Symptomatic response was rapid and the two doses of cimetidine (800, 1600 mg/day) had similar effects. Prolongation of therapy beyond 3 months to 6 months was no more effective in the relief of symptoms and produced only a small improvement in ulcer healing. Of particular interest were two patients with asymptomatic re-ulceration despite continued therapy with cimetidine. The recurrence of severe symptoms in 15 of the 19 patients so soon after stopping either dose of cimetidine is disappointing. Low-dose maintenance cimetidine therapy may prevent such symptomatic relapse (Blackwood, Maudgal & Northfield, 1978).

Our pharmacokinetic results, taken alone, are in keeping with other studies in animals, normal subjects (Burland, Duncan, Hesselbo, Mills, Sharpe, Haggie & Wyllie, 1975) and patients with duodenal ulcer (Bodemar, Norlander, Fransson & Walan, 1979). The discontinuous absorption of cimetidine after oral dosing has been noted previously (Bodemar *et al.*, 1979) although the explanation is unclear. Enterohepatic circulation of cimetidine has been thought to be insignificant (Spence, Celestin, de la Guardia, McMullen & McCormick, 1977) and delayed intestinal absorption the more likely. However, a recent publication (Pedersen & Miller, 1980) suggests that the observed effects may indeed be due to recycling phenomena between cimetidine located in the gut and in a depot compartment. If this explanation is true, and if (as stipulated by the model used) this recirculation occurs to a much greater extent after oral administration of the compound, then the

measurement of bioavailability as the ratio of areas under the intravenous and oral curves becomes less valid. The error incurred in such estimates will be greater the greater the difference in the extent of recycling following oral and intravenous administration. It is perhaps significant that the bioavailabilities calculated by Pedersen & Miller (1980) for cimetidine by the usual model-independent method of ratios and using their specific recirculation model are very similar (61% and 64% respectively). Published values for bioavailability of cimetidine range from 62% in healthy volunteers (Walkenstein, Dubb, Randolph, Stote & Intoccia, 1978) to 100% (Grahnen, von Bahr, Lindström & Rosén, 1979). Our mean value of 78% is compatible with these results and our study has the advantage of having been conducted in patients with duodenal ulcer.

Our data on cimetidine clearance support the view that renal tubular secretion may be a principal route of elimination of cimetidine. Cimetidine did not accumulate with chronic dosing in our patients and the pharmacokinetic profile did not change over the 6 months of the study.

Despite some limitations in the presence of significant enterohepatic circulation, AUC remains a valuable index of overall drug absorption and offered the most appropriate means in our study of comparing groups. We also compared peak concentrations and times to peak concentrations but these provided no additional information.

Our clinical experience and kinetic data show that there is no correlation between cimetidine pharmacokinetics and clinical response to the drug or relapse. A variable proportion of patients with duodenal ulcer fail to respond to cimetidine despite high doses and prolonged courses, or relapse very quickly after treatment is stopped. This study shows that pharmacokinetic factors are unlikely to account for these unfavourable responses.

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