Cimetidine does not alter ibuprofen kinetics after a single dose

K. A. CONRAD, M. MAYERSOHN & MARLA BLISS

Colleges of Medicine and Pharmacy, University of Arizona, Tucson, Arizona, USA

Cimetidine does not slow the disappearance of ibuprofen from the serum after a single dose in healthy male volunteers. This suggests that no change in ibuprofen dosing is necessary when cimetidine is co-administered.

Keywords cimetidine ibuprofen

Introduction

Cimetidine has been shown to impair the hepatic metabolism of a number of compounds (Sorkin & Darvey, 1983). It has been proposed that cimetidine inhibits microsomal oxidation mediated by cytochrome P-450. In addition, cimetidine may reduce hepatic blood flow (Feely *et al.*, 1981). These effects produce increased plasma levels of the compounds involved thereby making toxicity more likely.

Ibuprofen is frequently given to patients with chronic inflammatory arthritis. These patients often develop gastritis or peptic ulceration, but their underlying disease requires continued anti-inflammatory medication for relief of symptoms. Cimetidine has been shown to prevent gastritis due to nonsteroidal anti-inflammatory agents and aspirin in animals (Mann & Sachdev, 1977). Furthermore, healing of salicylate-induced ulcers has been shown with cimetidine despite continued administration of aspirin (O'Laughlin *et al.*, 1981). Anti-ulcer medications, including cimetidine, are often used to treat gastrointestinal symptoms produced or aggravated by anti-inflammatory drugs, including ibuprofen.

Because ibuprofen is extensively metabolized by hydroxylation and carboxylation in the liver (Mills *et al.*, 1973; Lockwood *et al.*, 1983), we designed this study to determine if cimetidine alters the hepatic metabolism of ibuprofen.

Methods

Six non-smoking male volunteers, age 23–32 years, weight 66–86 kg, were studied. These

volunteers were judged to be healthy on the basis of a medical history, physical examination, and serum chemistries including BUN, creatinine, bilirubin, SGOT, and alkaline phosphatase. None ingested excessive quantities of alcohol or caffeine.

Ibuprofen, as Motrin® 400 mg tablets, was given by mouth with 250 ml of water on two separate occasions. During the experimental phase, ibuprofen was given after 1 week's pretreatment with cimetidine (Tagamet®), 300 mg orally every 6 h. Cimetidine was continued throughout the duration of blood sampling for ibuprofen. On another occasion, ibuprofen was administered without concomitant cimetidine ingestion. The sequence of the trials was randomized, and experiments were separated by 2 weeks.

Serum for ibuprofen determinations was collected from an indwelling venous catheter before administration of ibuprofen and at 0.25, 0.5, 0.75, 1.0, 1.25, 1.5, 1.75, 2.0, 2.5, 3.0, 3.5, 4.0, 5.0, 6.0, 8.0 and 10.0 h after ibuprofen was ingested. Prior to sampling 1 ml of blood was obtained and discarded. After each sample was collected, the venous cannula was flushed with 0.5 ml heparinized saline. Blood was centrifuged; the serum was separated and frozen at –20°C until assayed.

Ibuprofen was extracted from serum samples using the procedure described by Lockwood & Wagner (1982). The internal standard (ibufenac) was added to the serum sample to produce a concentration of 25 µg/ml. Plasma concentrations were determined by high pressure liquid chromatography using a mobile phase of methanol:water (80:20) containing phosphoric

acid (1 ml/l). The mobile phase was passed through a reverse phase column (Ultrasphere ODS, 5 microns, 25 cm $\times$ 4.6 mm internal diameter, Altex Scientific Inc., Berkeley, CA) at a rate of 1.5 ml/min. The drug was detected at 220 nm and quantitation was achieved with reference to a standard curve of peak height ratio (ibuprofen/internal standard) vs ibuprofen concentration. The retention times of ibuprofen and internal standard were 4.5 and 5.5 min respectively. The standard curve was linear and reproducible over the concentration range of 1 to 70 $\mu\text{g/ml}$ ibuprofen. The between-day coefficient of variation at 5 $\mu\text{g/ml}$ was 6.9%. Standard curves were run whenever samples were processed.

The ibuprofen serum concentration-time data were plotted on semi-logarithmic graph paper and a value for the terminal elimination rate constant (k_{el}) was obtained from linear regression analysis of the data in the post-absorption, post-distribution phases. The elimination half-life ($t_{1/2,z}$) was calculated from the rate constant of elimination, $t_{1/2,z} = 0.693/k_{\text{el}}$. The area under the ibuprofen serum concentration-time curve from time zero (or from the first measurable concentration) to the last measurable concentration was determined by the linear trapezoidal rule. The remaining area from the last measurable point to time infinity was determined by dividing the concentration at the last time point (on the regression line) by k_{el} . The sum of these two areas gave the total area under the curve (AUC). Statistical comparisons of k_{el} and AUC were made with the Student's *t*-test.

Results

The results of the study are summarized in Table 1 and Figure 1. The average ($\pm$ s.d.) area

under the serum concentration time curve for ibuprofen was $135 \pm 21 \mu\text{g ml}^{-1} \text{ h}$ when ibuprofen was given alone and $139 \pm 16 \mu\text{g ml}^{-1} \text{ h}$ when cimetidine was co-administered with ibuprofen. These results were not significantly different ($P > 0.05$). The average ($\pm$ s.d.) elimination rate constant for ibuprofen was $0.364 \pm 0.068 \text{ h}^{-1}$ when ibuprofen was given alone and $0.361 \pm 0.037 \text{ h}^{-1}$ when cimetidine was coadministered ($P > 0.05$). The elimination half-life of ibuprofen given alone was 1.9 h; this value was unchanged when cimetidine was co-administered.

Discussion

Cimetidine reduces the hepatic metabolism of a large number of drugs which are metabolized by hepatic function oxidases. This effect is most likely due to inhibition of cytochrome P-450 in hepatic microsomes. Ibuprofen is extensively metabolized by the liver to a hydroxy metabolite and to a carboxy metabolite. Conjugated forms of these metabolites can also be measured in human urine. The hydroxy and carboxy metabolites and the conjugated forms of these metabolites appear in the urine in a ratio of 1:2 (hydroxy:carboxy). Cimetidine did not change the disappearance from the serum of the parent compound. This probably occurs because cimetidine does not affect either the hydroxylation or the carboxylation of ibuprofen. It is well known that cimetidine does not directly affect glucuronidation (Mojaverian *et al.*, 1982; Sorkin & Darvey, 1983). We did not measure the urinary metabolites of ibuprofen in this study, so we are unable to determine if there is any change in the pattern of metabolite formation when cimetidine is given with ibuprofen.

Table 1 Pharmacokinetic parameters of ibuprofen in the absence (Ib) and presence (Ib/Cim) of cimetidine

Subject	k_{el} (h^{-1})		$t_{1/2,z}$ (h)		AUC ($\mu\text{g ml}^{-1} \text{ h}$)	
	Ib	Ib/Cim	Ib	Ib/Cim	Ib	Ib/Cim
1	0.496	0.412	1.40	1.68	98.9	132.5
2	0.338	0.359	2.05	1.93	140.8	1145.1
3	0.340	0.349	2.04	1.99	142.9	150.4
4	0.362	0.385	1.91	1.80	141.2	140.7
5	0.302	0.302	2.29	2.29	161.7	154.3
6	0.344	0.360	2.01	1.93	124.8	110.8
Mean	0.364	0.361	1.90*	1.92*	135.0	139.0
$\pm$ s.d.	0.068	0.037			21.2	15.8

k_{el} —first-order elimination rate constant, $t_{1/2,z}$ —terminal elimination half-life, AUC—area under the plasma concentration-time curve from 0 to infinity,

* Harmonic mean.

Figure 1 Ibuprofen plasma concentration-time curves for each subject after a single oral 400 mg dose of ibuprofen in the absence (●) and presence (■) of cimetidine. The solid line represents the linear regression equation of the data in the post-absorption, post-distribution phase.

The results of this single dose study suggest that co-administration of cimetidine to patients receiving ibuprofen should not produce any

change in the serum concentrations of ibuprofen, nor should any dosage modifications be required.

References

- Feely, J., Wilkinson, G. R. & Wood, A. J. J. (1981). Reduction of liver blood flow and propranolol metabolism by cimetidine. *New Engl. J. Med.*, **304**, 692-695.
- Lockwood, G. F. & Wagner, J. G. (1982). High performance liquid chromatographic determination of ibuprofen and its major metabolites in biological fluids. *J. Chromatog.*, **232**, 335-343.
- Lockwood, G. F., Albert, K. S., Gillespie, W. R., Bole, G. G., Harkcom, T. M., Szpunar, G. J. & Wagner, J. G. (1983). Pharmacokinetics of ibuprofen in man. I. Free and total area/dose relationships. *Clin. Pharmac. Ther.*, **34**, 97-103.
- Mann, N. S. & Sachdev, A. J. (1977). Acute erosive gastritis induced by aspirin, ketoprofen, ibuprofen, and naproxen: its prevention by metiamide and cimetidine. *Southern med. J.*, **70**, 562-564.
- Mills, R. F. N., Adams, S. S., Cliffe, E. E., Dickinson, W. & Nicholson, J. S. (1973). The metabolism of ibuprofen. *Xenobiotica*, **3**, 589-598.
- Mojaverian, P., Fedder, I. L., Vlasses, P. H., Rotmensch, H. H., Rocci, M. L., Swanson, B. N. & Ferguson, R. K. (1982). Cimetidine does not alter morphine disposition in man. *Br. J. clin. Pharmac.*, **14**, 809-813.
- O'Laughlin, J. C., Silvano, G. R. & Ivey, K. J. (1981). Healing of aspirin-associated peptic ulcer disease despite continued salicylate ingestion. *Arch. int. Med.*, **141**, 781-783.
- Sorkin, E. M. & Darvey, D. L. (1983). Review of cimetidine drug interactions. *Drug Intell. Clin. Pharmac.*, **17**, 110-120.

(Received March 16, 1984,
accepted June, 2, 1984)