CONCURRENT ADMINISTRATION OF CIMETIDINE AND ENTERIC-COATED PREDNISOLONE: EFFECT ON PLASMA LEVELS OF PREDNISOLONE

The histamine H₂-receptor antagonist cimetidine is widely used in the treatment of peptic ulcer. Although the evidence that prednisolone therapy results in peptic ulceration is disputed (Conn & Blitzer, 1976), enteric-coated prednisolone tablets, which have been claimed to reduce gastro-intestinal irritation (Kammerer, Freilberger & Rivelis, 1958) are commonly used. It is therefore conceivable that cimetidine and prednisolone might be used concurrently. Enteric-coated preparations are designed to resist the acid gastric fluids and to disrupt or dissolve in the intestine. Cellulose acetate phthalate, the enteric coating used on the brand of prednisolone employed in the present study, is 'insoluble' at pH 1 to 3 but 'soluble' at pH 5 to 7 (Gibaldi, 1977). Alteration of gastric pH by concurrent cimetidine administration might therefore also alter the biopharmaceutical performance of the enteric coating thereby changing the dissolution and bioavailability of the preparation.

A study was undertaken in six healthy adult volunteers (three males, three females, ages 24–36 years, body weights 48–68 kg) to investigate the effects of concurrent cimetidine treatment on the bioavailability of enteric-coated prednisolone.

This study was a randomized double-blind crossover and subjects were allocated to one of the following treatments.

(i) 10 mg enteric-coated prednisolone (as 2 × 5 mg Deltacortril®, Pfizer, Sandwich, Kent) following 5 days treatment with cimetidine (Tagamet®, Smith Kline & French, Welwyn Garden City, Herts) 200 mg three times a day after meals and 400 mg at bedtime. Cimetidine was continued for 24 h after the dose of prednisolone.

(ii) 10 mg enteric-coated prednisolone following 5 days treatment as above but with placebo tablets matching cimetidine which were continued for 24 h after the dose of prednisolone.

After a period of at least 7 days the subjects received the alternative treatment. Smoking and caffeine-containing drinks were not permitted on treatment days. On each treatment day subjects were given a standard breakfast of toast, margarine, marmalade and 300 ml of decaffeinated coffee. They then received the appropriate treatment regime, the cimetidine being given 30 min before the prednisolone. Subjects remained ambulant throughout the day and received a standard meal 4 h after dosing and were allowed water at any time after

dosing. Samples of venous blood (15 ml) were collected at appropriate times after dosing and plasma and whole blood samples were stored at –20°C pending analysis for prednisolone and cimetidine respectively. Plasma prednisolone concentrations were estimated by high performance quantitative thin-layer chromatography with fluorodensitometry (Morrison, Bradbrook & Rogers, 1977). Whole blood cimetidine levels were measured by the Biochemistry Department, Smith, Kline & French Laboratories Research Institute, Welwyn Garden City, Herts, by high pressure liquid chromatography (Randolph, Osborne, Walkenstein & Intoccia, 1977).

Areas under the plasma concentration-time curves (AUC) were calculated using a computerized Spline-Akima method for curve smoothing (Fried & Zietz, 1973). The apparent first order rate constants of the decline of the terminal phases of the plasma prednisolone-time curves were obtained from least squares linear regression of ln (plasma concentration) against time: regressions were performed with the last three data points and then the last four, the last five, etc. until a maximum value for the correlation coefficient was estimated.

Figure 1 shows the mean values for the plasma prednisolone concentrations and the blood cimetidine concentrations. The overall impression given by this plot that the concurrent administration of cimetidine does not importantly alter the absorption of prednisolone is borne out by statistical analysis, but the plot obscures the inter-individual differences observed. For prednisolone the mean AUC for concurrent placebo treatment was 1861 ng ml⁻¹h (s.d. 700) and for concurrent cimetidine treatment was 1893 ng ml⁻¹h (s.d. 880). Cross-over analysis of variance showed no significant differences between cimetidine or placebo treatments ($P > 0.2$). There did, however, appear to be a significant order of treatment effect ($P \approx 0.01$) since the three subjects who received placebo treatment first developed lower plasma prednisolone levels than those who received cimetidine first. There was no significant difference between the subjects within the treatment order groups. The peak plasma prednisolone concentrations recorded were 338 ng ml⁻¹ (s.d. 124) for placebo treatment and 340 ng ml⁻¹ (s.d. 173) on cimetidine. Cross-over analysis of variance showed that again there was a significant treatment order effect ($0.01 < P < 0.05$), but there was no between

Figure 1 Mean blood cimetidine concentrations during multiple dosing schedule (see text) and mean plasma prednisolone concentrations following 10 mg enteric coated prednisolone administered to six normal subjects with cimetidine (●) and placebo (○).

treatment effect ($P > 0.2$). The mean times at which peak prednisolone concentrations occurred were 4.8 h (s.d. 1.3) for placebo and 5.3 h (s.d. 0.5) for cimetidine. Cross-over analysis of variance demonstrated no significant difference between treatments ($P > 0.2$) or between treatment order effects ($0.1 < P < 0.2$). The mean times to first detection of prednisolone in the plasma were 4.3 h (s.d. 1.4) for placebo and 3.7 h (s.d. 1.0) for cimetidine. There was no significant difference between treatment order effects ($0.1 < P < 0.2$) or between treatments ($P > 0.2$). Figure 1 shows shorter lag times than these means since prednisolone was detected in the plasma at 2 h in one subject on both treatments.

The mean first order elimination rate constants were 0.280 h^{-1} (s.d. 0.091) for placebo treatment and 0.263 h^{-1} (s.d. 0.05) for cimetidine treatment. These were not significantly different ($t = 0.55$; $0.6 < P < 0.7$). The mean $T_{1/2}$ values for prednisolone were 2.48 h and 2.64 h respectively.

As the subjects were taking cimetidine prior to the administration of prednisolone, it was necessary to analyse the AUCs for cimetidine during the first four hours dosage interval. Again a treatment order effect was noted in that those subjects who received cimetidine as their second treatment had a mean AUC of $3.75 \mu\text{g ml}^{-1} \text{ min}$, whilst those receiving cimetidine first had a mean AUC of

$9.06 \mu\text{g ml}^{-1} \text{ min}$. These differences were significant ($t = 5.22$, $P < 0.001$).

No significant alterations in haematology or biochemistry were observed during the study and no adverse reactions were reported.

There are theoretical reasons for anticipating alterations in the absorption and bioavailability of drugs concurrently administered with cimetidine. We have, however, failed to demonstrate a clinically significant effect on the absorption of orally administered tetracycline (Fisher, House, Inns, Morrison, Rogers & Bradbrook, 1980). A preliminary report by Sternberg, King & Toskes (1978) has described inhibition of the absorption of protein bound vitamin B_{12} by cimetidine although the clinical importance of this observation has not been established. Other mechanisms of interaction may also occur and Breckenridge, Challiner, Mossman, Park, Serlin, Sibeon, Williams & Willoughby (1979) have reported an increased anticoagulant effect of warfarin apparently on the basis of inhibition of warfarin metabolism.

Concurrent administration of food does not affect the absorption of enteric-coated prednisolone (Lee, Taylor, Walker & James, 1979). Similarly, food does not reduce cimetidine bioavailability (Bodemar, Norlander, Fransson & Walen, 1979). As is seen from Figure 1, the mean blood concentration of cimetidine was maintained above $1 \mu\text{g ml}^{-1}$ virtually throughout the study. This implies adequate suppression of gastric acid secretion since the cimetidine concentration required to produce a 50% reduction of maximal histamine-induced acid output is $0.5 - 1 \mu\text{g ml}^{-1}$ (Burland, Duncan, Hesselbo, Mills, Sharpe, Haggie & Wyllie, 1975).

The plasma levels of prednisolone attained following the administration of 10 mg enteric-coated prednisolone are broadly comparable with previous data reported by ourselves (Morrison *et al.*, 1977) and others (Lee *et al.*, 1979). The half-life is also similar to that found in our previous work and was unaltered by cimetidine suggesting that no gross change in prednisolone disposition is produced by the latter drug.

A relatively large inter-individual variation in plasma prednisolone levels, as has been noted previously (Lee *et al.*, 1979; Morrison *et al.*, 1977), was present in this data. The effect of order of cimetidine administration on prednisolone AUC could be explained by the chance inclusion of three subjects who are relatively poor drug absorbers in the group receiving cimetidine second. This hypothesis is strengthened by the finding that these same three subjects were also 'poor' absorbers of cimetidine. The absorption characteristics of the volunteers were consistent and subjects designated as 'poor' absorbers retained this characteristic in both parts of the experiment.

The values for prednisolone AUC, $C_{\max}$ or $t_{\max}$ were unaltered by previous and concurrent cimetidine administration although there was less scatter of the timing of peak concentrations of prednisolone when taken with cimetidine. It thus appears that administration of cimetidine under circumstances similar to those in which it is used by patients does not alter the bioavailability of prednisolone from an enteric-coated formulation. Possibly the results may be extended further, to similar enteric-coated tablets.

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References

- BODEMAR, G., NORLANDER, B., FRANSSON, L. & WALEN, A. (1979). The absorption of cimetidine before and during maintenance treatment with cimetidine and the influence of a meal on the absorption of cimetidine—studies in patients with peptic ulcer disease. *Br. J. clin. Pharmac.*, **7**, 23–32.
- BRECKENRIDGE, A.M., CHALLINER, M., MOSSMAN, S., PARK, B.K., SERLIN, M.J., SIBEON, R.G., WILLIAMS, J.R.B. & WILLOUGHBY, J.M.T. (1979). Cimetidine: interaction with warfarin in man. *Br. J. clin. Pharmac.*, **8**, 392–393p.
- BURLAND, W.L., DUNCAN, W.A.M., HESSELBO, T., MILLS, J.G., SHARPE, P.C., HAGGIE, S.J. & WYLLIE, J.H. (1975). Pharmacological evaluation of cimetidine, a new histamine H_2 -receptor antagonist, in healthy man. *Br. J. clin. Pharmac.*, **2**, 481–486.
- CONN, H.O. & BLITZER, B.L. (1976). Nonassociation of adrenocorticosteroid therapy and peptic ulcer. *N. Engl. J. Med.*, **294**, 473–479.
- FISHER, P., HOUSE, F., INNS, P., MORRISON, P.J., ROGERS, H.J. & BRADBROOK, I.D. (1980). Effect of cimetidine on the absorption of orally administered tetracycline. *Br. J. clin. Pharmac.*, **9**, 153–158.
- FRIED, J. & ZIETZ, S. (1973). Curve fitting by Spline and Akima methods: possibility of interpolation error and its suppression. *Phys. Med. Biol.*, **18**, 550–558.
- GIBALDI, M. (1977). *Biopharmaceutics and clinical pharmacokinetics*, p. 49. Philadelphia: Lea & Febiger.
- KAMMERER, W.H., FREIBERGER, R.H. & RIVELIS, A.L. (1958). Peptic ulcer in rheumatoid patients on corticosteroid therapy. *Arth. Rheum.*, **1**, 122–141.
- LEE, D.A.H., TAYLOR, G.M., WALKER, J.G. & JAMES, V.H.T. (1979). The effect of food and tablet formulation on plasma prednisolone levels following administration of enteric-coated tablets. *Br. J. clin. Pharmac.*, **7**, 523–528.
- MORRISON, P.J., BRADBROOK, I.D. & ROGERS, H.J. (1977). Plasma prednisolone levels from enteric and non-enteric coated tablets estimated by an original technique. *Br. J. clin. Pharmac.*, **4**, 597–603.
- RANDOLPH, W.C., OSBORNE, V.L., WALKENSTEIN, S.S. & INTOCCIA, A.T. (1977). High pressure liquid chromatographic analysis of cimetidine, a histamine H_2 -receptor antagonist in blood and urine. *J. pharm. Sci.*, **66**, 1148–1150.
- STERNBERG, W., KING, C. & TOSKES, P. (1978). Cimetidine inhibits the absorption of protein-bound vitamin B_{12} but not crystalline vitamin B_{12} . *Gastroenterology*, **74**, 1099.

ACUTE CARDIAC FAILURE DURING TREATMENT WITH DIGITOXIN—AN INTERACTION WITH RIFAMPICIN

Rifampicin has been shown experimentally to induce hepatic enzymes and thereby increase the rate of metabolism of drugs that are hydroxylated (Zilly, Breimer & Richter, 1977). In clinical practice rifampicin has been seen to interact with coumarin drugs (Michot, Bürgi & Büttner, 1970; O'Reilly, 1975), digitoxin (Peters, Hausamen & Grosse-Brockhoff, 1974), oral contraceptives (Nocke-Finck, Breuer & Reimers, 1973) and cortisol (Edwards, Courtenay-Evans, Galley, Hunter & Tait, 1974). The clinical observations published are few, however, and we therefore wish to report a case presenting

dramatic symptoms of an interaction between rifampicin and digitoxin.

The patient was a 59-year-old woman with a history of pulmonary tuberculosis in the 1930s and urogenital tuberculosis. Leftsided heminephrectomy was undertaken in 1941 and rightsided total nephrectomy in 1942. Hypertension developed during the 1950s. In 1975 renal failure was diagnosed, which gradually increased during the following years and necessitated treatment with chronic intermittent haemodialysis. Symptoms of cardiac failure in the form of exercise dyspnoea developed. On treatment