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CONCURRENT ADMINISTRATION OF ANTACIDS AND PREDNISONE: EFFECT ON SERUM LEVELS OF PREDNISOLONE

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1 Specific radioimmunoassays have been developed for the measurement of prednisolone and prednisone in serum.

2 Serum prednisolone levels have been measured following the administration of prednisone both with and without antacids.

3 There were no significant differences in the values of C_{max} (mean ± s.d.) (251 ± 80 ng/ml with, 245 ± 69 ng/ml without antacid), AUC (1430 ± 469 ng ml^{-1} h^{-1} with, 1406 ± 530 ng ml^{-1} h^{-1} without antacid) or T_{max} (1.6 ± 0.6 h with, 1.6 ± 0.8 h without antacid).

4 Serum prednisone levels were less than 20% of prednisolone levels at all time intervals in the subjects studied.

5 Concurrent antacid administration has no significant effect on serum prednisolone levels attained.

Introduction

There are considerable data demonstrating that antacids may interfere with drug absorption by interactions within the gut lumen (Harvey, 1975). Indeed, some antacids have been shown to be as effective as cholestyramine with regard to binding properties (Clain, Malagelada, Chadwick and Hoffman, 1977). Antacid compounds are frequently administered concurrently with corticosteroids (Fenster, 1973), in the belief that they reduce dyspeptic symptoms, despite evidence that antacids are no better than placebo for the relief of dyspeptic symptoms (Peterson, Sturoevant & Frankl, 1977; Hollander & Harlan, 1973). It is possible that any effect of concurrent administration of antacids on symptoms is secondary to alteration of serum levels of corticosteroids, rather than the result of any local gastric effect. We have therefore measured serum levels of prednisolone following an oral dose of prednisone in seven subjects. In each subject the prednisone has been administered alone and on a separate occasion with a standard dose of antacid.

Methods

Prednisone was administered to the seven subjects after informed consent had been obtained and prednisolone serum levels were measured. There were two healthy subjects and five subjects who all suffered from chronic neurological diseases for which steroid therapy was being used. None of the subjects had any gastrointestinal disease known to alter drug absorption. Each subject was studied on two separate occasions, initially without antacids and 48 h later taking 20ml 'Gastrogel' (aluminium hydroxide 250 mg, magnesium trisilicate 120 mg and magnesium hydroxide 120 mg per 5 ml) together with the prednisone. Each subject served as his own control. Prednisone was administered orally at 08.00 h to the subjects who had fasted from midnight after a baseline blood sample had been taken. Blood samples were then taken at 0.5, 1, 2, 3 and 6 h following this dose. The subjects with neurological disease all received 10 mg prednisone. To assess any difference resulting from higher dosages the healthy subjects were given 20 mg prednisone but were otherwise treated identically.

Prednisolone levels were measured by a specific radioimmunoassay (Caffin, Halliday & Powell, 1978). Samples of serum (0.1 ml) were extracted with 1 ml of ethanol, the ethanol was then removed by evaporation to dryness in a vacuum oven and the serum extract was redissolved in assay buffer. To each tube, 0.5 ml of antiserum diluted 1:400 to 1:1000 (depending on titre) was added, mixed and incubated at room temperature for 30 m. [^{3}H]-prednisolone in assay buffer (0.1 ml) was then added to all tubes which were mixed and further incubated at room temperature for 1.5 h and at 4°C for 18 h. Unbound steroid was removed by the addition of 0.2 ml charcoal suspension

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to each tube followed by centrifugation at 4°C for 5 min at 2000 *g*. The supernatant (0.5 ml) was placed in a scintillation vial for determination of radioactivity. Extracted steroid-free plasma containing known amounts (0–600 pg) of prednisolone provided the standard curve. Antiserum has been raised to prednisolone-21-hemisuccinate/bovine serum albumin conjugates in rabbits. The cross reactivity of this antiserum with prednisone and endogenous steroids has been shown to be less than 10%. In two subjects prednisone levels were also measured at each time interval using a similar method to that outlined above but using a specific antiserum against prednisone.

A time-concentration curve has been plotted in each instance and from this the following data have been determined, the peak serum concentration (C_{max}), the peak time (T_{max}), the elimination half-life ($T_{\frac{1}{2}}$ of the terminal slope) and area under plasma concentration : time curve extrapolated to infinity (AUC). Statistical analyses have been performed on each instance and from this the following data have been determined, the peak serum concentration (C_{max}), the peak time (T_{max}), the elimination half-life ($T_{\frac{1}{2}}$ of the terminal slope) and area under plasma concentration : time curve extrapolated to infinity (AUC). Statistical analyses have been performed on each pair of results using Wilcoxon's ranking test for matched samples.

Results

There were marked differences in C_{max} dependent on the dose administered and also reflecting inter-individual variation (range 169–392 ng/ml) (Table 1). However the values were remarkably constant for each individual on separate occasions (251 ± 80 ng/ml with antacid, 245 ± 69 ng/ml without antacid). Concurrent antacid administration has not shown any significant alteration of the C_{max}.

Values for AUC, reflecting the total amount of drug absorbed, were similarly variable, depending on the dose and individual (range 869–2301 ng ml^{-1} h^{-1}) but the values again remained constant for each individual whether or not antacid was administered (1430 ± 469 ng ml^{-1} h^{-1} with antacid, 1406 ± 530 ng ml^{-1} h^{-1} without antacid).

The values for T_{max} obtained did not show any significant difference (1.60 ± 0.64 with antacid and 1.60 ± 0.76 without antacid). The values for $T_{\frac{1}{2}}$ showed considerable interindividual variation that appears to be independent of dose (range 2.19–5.08 h). There was a trend towards a shorter $T_{\frac{1}{2}}$ in the antacid group but this was statistically insignificant in the numbers studied (3.51 ± 0.63 with antacid, 4.00 ± 0.69 without antacid).

In two patients prednisone levels were measured at each time interval and are tabulated together with the corresponding prednisolone level in Table 2. Prednisone levels represented less than 20% of prednisolone at all plasma levels.

Figure 1 illustrates typical time : concentration curves in subject 5.

Discussion

In this study the values for AUC and C_{max} of serum prednisolone were not altered significantly by the administration of antacids. It therefore appears that

Table 1 Tabulated results determined from time-concentration prednisolone curves for each subject. Column 'a' represents studies with antacid, column 'b' those without antacid. [1] indicates subjects given 20 mg prednisone and [2] subjects given 10 mg prednisone.

Subject	C_{max} *(ng/ml)*		*AUC (ng ml h^{-1})*		T_{max} *(h)*		$T_{\frac{1}{2}}$ *(h)*	
	a	*b*	*a*	*b*	*a*	*b*	*a*	*b*
1[1]	392	356	1928	1809	1.5	2.0	3.85	3.62
2[1]	336	329	2021	2301	2.0	2.5	3.41	3.77
3[2]	214	212	1534	1363	1.0	2.0	4.09	5.08
4[2]	223	230	1608	1579	2.25	2.25	3.34	4.29
5[2]	169	170	1162	968	2.0	1.0	3.84	3.25
6[2]	203	167	889	858	0.5	0.5	3.79	4.05
7[2]	222	251	869	963	2.0	1.0	2.19	2.99
Mean ± s.d.	251 ± 80	245 ± 69	1430 ± 469	1406 ± 530	1.60 ± 0.64	1.60 ± 0.76	3.51 ± 0.63	4.00 ± 0.69

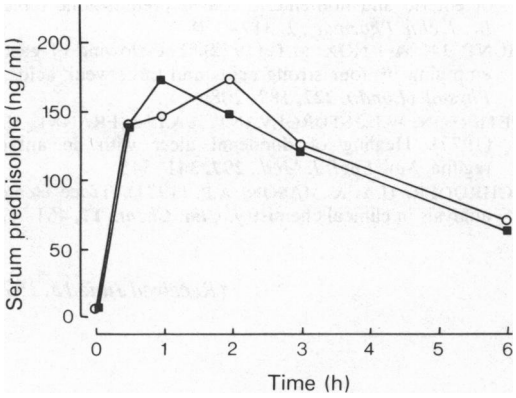

Figure 1 Time-concentration curves of serum prednisolone levels (ng/ml) in subject 5 with (□) and without (■) antacid.

antacids do not influence the bioavailability of prednisone. This is of importance clinically since it confirms that antacid preparations may be given concurrently and that it is not necessary to adjust prednisone dosage. In this study we have looked at concurrent administration of 'Gastrogel' which is a standard aluminium hydroxide/magnesium hydroxide/magnesium trisilicate containing antacid of moderate potency. These observations may be extended to other antacids of similar composition since their binding properties and acid neutralizing ability would be similar.

Table 2 Tabulated results of serum prednisolone concentrations in ng/ml (column 'a') and serum prednisone concentrations in ng/ml (column 'b') at each time interval in subjects 2 and 7.

Time (h)	*Subject 7*		*Subject 2*	
	a	*b*	*a*	*b*
0	22	2	55	6
0.5	152	30	108	7
1.0	251	27	196	23
2.0	172	31	223	26
3.0	145	24	259	29
6.0	75	14	130	23

We have measured prednisolone in this study since it is the biologically active metabolite of prednisone with a glucocorticoid potency of 23 as compared to 0.3 for prednisone, assigning to cortisol the value of 10 (Ballard, Carter & Graham, 1975). When prednisone levels were measured they always represented less than 20% of the prednisolone levels at all dosage levels (Table 2) demonstrating virtually complete hepatic conversion to prednisolone at all levels seen in this study.

Perhaps surprisingly the T_{max} was not altered significantly by antacid administration since alkalinization of the stomach usually results in more rapid gastric emptying (Hunt & Knox, 1972). On the other hand alkalinization might have been expected to delay the dissociation and absorption of prednisone. Recent studies (Hulme, James & Rault, 1975) however have suggested that the site of prednisone absorption is in the upper jejunum where the pH is close to 6. It is therefore not surprising that we did not demonstrate any change in T_{max}. The $T_{\frac{1}{2}}$ in this study has not been significantly altered by antacid administration. The antacid used in this study is regarded as non-systemic although appreciable absorption of aluminium hydroxide containing antacids has been described by some workers (Schroder & Mason, 1971). If components of gastrogel have been absorbed by our subjects, they have not influenced the elimination half-life of prednisolone.

Finally, it has been demonstrated that antacids may accelerate the healing of peptic ulcers (Peterson *et al.*, 1977) but this has only been demonstrated with large regular doses of antacids. It is unlikely that the doses of antacids used in this study would have had any influence on ulcer healing. It is therefore improbable that any change in dyspeptic symptoms in these circumstances would reflect ulcer healing. Thus we have demonstrated that concurrent administration of antacids with prednisone does not alter serum levels of prednisolone attained, and is therefore unlikely to alter therapeutic efficacy.

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