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PLASMA PREDNISOLONE LEVELS IN MAN FOLLOWING ADMINISTRATION IN PLAIN AND ENTERIC-COATED FORMS

C.G. WILSON,* C.S. MAY & J.W. PATERSON

Asthma Research Council Clinical Pharmacology Unit, Department of Medicine, Cardiothoracic Institute, Brompton, London SW3 6HP

1 Prednisolone plasma levels were measured in seven patients by a competitive protein binding method after administration of prednisolone (20 mg) by mouth as plain or enteric-coated tablets.

2 The mean peak plasma prednisolone concentration after the enteric-coated preparation, 199 ng ml^{-1}, was significantly lower than after the plain tablet, 268 ng ml^{-1}, and occurred later, at 4.69 h compared with 1.72 h. The bioavailability of the two preparations was similar.

3 It is concluded that, although the plasma concentration versus time profiles are different, the absorption of prednisolone from plain and enteric-coated preparations is equal.

Introduction

Enteric-coated prednisolone preparations have been found to be equivalent in therapeutic effect to plain tablets in the treatment of rheumatoid arthritis (West, 1959a, 1959b), without the accompanying gastro-intestinal distress associated with prednisolone and similar cortisol analogues (Kammerer, Freiberger & Rivelis, 1958). In the present study, plasma levels of prednisolone were compared following oral administration of prednisolone in enteric-coated ['Deltracortril' 'Enteric' tablets 2.5 mg (Pfizer, Sandwich, Kent)] and plain ['Deltracortil', tablets 5.0 mg (Pfizer, Sandwich, Kent)] forms using the competitive protein binding method of English, Chakraborty & Marks (1974) as modified by Wilson, Ssendagire, May & Paterson (1975).

Methods

Seven patients with various lung disorders who were receiving prednisolone as part of their therapy were studied. None had any clinical evidence of liver disease. Prednisolone plasma levels were measured after an oral dose of prednisolone (20 mg) as enteric-coated and as conventional tablets on two separate occasions.

Prednisolone was suspended for at least 12 h prior to each study and on each day a very light breakfast was allowed at least 1 h before the dose was given. No further food was allowed for 4 hours.

* Present address: Department of Physiology, Medical School, University of Nottingham, Nottingham NA7 2RD.

An indwelling cannula was inserted in a vein on the dorsum of the hand, and an initial blood sample of 10 ml taken. The cannula was flushed with dilute heparin/saline, and before each sample, 2 ml of blood was withdrawn and discarded. 10 ml blood samples were drawn at 0, 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 7 and 8 h after administration of prednisolone (20 mg) by mouth.

The blood was immediately centrifuged and the plasma stored at −30°C until assayed. Plasma prednisolone levels were measured by a competitive protein binding method (Wilson *et al.*, 1975).

Peak plasma prednisolone concentration C_{max} (ng ml^{-1}) and the time of peak concentration T_{cmax} (h) were obtained from the plasma concentration-time profile.

Plasma half-life $T_{\frac{1}{2}}$ (h) was calculated by linear least squares regression analysis, and the elimination rate constant k_{el} (h^{-1}) derived from the equation $k_{el}=0.6932/T_{\frac{1}{2}}$.

The absorption rate constant k_{abs} (h^{-1}) and the lag time for absorption t (h) were obtained by the method of residuals using the first three points of the absorption phase of the plasma concentration time curve (Notari, 1971).

The area under the concentration versus time profile (AUC) was calculated as the sum of (i) the area obtained by cutting out and weighing the profile (t = 0- - - >8 h) drawn on paper of uniform thickness, subsequently converting to units of h ng ml^{-1}, and (ii) the area calculated as the extrapolation of the exponential portion of each curve after the last data point (i.e. AUC from t = 8- - - > ∞).

Table 1 Pharmacokinetic parameters for prednisolone after oral administration as plain and enteric-coated tablets

	Prednisolone (20 mg)													
	Plain tablet							*Enteric-coated*						
Patient	$T_{\frac{1}{2}}$ *(h)*	*AUC (h ng ml^{-1})*	C_{max} *(ng ml^{-1})*	$T_{c\,max}$ *(h)*	t_o *(h)*	(k_{abs}) *(h^{-1})*	(k_{el}) *(h^{-1})*	$(T_{\frac{1}{2}})$ *(h)*	*AUC (h ng ml^{-1})*	C_{max} *(ng ml^{-1})*	$T_{c\,max}$ *(h)*	(t_o) *(h)*	(k_{abs}) *(h^{-1})*	(k_{el}) *(h^{-1})*
1	1.58	435.5	161	2.05	0.6	0.55	0.44	1.60	655.3	152	2.5	1.45	1.12	0.43
2	0.95	424.0	217	1.0	0.35	2.39	0.73	1.26	701.7	166	5.7	3.2	0.96	0.55
3	2.31	1702.4	350	2.5	0.4	1.37	0.30	1.88	1364.6	199	3.2	1.9	0.66	0.37
4	2.01	1525.4	218	3.0	0.1	0.60	0.34	2.31	1159.8	211	6.0	3.3	0.99	0.30
5	1.07	464.0	199	1.05	0.4	4.08	0.65	0.52	384.4	90	4.2	1.55	1.39	1.33
6	4.3	2410.2	325	1.45	0.45	2.31	0.16	2.15	1624.8	336	5.0	3.15	1.31	0.32
7	2.51	2061.1	405	1.0	0	1.54	0.28	2.51	1661.3	236	6.25	2.2	0.51	0.28
Mean ($n=7$)	2.10	1288.9	267.9	1.72	0.33	1.83	0.41	1.75	1078.8	198.6	4.69	2.39	0.99	0.51
								NS	NS	<0.05	<0.01	<0.001	NS	NS

AUC area under the concentration *v.* time profile;
C_{max} peak plasma prednisolone concentration;
$T_{c\,max}$ time of peak concentration;
t_o day time for absorption;
k_{abs} absorption rate constant;
k_{el} elimination rate constant.

Table 2 Plasma prednisolone concentrations (ng ml^{-1}) after oral administration of prednisolone (20 mg) as plain tablets

	Time after administration (h)											
Patient	*0*	*0.5*	*1*	*1.5*	*2*	*2.5*	*3*	*4*	*5*	*6*	*7*	*8*
1	0	10	30	80	160	148	128	86	54	36	20	10
2	0	160	218	166	116	76	50	0	0	0	0	0
3	20	140	220	300	340	350	300	214	157	112	84	66
4	16	70	176	202	214	218	218	211	194	160	108	70
5	0	112	196	160	112	82	65	40	22	8	0	0
6	10	98	250	326	318	298	274	234	203	176	154	132
7	0	366	400	400	375	298	250	190	153	124	100	80
Mean	6.6	135.6	212.9	233.4	233.6	210.7	183.6	139.3	111.9	88.0	66.6	51.1
s.e. mean	3.3	42.5	41.3	42.3	41.7	41.8	38.5	36.0	31.9	27.4	22.8	18.8

Table 3 Plasma prednisolone concentrations (ng ml^{-1}) after oral administration of enteric-coated prednisolone (20 mg)

	Time after administration (h)											
Patient	*0*	*0.5*	*1*	*1.5*	*2*	*2.5*	*3*	*4*	*5*	*6*	*7*	*8*
1	0	0	0	60	120	148	150	114	94	66	40	—
2	0	0	0	0	0	6	46	104	160	164	100	50
3	0	0	0	0	64	170	188	198	190	176	145	100
4	0	0	0	0	0	0	2	111	208	210	184	120
5	0	4	8	24	40	56	70	84	80	68	38	6
6	0	0	0	0	0	0	10	220	336	290	190	140
7	0	0	0	18	36	60	84	140	202	233	228	170
Mean	0	0.6	1.1	14.6	37.1	62.9	78.6	138.7	181.4	172.4	132.1	88.7
s.e. mean	0.0	0.6	1.1	8.5	16.7	26.7	26.2	19.3	32.2	31.3	28.4	22.7

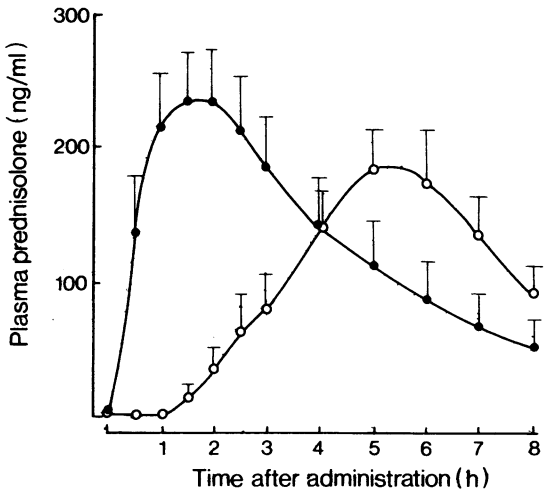

Figure 1 Mean ($n=7$) plasma prednisolone concentrations after oral administration of prednisolone (20 mg) as plain (●) and enteric-coated (O) tablets. Vertical bar lines indicate 1 s.e. mean.

Pharmacokinetic parameters deduced from the plasma-time curves were compared for the same group of patients receiving the two treatments using Student's paired *t*-test.

Results

A summary table of the pharmacokinetic parameters associated with the plain and enteric-coated preparations is presented in Table 1. Curves of the mean plasma levels after enteric-coated preparations were constructed from data obtained for the seven patients and are shown in Figure 1.

The plasma prednisolone level rose rapidly to a mean peak concentration of 268 ng ml^{-1}, 1.72 h after ingestion of prednisolone (20 mg) as the plain preparation.

There was a wide variation in peak plasma prednisolone concentration as has previously been communicated (Wilson *et al.*, 1975). Mean peak levels for the same seven patients after the enteric-coated drug were significantly lower (199 mg ml^{-1}) and appeared later T_{cmax} = 4.69 h). The lag time was similarly longer for the enteric-coated (2.39 h) than for the standard preparation (0.33 h).

There was no difference in the mean elimination rate constants for each preparation, and although the mean absorption rate constants for conventional and enteric-coated preparations appear dissimilar, 1.83 and 0.99 h^{-1}, this difference was not statistically significant.

The mean area under the plasma concentration—time curve for the conventional preparation was 1288.9 h ng ml^{-1}, and for the enteric-coated tablet 1078.8 h ng ml^{-1} (difference NS). Since there was no change in the plasma half-life between studies, the bioavailability of prednisolone from the two preparations was of the same order.

Discussion

Kammerer *et al.* (1958) in early studies of rheumatoid arthritis patients accumulated evidence of peptic ulceration in patients receiving oral corticosteroid therapy. These findings suggested that cortisol analogues effect the stomach wall directly since the incidence of dyspepsia was low in patients receiving corticotrophin or who displayed Cushing's syndrome (West, 1957; Kirsner & Palmer, 1952). These findings led to the development of enteric-coated preparation of cortisol analogues such as prednisolone (West, 1959a, 1959b) which do not release the steroid into the stomach, but at a different site, lower in the gastro-intestinal tract. It is of considerable importance to compare the bioavailability of enteric-coated and standard formulations.

In our studies, we found that the bioavailability of the two preparations was not significantly different, but the mean peak plasma concentration of prednisolone achieved by the enteric-coated form was lower than that after the same dose as conventional tablets. The peak level depends on the amount of drug absorbed, and the rate of absorption, and though neither of these was significantly different for each preparation, both were somewhat less for the enteric-coated form. The combined effect of this accounts for the significant difference in peak level.

Since the experimental studies described in this paper were carried out, similar studies by Leclercq & Copinschi (1974) and Hulme, James & Rault (1975) have appeared in the literature. The former group studied plasma levels following oral dosage of normal male subjects with enteric-coated and plain preparations of prednisolone; the latter group studied renal transplant recipients. Both groups used similar methods of steroid analysis. Leclercq & Copinschi (1974) did not use chromatography to separate steroids in their plasma samples. They therefore had to use dexamethasone to suppress endogenous cortisol and assume that the only thing measured by the assay was prednisolone. In their study plasma levels after either preparation tend to be somewhat higher than our own study; in addition the time at which the peak plasma levels occurs is somewhat different in the two studies. The plasma half-life is longer in their patients with both types of tablets than in our patients. Following enteric-coated tablets, in both studies the peak levels were lower and the time to achieve them was longer.

In the study by Hulme *et al.* (1975) five renal transplant patients were studied after an oral dose of 30 mg of prednisolone as both plain and enteric-coated formulations. These patients had been on chronic prednisolone therapy and chronic therapy with immunosuppressants, in this case azathioprine. It was assumed that the chronic steroid therapy would have led to adrenal suppression and therefore no chromatographic separation of the plasma steroids was employed. In this study there was a big difference between the enteric-coated and the plain preparations in contrast to the other two studies. Also the plasma levels after both plain and enteric-coated prednisolone were higher than in the present study or that of Leclercq & Copinschi (1974). This may well reflect differences in the patient population, differences in the tablet formulation or possibly modification of the intestinal bacteria by chronic immuno-suppression.

Reprint requests should be addressed to Dr C.G. Wilson.

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