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THE EFFECT OF PREDNISONE TREATMENT ON THE HALF-LIFE OF INTRAVENOUS HYDROCORTISONE

GILLIAN M. SHENFIELD & J.W. PATERSON
Asthma Research Council Clinical Pharmacology Unit,
Department of Medicine, Cardiothoracic Institute, Fulham Road, London SW3 6HP

J.F. COSTELLO & O. IJADUOLA
Brompton Hospital, London SW3 6HP

1 The half-life of hydrocortisone (cortisol) has been measured in six patients before and after a three-week course of prednisone given for asthma.

2 There was considerable variation in peak plasma level of cortisol both within and between patients, but on both occasions the plasma half-lives were the same.

3 It was concluded that short courses of prednisone have no effect on the handling of hydrocortisone.

Introduction

Patients may die from asthma without having received adequate corticosteroid treatment (Speizer, Doll & Heaf, 1968). Dwyer, Lazarus & Hickie (1967) suggested that the plasma cortisol level should be elevated to over 100 μg/100 ml to alleviate a severe attack of asthma. They found that in normal subjects and in some asthmatics intravenous injection of 100 mg hydrocortisone (cortisol) readily achieved higher levels than this. However in asthmatics who had received chronic steroid therapy a much higher dose of intravenous hydrocortisone was needed to achieve this plasma level of cortisol. They found that in these patients the metabolic clearance rate of cortisol was always greater than in patients who had not been treated with steroids. Collins, Harris, Clark & Townsend (1970) found no difference in the plasma level measured at 60 min in normal controls, asthmatics, and patients with chronic airways obstruction following intravenous hydrocortisone.

To see whether steroid therapy affects the handling of hydrocortisone, we have measured the distribution and excretion half-lives of cortisol following intravenous injections of hydrocortisone in the same asthmatic patients before and after a short course of prednisone therapy.

Methods

Six patients were studied and the clinical details are outlined in Table 1. The patients had not

Table 1 Clinical details of the patients studied

Patient	*Age (years)*	*Sex*	*Diagnosis*	*Prednisone (mean dose mg/day)*
A.W.	61	F	Intrinsic asthma	13.3
S.K.	19	M	Allergic aspergillosis	30.0
A.B.	62	M	Extrinsic asthma	18.6
E.S.	48	M	Extrinsic asthma	15.0
E.Sp.	59	M	Intrinsic asthma	15.0
G.L.	60	M	Extrinsic asthma	20.0

received any form of corticosteroid in the year preceding the study, and were on no sedation. All were in-patients and were prescribed prednisone for the treatment of their disease. Cortisol half-lives were measured on two separate occasions: the first study was done before starting prednisone therapy and the second exactly three weeks later at the same time of day.

For rapid venous sampling, an indwelling cannula was inserted and the patient was allowed to rest following this. An intravenous injection of hydrocortisone sodium succinate (Organon-London) (4 mg/kg) was given in the opposite arm. Blood samples were taken at 5, 10, 20, 30, 45 min; and 1, 1.5, 2, 3, 4, and 6 h after the injection. The same procedure was carried out for the second study when the patient had taken prednisone for three weeks. In one patient (S.K.) samples were also taken at one minute.

The specimens were immediately placed in heparinized tubes and spun down. Aliquots of plasma (1 ml) were removed and stored at -20°C. They were later analysed for 11-hydroxy-corticosteroids using the fluorimetric method of Mattingly (1962) as recommended by the M.R.C. Working Party (1971). All measurements were done in triplicate.

Results

Table 2 shows the baseline and peak plasma cortisol level, the time at which the peak occurred, and the cortisol half-life for each patient before and after three weeks' treatment with prednisone. The baseline cortisol levels were lower in each patient after three weeks' prednisone treatment, indicating adrenal suppression. The peak plasma level occurred within 10 min in studies carried out before and after prednisone. In patient S.K. where 1 min levels were measured, these were below the 5 min levels on both occasions. It is of interest that there is considerable variation in the peak plasma level achieved. This could not be correlated with the age of the patient, the degree of adrenal suppression, or the previous dosage of prednisone.

Figure 1 illustrates how the data were analysed for each patient. The elimination half-life was calculated by drawing the line of best fit to the plasma level points from 60 min onwards. The distribution half-life was estimated by the method of feathering (Notari, 1971). This was done by extrapolating the elimination curve to zero and then subtracting the values obtained on this curve from the plasma levels measured. The line of best fit was then drawn through the resulting points and the half-life of this was taken as the distribution half-life. This was the same before and after

Table 2 Individual data on plasma cortisol levels following the i.v. administration of hydrocortisone sodium succinate (4 mg/kg) before and after three weeks' treatment with prednisone

	Before prednisone				*After prednisone*			
Patient	*Baseline cortisol (μg/100 ml)*	*Peak cortisol (μg/100 ml)*	*Time of peak (min)*	*$T_{½}$ (min)*	*Baseline cortisol (μg/100 ml)*	*Peak cortisol (μg/100 ml)*	*Time of peak (min)*	*$T_{½}$ (min)*
A.W.	17.5	548	5	90	12.5	638	10	88
S.K.	22.5	227	5	98	5.0	412	5	96
A.B.	20.0	1178	5	110	7.5	714	5	110
E.S.	19.2	800	5	115	2.4	592	5	116
E.Sp.	28.8	513	10	155	14.0	317	10	155
G.L.	21.0	356	10	110	6.0	702	5	120
Mean ± s.e.	21.5	603.7	6.7	113	7.9	562.5	6.7	114.2
	1.61	139.4		9.2	1.8	66.3		9.6

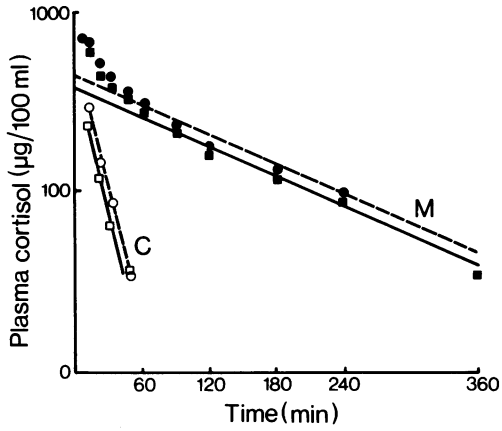

Fig. 1 Patient A.B. Measured (M) plasma cortisol levels after intravenous hydrocortisone sodium succinate (4 mg/kg) before (■) and after (●; dotted line) three weeks' prednisone treatment (18.6 mg/day). Calculated (C) plasma cortisol levels before (□) and after (○; dotted line) three weeks' prednisone treatment.

prednisone, and in the six patients averaged 11.8 min (±1.01 min, s.e. mean).

The elimination half-lives are shown for all patients on both regimes in Table 2. There is variation between patients but individual patients showed the same result before and after treatment with prednisone.

In Table 3, the mean plasma cortisol levels at each time before and after treatment with prednisone are shown (±s.e. mean). It can be seen that the greatest range in plasma levels occurred early after the injection, but that after 60 min the variation in plasma level was much less. The mean elimination half-lives were 113 min before prednisone and 114 min after.

Discussion

The present study has shown that three weeks' treatment with prednisone does not alter the distribution or elimination half-lives of hydrocortisone (cortisol). The similarity in distribution half-lives before and after treatment suggests that there was no change in the volume of distribution of cortisol. Peak plasma levels of cortisol were only reached 5 to 10 min after intravenous injection. This delay probably indicates the time needed for circulating esterases to split hydrocortisone from the sodium succinate salt (James & Landon, 1968). There was no consistent change in these peak levels or the time at which they occurred, suggesting that treatment with prednisone had not caused any alteration in the activity of the esterase enzymes.

There was considerable variation in the peak plasma levels achieved both between and within patients. The variations did not correlate with any parameter measured, but it is possible that they could be explained partly by variations in the speed of injection although in patient S.K. the injections were timed and differences in peak level still occurred. The dose used, 4 mg/kg as recommended by Collins *et al.* (1970), always achieved a plasma level well in excess of 100 µg/100 ml as recommended by Dwyer *et al.* (1967) for the treatment of severe asthma. The latter workers demonstrated an increased metabolic clearance rate of [H^3]-cortisol in asthmatic patients receiving steroid therapy, and found that the 30 min plasma cortisol after an injection of intravenous hydrocortisone was significantly lower in such patients when compared to either normals or asthmatics not receiving steroids. They considered that the increased metabolic clearance rate was due to induction of liver microsomal enzymes and in addition that suppression of adrenocorticotrophic hormone (ACTH) release affected extra-adrenal metabolism of cortisol. Although we found considerable variation in peak plasma levels at 5 and 10 min, there was no significant effect of prednisone treatment and no significant difference at 30 minutes. Thus it would appear that the changes described by Dwyer *et al.* (1967) must take more than three weeks to develop.

Table 3 Mean plasma levels of cortisol (µg/100 ml) following the i.v. administration of hydrocortisone sodium succinate (4 µg/kg) before and after three weeks' treatment with prednisone (n = 6)

	Time (min)										
	5	*10*	*20*	*30*	*45*	*60*	*90*	*120*	*180*	*240*	*360*
Before											
Mean	644	545	431	376	319	278	226	184	125	96	56
s.e. mean	122	60	33	34	23	23	16	20	16	17	10
After											
Mean	602	594	450	393	288	254	192	154	106	80	45
s.e. mean	60	47	28	20	23	19	13	9	8	8	7

An alternative possibility is that Dwyer *et al.* (1967) were studying a more severely ill group of patients. Schwartz, Lowell & Melby (1968) have reported that after intravenous hydrocortisone the drop in eosinophil count at 4 h was only 36% in 'resistant' asthmatics, compared with 77% in less severe cases. They found that the half-life of cortisol in the 'resistant' group was 86 min compared with a half-life of 128 min in the responsive group. Both groups were on steroids but the 'resistant' group were on higher doses. It is thus possible that in severely ill patients cortisol is more quickly cleared. In our own study each patient was used as his own control and this variable was avoided. No change in cortisol clearance was produced by treatment with prednisone.

It is of interest in our own series that after 30 min plasma cortisol levels agree more closely within and between patients, but that prior to this there is wide variation and this is in agreement with the studies of Schwartz *et al.* (1968) and Collins *et al.* (1970). However, in our study we have measured plasma levels earlier than 30 min and here variation is much larger and therefore we would agree with previous workers that in general asthmatic patients in a severe attack should receive very large doses of hydrocortisone of the order of 4 mg/kg to ensure adequate plasma levels. Further work would be necessary to see whether longer treatment with prednisone would affect the distribution and/or elimination half-lives of cortisol in individual patients.

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Requests for reprints to J.W.P.

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