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Single daily dose corticosteroid treatment

Effect on adrenal function and therapeutic efficacy in various diseases

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In the normal subject the level of circulating cortisol is regulated by a feed-back mechanism so that an increase in plasma cortisol results in diminished secretion of corticotrophin by the pituitary. Synthetic corticosteroids act on the feed-back mechanism in a similar manner to endogenous cortisol, and a single dose will inhibit corticotrophin release and hence cortisol production. The degree and duration of pituitary-adrenal inhibition depends on the potency of the preparation, the dose, and the time of administration.

Inhibition following a single corticosteroid dose is a physiological response, and endogenous cortisol will be secreted as soon as the circulating level of administered corticosteroid declines. Furthermore, this inhibition can be overcome by stress or the administration of ACTH, either of which will promptly restore adrenal secretion of cortisol to normal.

Corticosteroid administration in divided doses throughout the day results in repeated episodes of inhibition with little or no intervening periods of autonomous adrenal function. Inhibition thus becomes continuous and may lead to chronic suppression, *i.e.* adrenal suppression which does not spontaneously recover when the administered corticosteroid is withdrawn, and which carries the risk of failure to respond to stress.

Suppression of adrenal function in patients receiving corticosteroid therapy has attracted more attention than any other corticosteroid side-effect as it may lead to failure of cortisol secretion during such stresses as a surgical operation or severe illness. It has been stated that this risk may persist for a year or longer after withdrawal of steroid therapy (Bayliss, 1958).

Attempts have been made to prevent the development of suppression during corticosteroid therapy by administering the drug on alternate days, or even less frequently (Adams, Gold, Gonick, and Maxwell, 1966; Fleisher, 1967).

With intermittent administration, continuous adrenal inhibition may be avoided, and satisfactory therapeutic results have been obtained in asthma and the nephrotic syndrome. It has proved less suitable in rheumatoid arthritis and other painful conditions, because the patients experienced a recurrence of symptoms on corticosteroid-free days.

Nichols, Nugent, and Tyler (1965) showed that administration of a corticosteroid at night, when the cortisol secretion rate is low, causes more profound and prolonged adrenal inhibition than a similar dose given in the morning. Ceresa, Angeli, Boccuzzi, and Molino (1969) consider that corticosteroid administration should take into account their hypothesis that there are two phases of ACTH secretion during the 24 hrs, only one of which, confined to the night, is highly sensitive to the feed-back effect of exogenous corticosteroids.

These reports led us to believe that it might be possible to combine the diminished inhibitory effect of intermittent therapy with the better symptomatic control afforded by daily administration if the corticosteroid were to be given in a single daily dose at a time when its effect on the feed-back mechanism would be minimal, *i.e.* in the morning. This paper reports an initial comparative study of single and divided daily dose therapy.

Methods

Eighteen outpatients were studied. They suffered from various chronic diseases (Table), and were considered to require long-term corticosteroid therapy. Prednisolone was used in every case in a dose of from 8 to 20 mg. daily (mean 12·5). Eight of the patients were already receiving corticosteroids in divided daily doses and ten had not previously received them.

The study proceeded in three phases. In the first the patients received prednisolone in a single daily dose

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Table *Clinical particulars of* 18 *cases*

Case No.	*Sex*	*Age (yrs)*	*Diagnosis*	*Prednisolone daily dose (mg.)*		*Duration of therapy (mths)*			*Grip strength*		*Peak flow rate (l./min.)*		*Synacthen test*	*Preference*
				Range	*Mean*	*Before trial*	*OD*	*BD*	*OD*	*BD*	*OD*	*BD*		
1	F	24	SLE	10	10	4	22	2	560	520			21/28	OD
2	M	59	RA, asthma	12·5	12·5	34	12	2	300	285	200	180	12/23	—
3	M	52	RA	10–15	12·5	—	4	2	600+	600+			—	—
4	F	20	Asthma	10	10	17	10	2			240	250	2/5	—
5	M	61	RA	10	10	4	21	2	540	580			20/38	—
6	M	57	RA	10–20	17	3	7	2	530	510			13/29	—
7	F	48	RA	9	9	32	16	2	245	260			5/15	—
8	F	57	RA, ITP	10–17·5	12·5	6	2	9	535	565			0/5	BD
9	M	56	RA fibrosing alveolitis	15–20	17·5	—	5	2	600+	600+			6/18	—
10	M	68	RA	8	8	—	8	2	530	510			7/29	—
11	F	72	RA	10	10	—	19	2	155	145			18/40	OD
12	M	65	Asthma	15–20	17·5	—	12	2			170	165	20/27	—
13	M	72	Cranial arteritis	15–20	17·5	—	8	2					6/13	—
14	M	63	Asthma	12·5	12·5	—	19	2			105	100	14/25	—
15	M	74	Reiter's disease	20	20	—	6	2					13/17	—
16	M	21	Dermatomyositis	10	10	—	4	2					9/20	OD
17	F	74	RA	8	8	—	9	2	280	255			16/30	—
18	F	70	RA	10	10	10	2	8	160	205			2/5	BD

Notes RA = Rheumatoid arthritis
SLE = Systemic lupus erythematosus
ITP = Idiopathic thrombocytopenic purpura
OD = Single daily dose
BD = Divided daily dose
Duration of therapy OD, includes the first phase of the study, which was two months in all cases, and the final phase.

taken at 10 a.m. for at least 8 weeks. In the second phase the same total daily dose was taken half at 10 a.m. and half at 10 p.m. for 8 weeks. The third phase was a return to the single daily dose regime exactly similar to the first and the patients were followed for a mean of 12 months (range 4 to 26). Two patients had a definite preference for the second regime of divided dosage and did not enter the third phase.

The patients were seen at intervals of 4 weeks or less between 9 and 11 a.m. for clinical assessment. The measurements recorded in rheumatoid arthritics were combined strength of grips of both hands, and in asthmatics the peak flow rate. In three patients (Case 13, 15, and 16—see Table), no simple objective test was available, but all patients were asked their opinion of the effectiveness of the treatment.

Blood was taken for plasma cortisol estimation at 10 a.m. before the morning dose of corticosteroid, at the start of the trial and thereafter at least once every 4 weeks. Cortisol was determined fluorimetrically (Spencer-Peet, Daly, and Smith, 1965). This method determines total fluorogenic corticosteroids, but the term plasma cortisol will be used here in the interest of brevity.

Synthetic corticotrophin tests were performed on all patients except Case 3 at the end of phase 3 of the study, using the intramuscular injection of 0·25 mg. Synacthen (Ciba), as described by Wood, Frankland, James, and Landon (1965).

Results

Treatment by a single daily dose was at least as effective as the divided daily dose regime in sixteen of the eighteen patients, judged by patient preference and clinical assessment (Table). Two patients (Cases 8 and 18), who had been receiving steroids in divided dosage before admission to the trial, had a clear preference for the divided daily dose regime, whereas three (Cases 1, 11, and 16) definitely preferred the single daily dose. The remainder considered that they were doing equally well on either regime.

The 10 a.m. plasma cortisol levels found during each regime are shown in Fig. 1. On the single daily dose regime the results were widely scattered, but the majority came within the normal morning range of 5 to 25 μg./100 ml. Nevertheless the mean of 11·6 μg./100 ml. (S.D. 6·4) compared with the normal mean in our laboratory of 17 μg./100 ml. suggests some degree of adrenal inhibition. On the divided dose regime almost all the individual results were below the normal range, showing a greater degree of inhibition: the mean plasma cortisol of 3·0 μg./100 ml. (S.D. 4·2) is significantly lower ($P < 0·005$) than on the single dose regime.

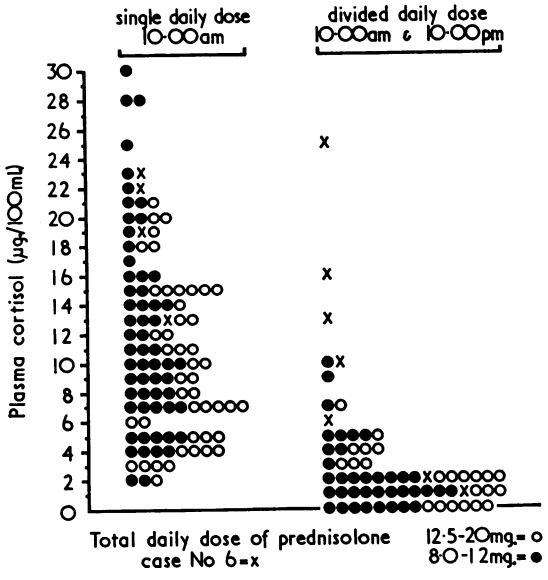

FIG. 1 *Plasma cortisol values at* 10 *a.m. during single and divided dose therapy.*

If the patients receiving 12·5–20 mg. prednisolone daily are considered separately, then the mean 10 a.m. plasma cortisol is 10·7 μg./100 ml. (S.D. 5·8) for the single dose, compared to 4·0 (S.D. 5·5) ($P < 0.005$) for the divided dose regime. Similarly, for the patients receiving 8·0–12·0 mg. prednisolone, the mean plasma cortisol is 12·2 μg./100 ml. (S.D. 6·8) for the single dose compared to 2·3 (S.D. 2·5) ($P < 0.005$) for the divided dose regime. This shows that the difference in the degree of depression of plasma cortisol between the single and divided dose regimes is not related to differences in the total daily prednisolone dosage over the range examined, but that, on the contrary, a large dose given once daily is less inhibitory to the plasma cortisol than a smaller quantity given in a divided dose.

One patient (Case 6), whose results are plotted individually in Fig. 1, behaved differently from the other patients in that his plasma cortisol was usually not below the normal range even on the divided dose regime, despite his being on one of the higher dose levels (see Table).

Fig. 2 shows the mean plasma cortisol levels of individual patients on each dose regime. Every subject showed a marked fall in level when on the divided dose, with recovery when he was restored to the single daily dose regime.

The mean rise in plasma cortisol 30 min. after synthetic corticotrophin was 10·8 μg./100 ml. (S.D. 6·1) compared with the mean of 18 μg./100 ml. found in normal subjects in our laboratory. The minimum normal rise is 7 μg./100 ml. Thus, as a group, the subjects studied showed diminished

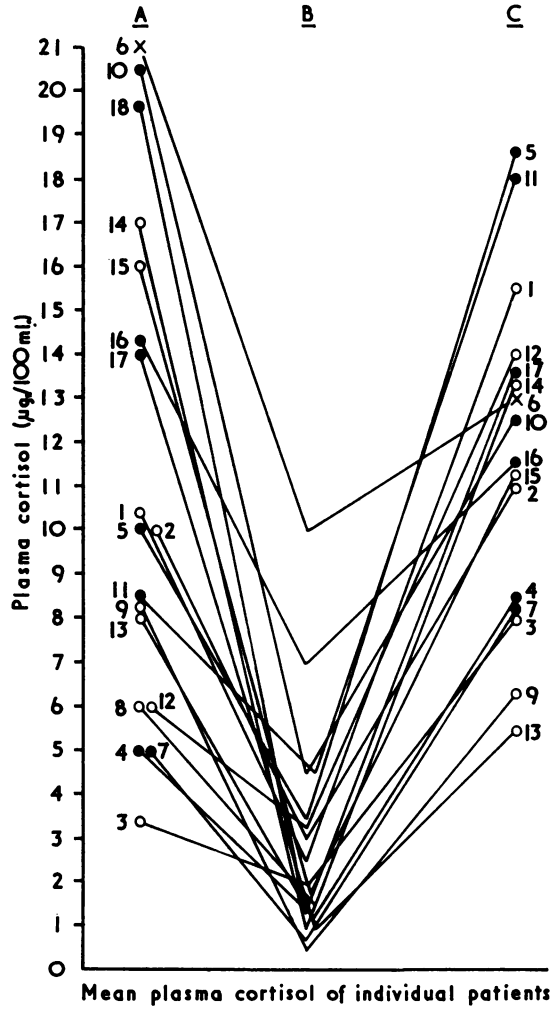

FIG. 2 *Variation in mean* 10 *a.m. plasma cortisol in each subject during each therapeutic regime—A and C single daily dose, B divided dose. The figures against each point are case numbers.*

corticotrophin responsiveness, but individually in only four patients did the response fall below the normal range (Table). Two of the four (Cases 8 and 18) were tested when receiving a divided daily dose. If they are excluded the mean rise of those tested on a single daily dose is 11·7 μg./100 ml. (S.D. 5·9).

Apart from the appearance of a 'moon-face', no steroid side-effects were noted on either regime.

Discussion

Various regimes of intermittent therapy have been described from different centres in the effort to reduce corticosteroid side-effects, in particular, to minimize the hazards of adrenal failure which may result from chronic suppression of the hypothalamo-

pituitary-adrenal (HPA) axis (Harter, Reddy, and Thorn 1963; Adams and others, 1966; Fleisher 1967; MacGregor, Sheagren, Lipsett, and Wolff, 1969.) These regimes have all involved giving the steroid less often than once daily.

Studies of single daily dose treatment have previously been made by Nugent, Ward, Macdiarmid, McCall, Baukol, and Tyler (1965) who compared the effect of taking prednisolone once a day with the effect of twice the dose on alternate days. The therapeutic and toxic effects were similar in the two groups. Demos, Krasner, and Groel (1964) compared single daily doses of triamcinolone with divided daily doses in a large group of patients with various diseases. Relief of symptoms was similar, except in the rheumatoid arthritics, in whom the single daily dose was less effective in 22 of 76 patients. Dubois and Adler (1963) found that a single morning dose of various synthetic corticosteroids produced similar symptomatic relief to a divided daily dose regime in patients with rheumatoid arthritis and systemic lupus erythematosus, except in two who had previously been treated with a divided daily dose regime. Demos and his colleagues (1964) also found particular difficulty when changing from a divided to a single dose regime. Tests of HPA function were not carried out in any of these studies.

In our study all but two subjects found the single daily dose effective and these two had changed over from a divided dose regime. Inhibition of adrenal function did not persist for 24 hrs in the majority of our patients when on a single daily dose, whereas during the divided dose regime nearly all still had subnormal cortisol levels in the morning when it was time for their next dose of corticosteroid. Thus there was no opportunity for the HPA axis to recover before it was once again inhibited. Judged by the criterion of morning cortisol levels, therefore, the single morning dose regime is less suppressive than the twice daily regime, even when the quantity given in the morning dose is greater than the total in the divided dose.

Persistent inhibition of pituitary-adrenal function produced by the twice daily dose regime has been shown to lead to adrenal suppression as judged by the synthetic corticotrophin test in about a third of cases (Daly, Myles, Bacon, Beardwell, and Savage, 1967; Jasani, Boyle, Greig, Dalakos, Browning, Thompson, and Buchanan, 1967). The response to synthetic corticotrophin in this study, however, suggests that adrenal responsiveness is better maintained on the single dose regime, for although the mean response was depressed below that of controls it remained within the normal range, and so did all but two of the individual responses. In interpreting these results it must be remembered that all the subjects had been on a twice daily dose regime at one stage of the study, and eight of them for varying periods before it began. The two who failed to respond normally included one (Case 4) who had received prolonged twice daily dosage before the study, and one (Case 15) who was on the highest dose used. The only two patients (Cases 8 and 18) who elected to remain on twice daily dosage also failed to respond normally.

The results of this study appear to establish a case for giving steroids in a single daily dose during the morning: when the plasma cortisol will be enabled to return towards the normal level at the time of the usual circadian peak. Further studies now in progress are designed to show to what extent the maintenance of normal morning cortisol levels, and normal adrenal responsiveness to ACTH, indicate normal pituitary responsiveness to stress.

Summary

Eighteen patients receiving prednisolone (dosage 8–20 mg. daily) were investigated for evidence of adrenal suppression during a single daily dose regime and a twice daily dose regime. Eight of the patients had been receiving corticosteroids before the study, and ten were starting them for the first time. The 10 a.m. plasma cortisol of each subject was measured several times during both regimes. It was depressed below the normal range on nearly every occasion during the twice daily dosage period, but was normal in the majority of instances on single daily dosage, at both the beginning and the end of the study. Synthetic corticotrophin tests were normal in thirteen out of fifteen subjects tested on the single dose regime. Both single and twice daily dose regimes appeared equally effective therapeutically.

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