Single daily dose corticosteroid treatment

A.B. MYLES, L. F. G. SCHILLER, D. GLASS, AND J. R. DALY

From the Department of Rheumatology, St. Peter's Hospital, Chertsey, Surrey;

Division of Clinical Research, Kennedy Institute of Rheumatology and Department of Chemical Pathology, Charing Cross Hospital Medical School, London

Myles, A. B., Schiller, L. F. G., Glass, D., and Daly, J. R. (1976). *Annals of the Rheumatic Diseases*, 35, 73–76. **Single daily dose corticosteroid treatment.** Thirteen patients with rheumatoid or psoriatic arthritis who had not previously received corticosteroids were treated with prednisolone in a single dose each morning. Insulin-hypoglycaemia tests were performed before starting steroids in each patient, and again at the conclusion of the study in twelve of the thirteen (duration of steroid treatment 8–40 m). There was no difference in the mean basal or peak levels of corticosteroids, or the mean peak of growth hormone (GH) in the tests done before or during treatment, although one patient lost GH responsiveness. There was thus no evidence of hypothalamo-pituitary-adrenal (HPA) suppression in any of the twelve patients, and there was a good therapeutic response in twelve out of thirteen. One patient was dropped from the trial because treatment failed. In contrast, of seven patients who had received a similar total dose of prednisolone twice daily, three showed HPA suppression and two had lost GH responsiveness.

Administration of corticosteroids invariably results in inhibition of the function of the healthy hypothalamo-pituitary-adrenal (HPA) axis. The degree and duration of inhibition varies with the corticosteroid preparation used, the dose, and time of day administered. If each episode of inhibition is profound and prolonged, so that there is no opportunity for recovery before the next dose of corticosteroid is administered, HPA suppression will eventually ensue. Suppression may be regarded as inhibition which cannot be overcome in response to stress, and which will not recover rapidly and spontaneously when the exogenous corticosteroid administration is stopped (Myles and Daly, 1974).

Suppression of the HPA axis is a potentially dangerous complication of long-term corticosteroid treatment because it may lead to collapse as a result of failure of the adrenal to respond normally to stress. Many studies have shown that the degree of suppression may be diminished if the corticosteroid is given intermittently, for instance in a single dose on alternate days or less frequently (Ackerman and Nolan, 1968; Carter and James, 1972; Harter, Reddy, and Thorn, 1963; MacGregor, and others, 1969; Soyka, 1972). Unfortunately, administration less frequently than every day does not always provide satisfactory symptomatic relief, particularly in the treatment of

painful conditions such as rheumatoid arthritis (Demos, Krasner, and Groel, 1964).

The HPA axis is least susceptible to inhibition by exogenous corticosteroids in the morning when plasma cortisol is high (Ceresa and others, 1969; Nichols, Nugent, and Tyler, 1965). In a previous study (Myles, Bacon, and Daly, 1971) it was shown that corticosteroids administered in a single daily dose in the morning allowed the plasma cortisol of most patients to rise to normal within 24 hours, and the majority retained a normal response to exogenous ACTH as shown by the tetracosactrin test. On the other hand, the same total daily dose of corticosteroid when administered half in the morning and half in the evening usually caused suppression both of the morning plasma cortisol and of the response to tetracosactrin. The present study was designed to evaluate the apparent advantage of single daily dose treatment more rigorously by using the insulin-hypoglycaemia test. This is probably the most valuable test of HPA function presently available, particularly when both plasma growth hormone (GH) and corticosteroids are measured, as it assesses the functional integrity of the entire HPA axis, not merely of the adrenal cortex, and the results correlate well with the patient's ability to respond to stress (Jacobs and Nabarro, 1969; Jasani and others, 1968).

Accepted for publication June 17, 1975.

Correspondence to Dr. J. R. Daly, Department of Chemical Pathology, Charing Cross Hospital Medical School, Fulham Palace Road, London W6 8RF.

Patients and methods

Twelve patients who had not previously received corticosteroids were studied. One had psoriatic arthritis, the remainder classical or definite rheumatoid arthritis. All had active arthritis and corticosteroid treatment was thought to be indicated. A thirteenth patient was withdrawn from the trial (see Results). Seven patients with rheumatoid arthritis who were already receiving corticosteroids twice daily were also studied.

TREATMENT

The patients were all receiving standard nonsteroid anti-inflammatory analgesic drugs, and corticosteroids were additional to these. Prednisolone was given in a starting dose of between 5 and 10 mg daily. The patients were instructed to take this at 10:00 am but to omit the drug on the morning of the insulin-hypoglycaemia test. Clinical follow-up was at intervals of 4–8 weeks.

The dose of prednisolone (Table I) was increased or decreased by steps of 1 mg according to the assessment of disease activity during follow-up.

ASSESSMENT

Before starting treatment the activity of the arthritis was assessed by ESR and the combined grip strength of the hands. The function of the HPA axis was estimated by the hypoglycaemia test, measuring both the corticosteroid and growth hormone responses to an intravenous injection of 0.15 unit of soluble insulin/kg body weight. Plasma corticosteroids were measured fluorimetrically (Spencer-Peet, Daly, and Smith, 1965) and serum growth hormone by a double antibody radioimmunoassay, using the MRC 'A' preparation for standard and label.

Table I Details of corticosteroid treatment

Case no.	Dose of prednisolone (mg/d) (range)	Duration of corticosteroid treatment (m)
<i>Single daily dose group</i>		
1	5–8	13
2	5–8	40
3	5 throughout	39
4	5 throughout	36
5	6–8	32
6	6 throughout	32
7	5 throughout	9
8	5 throughout	13
9	5 throughout	14
10	5 throughout	8
11	5–10	23
12	3–6	37
13	Withdrawn from trial	—
<i>Twice-daily dose group</i>		
14	4–7.5	24
15	5 throughout	12
16	5–9	36
17	4–10	30
18	5–10	8
19	5–7	48
20	7–8	48

FOLLOW-UP

Patients were asked about the effectiveness of the treatment in relieving pain and morning stiffness, the grip strength of the hands was estimated and blood was taken for ESR. The insulin-hypoglycaemia test was repeated at the end of the study. Statistical comparison of results at the beginning and end of the study was by the 't' test for paired differences.

TWICE-DAILY DOSE PATIENTS

The insulin-hypoglycaemia test was also performed on seven patients with rheumatoid arthritis who were receiving prednisolone twice daily in a similar total daily dose and for a comparable period to the single daily dose group (Table I). Statistical comparison of results between the twice-daily and once-daily dose groups was by Student's 't' test.

Results

One patient's arthritis remained very active and he continued to have severe early morning stiffness. It was therefore decided that he should have prednisolone in the evening and he was removed from the trial. In the remaining twelve the symptoms were reasonably well controlled, and morning stiffness was relieved. There was a significant fall in the ESR and rise in the grip strength (Table II).

In the single daily dose group there was no significant difference between the corticosteroid response to insulin in hypoglycaemia at the beginning and end of the study. Growth hormone responsiveness to hypoglycaemia was maintained in all but one subject (Table III).

The corticosteroid response was significantly lower in the twice-daily dose group compared with that in

Table II Clinical assessment of subjects at beginning and end of study

Case no.	Grip strength (mm/Hg)		ESR (mm/h)	
	Beginning	End	Beginning	End
1	220	255	101	89
2	185	170	60	42
3	300	473	99	45
4	135	120	60	39
5	250	310	91	71
6	110	120	29	21
7	320	420	45	19
8	225	435	64	16
9	295	543	18	10
10	210	288	72	43
11	195	290	65	41
12	>600*	>600*	65	27
Mean ± SD	254 ± 126	335 ± 159	64 ± 25	38 ± 23
	P < 0.01		P < 0.001	

* For the calculation of means these values were taken to be 600 mm/Hg.

Table III Results of insulin-hypoglycaemia tests at beginning and end of study. The twice-daily dose group (Cases 14–20) were not tested at the beginning of this treatment

Case no.	Plasma corticosteroids ($\mu\text{g}/100\text{ml}$)			Plasma corticosteroids ($\mu\text{g}/100\text{ml}$)			Peak serum growth hormone (ng/ml)	
	Beginning			End			Beginning	End
	Basal	Peak	Increment	Basal	Peak	Increment		
1	16.0	28.5	12.5	12.0	28.0	16.0	9	17
2	15.0	36.5	21.5	15.0	31.0	16.0	12	20
3	22.5	33.5	11.0	19.5	35.0	15.5	50	15
4	13.0	34.0	21.0	19.0	42.0	23.0	20	18
5	20.0	50.0	30.0	12.0	26.5	14.5	14	14
6	14.0	40.0	26.0	8.0	22.0	14.0	21	17
7	9.5	20.5	11.0	13.0	32.0	19.0	46	50
8	16.5	28.5	12.0	19.5	29.5	10.0	—*	17
9	18.5	28.0	9.5	12.5	29.5	17.0	—*	26
10	14.0	23.0	9.0	26.0	44.0	18.0	16	60
11	11.5	40.5	29.0	12.0	25.0	13.0	>60	>60
12	18.5	32.0	13.5	8.5	28.5	20.0	30	1
Mean $\pm$ SD	15.8 $\pm$ 3.7	32.9 $\pm$ 8.1	17.2 $\pm$ 7.9	14.8 $\pm$ 5.3	31.1 $\pm$ 6.5	16.3 $\pm$ 3.4	27.8 $\pm$ 18†	26.3 $\pm$ 19.2‡
P	No significant difference between any corresponding 'beginning' and 'end' values							
14	—	—	—	6.5	14.0	7.5	—	38
15	—	—	—	22.5	28.0	7.5	—	<1
16	—	—	—	22.0	33.0	11.0	—	33
17	—	—	—	15.5	25.5	10.0	—	2
18	—	—	—	9.5	37.0	27.5	—	82
19	—	—	—	11.0	16.0	5.0	—	30
20	—	—	—	3.5	7.0	3.5	—	89
Mean $\pm$ SD	—	—	—	12.9 $\pm$ 7.4	22.9 $\pm$ 10.9	10.3 $\pm$ 8.0	—	38.0 $\pm$ 33.3
P‡	—	—	—	NS	<0.05	<0.05	—	NS

* These values were unfortunately lost owing to technical difficulties with the assay.

† In calculating the means the individual values >60 ng/ml were treated as 60 ng/ml.

‡ Significance of difference between corresponding results of single dose and twice daily dose group.

the single dose group, and in three patients was abnormal (normal response = base-line level of plasma corticosteroid >5 rising to >20 $\mu\text{g}/100\text{ml}$). The overall mean growth hormone response was not suppressed in this group, although individual responses were abnormal in two out of the seven patients.

Discussion

Our results indicate that administration of prednisolone in such a way as to permit recovery from HPA inhibition between doses will prevent suppression. This is achieved by giving the drug only once daily in the morning, which limits both the depth and duration of inhibition. It could be argued that the total daily dose used in this study was too low for HPA suppression to occur, whatever the frequency of administration. Nevertheless, the results in the group of seven patients who had received prednisolone twice daily in similar total daily doses for comparable periods indicate that this is not the case. Three of these seven showed signs of HPA suppression, whereas none at all of the twelve on the once-daily regimen did so. Furthermore, in a previous study comparing the effect of corticotrophin and corticosteroids on the HPA axis, definite suppression was found in a

group of twelve patients after treatment with comparable corticosteroid doses on a twice-daily regimen (Daly and others, 1974).

The effect on the growth hormone response to hypoglycaemia showed a less clear-cut division between the groups, but there may be some protection against growth hormone suppression also. One out of twelve on the single dose regimen showed no response, compared to two out of seven on the twice-daily regimen.

The symptomatic relief, fall in ESR, and increase in grip strength suggest that this mode of administering corticosteroids is effective, and that the preservation of HPA function during once-daily morning corticosteroid treatment is not usually achieved at the cost of therapeutic efficacy, although one patient out of thirteen did not respond satisfactorily.

Corticosteroids are therapeutic in a wide range of conditions, possibly being second only to the antibiotics. In 1971, 2.2 million prescriptions for systemic corticosteroids were dispensed outside the hospital service, the figure for hospital prescriptions being unrecorded (Department of Health and Social Security, 1972). It is obviously vital that these drugs should be administered in the manner least likely to produce serious side effects, and avoidance of HPA suppression removes one of the major hazards of

corticosteroid treatment. The importance of stopping therapy as soon as possible has been stressed previously (Glass and others, 1971), and we would now also recommend that whenever corticosteroids are given in low doses, as in rheumatoid arthritis, asthma, or various dermatoses, they should be given in a single dose in the morning, although change to evening administration may occasionally be necessary for the relief of morning stiffness in rheumatoid arthritis. In diseases for which higher doses are required administration on alternate days,

or even less frequently, may be necessary to avoid HPA suppression. It must be pointed out that our data relate to prednisolone, and that very potent steroids such as dexamethasone, betamethasone, or triamcinolone may cause suppression even when given only twice weekly (Rabhan, 1968). They should therefore be avoided unless essential for very high dose medication.

This study was aided by the research funds of the South West Metropolitan Regional Hospital Board.

References

- ACKERMAN, G. L., AND NOLAN, C. M. (1968) *New Eng. J. Med.*, **278**, 405 (Adrenocortical responsiveness after alternate day corticosteroid therapy)
- CARTER, M. E., AND JAMES, V. H. T. (1972) *Ann. rheum. Dis.*, **31**, 379 (Effect of alternate day, single-dose corticosteroid therapy on pituitary-adrenal function)
- CERESA, F., ANGELI, A., BOCUZZI, G., AND MOLINO, G. (1969) *J. clin. Endocr.*, **29**, 1074 (Once-a-day neurally stimulated and basal ACTH secretion phases in man and their response to corticoid inhibition)
- DALY, J. R., FLETCHER, M. R., GLASS, D., CHAMBERS, D. J., BITENSKY, L., AND CHAYEN, J. (1974) *Brit. med. J.*, **2**, 521 (Comparison of effects of long-term corticotrophin and corticosteroid treatment on responses of plasma growth hormone, ACTH and corticosteroid to hypoglycaemia)
- DEMOS, C. H., KRASNER, F., AND GROEL, J. T. (1964) *Clin. Pharmacol. Ther.*, **5**, 721 (A modified (once a day) corticosteroid dosage regime)
- DEPARTMENT OF HEALTH AND SOCIAL SECURITY (1972) In 'Annual Report, 1971, Appendix IX, Table 12'. H.M.S.O., London
- GLASS, D., SNAITH, M. L., RUSSELL, A. S., AND DALY, J. R. (1971) *Lancet*, **2**, 334 (Possible unnecessary prolongation of corticosteroid therapy in rheumatoid arthritis)
- HARTER, J. G., REDDY, W. J., AND THORN, G. W. (1963) *New Eng. J. Med.*, **269**, 591 (Studies on an intermittent corticosteroid dosage regime)
- JACOBS, H. S., AND NABARRO, J. D. N. (1969) *Quart. J. Med.*, **38**, 475 (Tests of hypothalamo-pituitary-adrenal function in man)
- JASANI, M. K., FREEMAN, P. A., BOYLE, J. A., REID, A. M., DIVER, M. J., AND BUCHANAN, W. W. (1968) *Quart. J. Med.*, **37**, 407 (Studies of the rise in plasma 11-hydroxycorticosteroids (11-OHCS) in corticosteroid-treated patients with rheumatoid arthritis during surgery: correlations with the functional integrity of the hypothalamo-pituitary-adrenal axis)
- MACGREGOR, R. R., SHEAGREN, J. N., LIPSETT, M. B., AND WOLFF, S. M. (1969) *New Eng. J. Med.*, **280**, 1427 (Alternate-day prednisolone therapy: evaluation of hypersensitivity responses, control of disease and steroid side effects)
- MYLES, A. B., AND DALY, J. R. (1974) In 'Corticosteroid and ACTH Treatment'. Arnold, London
- , BACON, P. A., AND DALY, J. R. (1971) *Ann. rheum. Dis.*, **30**, 149 (Single daily dose corticosteroid treatment: effect on adrenal function and therapeutic efficacy in various diseases)
- NICHOLS, F., NUGENT, C. A., AND TYLER, F. H. (1965) *J. clin. Endocr.*, **25**, 343 (Diurnal variation in suppression of adrenal function by glucocorticoids)
- RABHAN, N. B. (1968) *Ann. intern. Med.*, **89**, 1141 (Pituitary-adrenal suppression and Cushing's syndrome after intermittent dexamethasone therapy)
- SPENCER-PEET, J., DALY, J. R., AND SMITH, V. (1965) *J. Endocr.*, **31**, 235 (A simple method for improving the specificity of the fluorimetric determination of adrenal corticosteroids in human plasma)
- SOYKA, L. F. (1972) *Advanc. Pediatr.*, **19**, 47 (Alternate day corticosteroid therapy)