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Effect of alternate-day, single-dose, corticosteroid therapy on pituitary-adrenal function

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Therapeutic doses of ACTH given daily and maintained for more than 2 years in patients with polyarthritis do not normally suppress hypothalamic-pituitary-adrenal (HPA) responsiveness to the stresses of insulin hypoglycaemia or surgery (Carter and James, 1970a, b). By contrast, corticosteroids in daily doses equivalent to 7·5 mg. or more of prednisolone will impair pituitary-adrenal function in most patients, but our attempts to mitigate their suppressive effect by combining steroid treatment with intermittent ACTH in reasonable therapeutic dosage were unsuccessful (Carter and James, 1970c). In fact, pituitary-adrenal suppression as judged by response to insulin-induced hypoglycaemia appeared to be increased rather than offset. Thus it seemed that the administration of therapeutic daily doses of steroids inevitably causes suppression.

Using a daily administration schedule, this suppression can be diminished by single as opposed to divided daily doses of steroid (Myles, Bacon, and Daly, 1971). In recent years, too, physicians treating patients with other chronic diseases, such as the nephrotic syndrome, ulcerative colitis, asthma, and sarcoidosis, in which much larger maintenance doses of corticosteroids tend to be used, have been exploring intermittent regimes with a view to diminishing some of the side-effects, including Cushingoid features, growth inhibition in children, osteoporosis, and impairment of HPA function, without loss of therapeutic effect (Soyka and Saxena, 1965; Ackerman and Nolan, 1968; Sadeghi-Nejad and Senior, 1969).

The most promising administration schedule appeared to be by a single dose once every 48 hours, and it seemed important to us to try to establish whether this method of steroid administration, especially as applied to the relatively small maintenance doses employed in the management of rheumatoid disease, would be therapeutically practicable, and would preserve the integrity of the HPA axis; this report relates our experience with such a regime in patients with active chronic polyarthritis.

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Material and methods

Of fourteen patients studied, twelve women and two men, ten were suffering from active classical rheumatoid arthritis, according to the A.R.A. criteria (Ropes, Bennett, Cobb, Jacox, and Jessar, 1958), two from probable rheumatoid arthritis, and two from psoriatic arthropathy. Their mean age is 48 years (range 15 to 73) and the mean duration from onset of disease is 8 years (range 1 to 18).

Only patients who were considered to require 10 mg. or more of prednisolone daily were included, and they were given the sum of their 48 hour four-times-a-day steroid requirement as a single dose after breakfast every other day. Seven patients (Group 1) who had not received steroids previously were started on the alternate-day steroid regime: two of these patients (S.S. and M.W.) had received daily ACTH injections before starting steroids. Seven patients (Group II) were transferred to the alternate-day single-dose regime from treatment with daily divided doses of steroids, or from steroids and ACTH in some combination used in our earlier studies. All patients were receiving a maintenance dose of enteric-coated aspirin 4 to 6 g. daily, and in an attempt to spare them any see-sawing effect of symptoms between steroid doses, they were instructed to take 100 mg. phenylbutazone three times a day on the non-steroid days.

As in our previous studies, pituitary-adrenal function was tested by insulin induced hypoglycaemia as described elsewhere (Greenwood, Landon, and Stamp, 1966). Tests were carried out at least 24 hours after the last dose of steroids was taken, and in some cases 48 hours after the last dose. No significant difference in test responses was found at 24 or 48 hours.

Plasma cortisol was estimated by an automated fluorimetric technique (Townsend and James, 1968). The corticosteroid used was enteric-coated prednisolone "Delta-Cortril" (Pfizer). Phenylbutazone was given as Butazolidin Alka (Geigy) in the hope of minimizing the dyspeptic and haemorrhagic risk with a combination of three potentially gastro-irritant drugs, and was found to be very well tolerated. No serious dyspepsia was encountered, and no frank bleeding episodes occurred.

Results

Figs 1 and 2 show the results of serial insulin stress tests performed on the patients in the two groups, *i.e.* those starting on steroids for the first time and those whose treatment has been converted from daily divided doses of steroids (sometimes in combination with ACTH) to the alternate-day regime. The graphs for each patient show the increment of plasma cortisol in μg./100 ml., from the resting level to the maximum stimulated level, in response to hypoglycaemia. Current treatment is given at the foot of the graphs, and the duration of treatment at the time of each test is shown above in weeks. Previous steroid or corticotrophin dosage and duration of treatment is indicated in the left hand column where applicable. Our normal criteria require a resting level of at least 5 μg./100 ml., an increment of at least 7 μg./100 ml., and a maximum stimulated level of at least 20 μg./100 ml.

GROUP I

Six of the seven patients who started treatment with steroids for the first time under the alternate-day single-dose regime, including the two who were converted from daily corticotrophin therapy, all maintained pituitary-adrenal responsiveness at or near the lower limit of the normal range, the longest period of follow up being 66 weeks. However, one

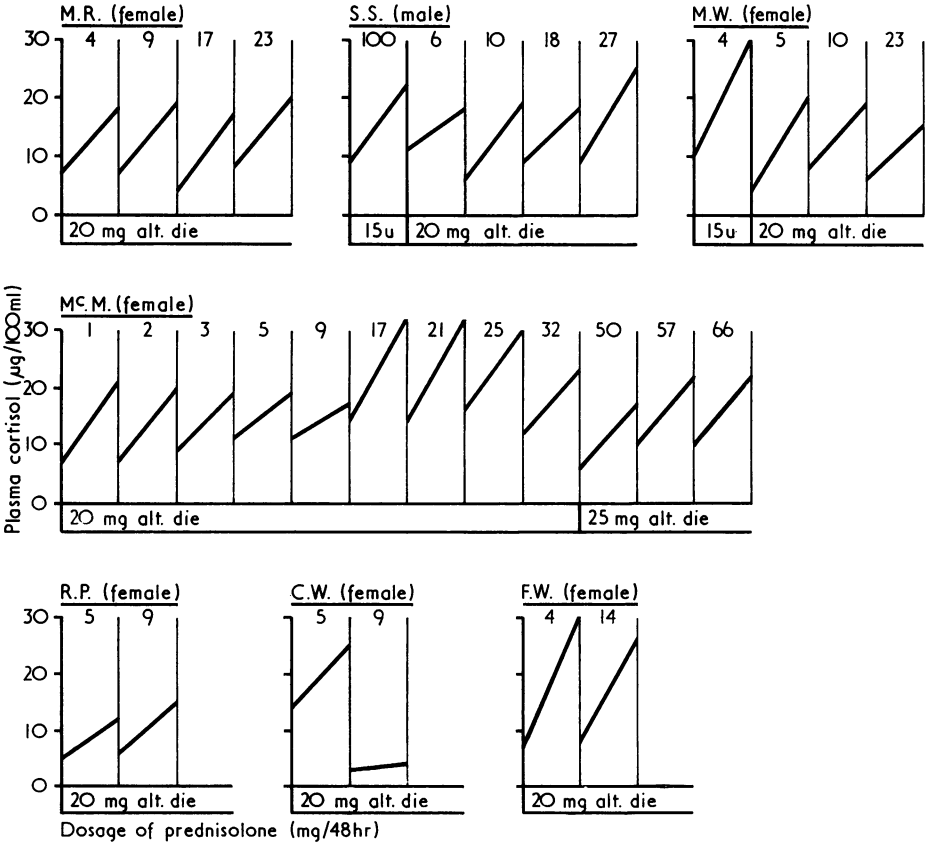

FIG. 1 *Group I. Serial plasma cortisol responses to insulin hypoglycaemia in seven patients receiving prednisolone in one dose on alternate days. Doses in mg./48 hrs are shown at the foot of each graph. Oblique lines show maximum increment in plasma cortisol for each test, measured in* μg/100 *ml (ordinate). Tests were carried out at intervals shown above the graph in weeks. In patients S.S. and M.W., the daily dose of ACTH and duration of treatment is given in the left-hand column*

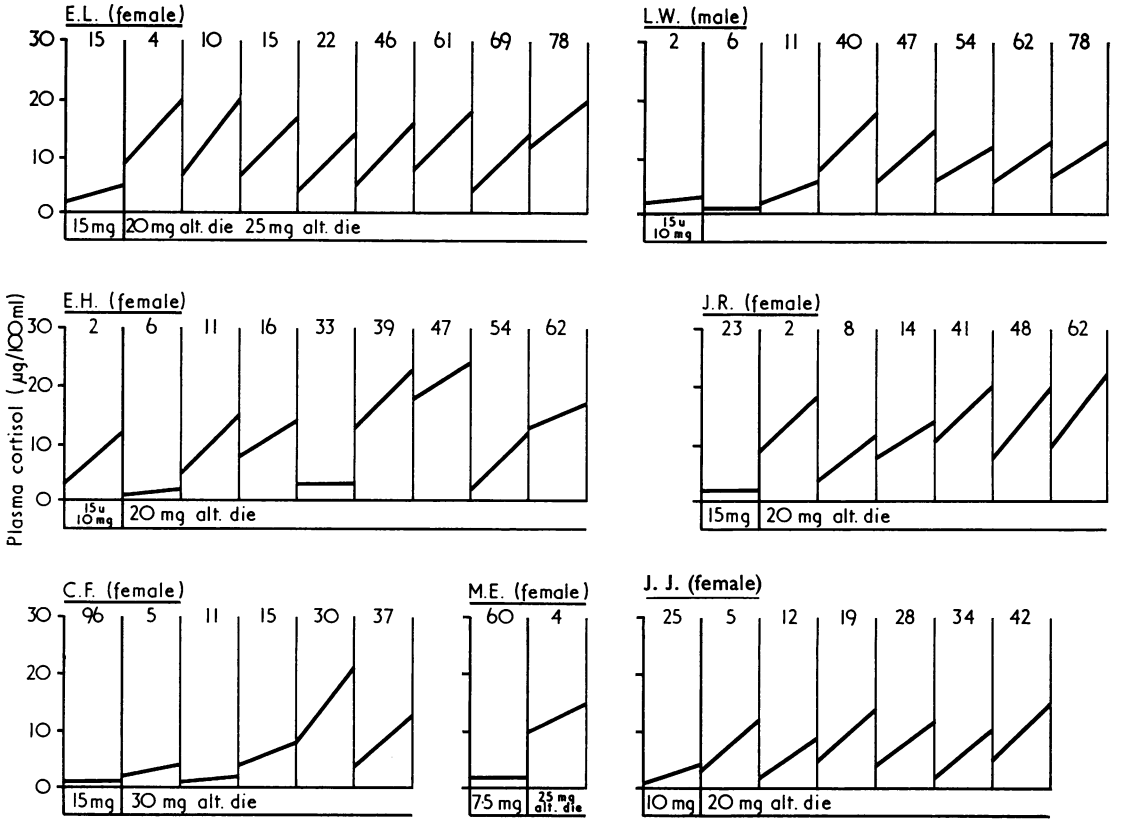

FIG. 2 *Group II. Serial plasma cortisol responses to insulin hypoglycaemia in six patients receiving prednisolone in one dose on alternate days. Doses in mg./48 hrs are shown at the foot of each graph. Oblique lines show maximum increment in plasma cortisol for each test, measured in µg./100 ml (ordinate). Tests were carried out at intervals shown above the graph in weeks. The previous treatment, divided daily doses of prednisolone, either alone or combined with ACTH, is shown in the left-hand column. Patients L.W. and E.H. had received both ACTH (15 units) and prednisolone (10 mg.) daily.*

patient (C.W.) who showed an excellent response at 9 weeks showed complete suppression 4 weeks later.

GROUP II

The seven patients who were converted from previous steroid therapy, or from steroids and ACTH combined, showed a rather less uniform picture. Patients E.L., J.R., and M.E. showed rapid improvement in their responses after changing from daily to alternate-day prednisolone. However, Patients C.F., J.J., and L.W. have recovered more slowly. Although C.F. had received by far the greatest amount of steroid in the whole group (10 g.) she showed a normal response to hypoglycaemia by 30 weeks. (Unfortunately there was an unavoidably long interval between her test at 15 weeks and the one at 30 weeks). L.W. and J.J., however, had received the smallest doses of steroid (140 mg. and 1·575 g.), yet neither had achieved a normal response by 30 weeks. The total steriod doses received by patients E.L., E.H., M.E., and J.R. were 1·575 g., 140 mg., 3·780 g., and 2·415 g. respectively.

Discussion

A number of investigators have examined the effects of alternate-day corticosteroid therapy on pituitary-adrenal function and in general they have concluded that this regime is beneficial to the patient in this respect as compared with continuous daily therapy. The parameters used to evaluate this effect have varied; some authors have studied resting plasma or steroid levels (Soyka and Saxena, 1967) and others have used metyrapone (Fleisher, 1967) or insulin hypoglycaemia (Ackerman and Nolan, 1968). None of these studies extended further than carrying out a single test on each patient; neither has the effect of previous steroid treatment been considered specifically. Our aim in this investigation was to study patients receiving alternate-day steroid therapy over an extended period of time, using repeated tests of pituitary-adrenal function. We have employed the response to insulin hypoglycaemia as providing, in our view, the most meaningful assessment of function in our patients.

Of the patients in this study who were started on steroids for the first time on the single-dose alternate-day regime, all but one maintained pituitary-adrenal responsiveness to the stress of insulin hypoglycaemia, within the lower limits of the normal range, for periods of up to 15 months of treatment in doses equivalent to 10 or 12·5 mg. prednisolone daily. In contrast, the majority of patients receiving daily divided doses of prednisolone in the same dose range rapidly and persistently show significant loss of HPA function (Fig. 3). It is nevertheless of considerable interest that one patient receiving alternate-day steroids showed an excellent response to hypoglycaemia when tested at 5 weeks, whilst 4 weeks later almost complete suppression had occurred.

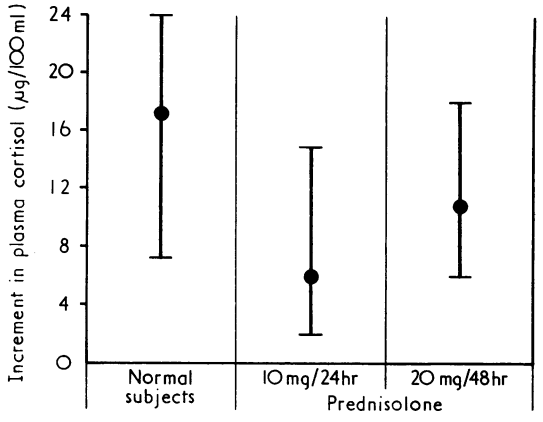

FIG. 3 *The range of plasma cortisol increments in response to insulin hypoglycaemia in normal (untreated) subjects is given on the left of the graph in μg./100 ml. (Mean 17 μg./100 ml.). The middle line represents the range (mean 6 μg./100 ml.) in patients receiving prednisolone 10 mg. daily in divided doses, and the right-hand line shows the range (mean 11 μg./100 ml.) in patients receiving 20 mg. prednisolone in one dose on alternate days.*

Those of our patients who had received treatment with daily divided doses of steroids, or with steroids combined with injections of ACTH, showed marked pituitary-adrenal suppression when tested before changing to the single-dose alternate-day steroid regime (Fig. 2). They all showed improvement in their test responses, but the time taken for this recovery varied from 2 weeks to several months. This recovery period was not apparently related to the total dosage or to the duration of the daily dosage of previous steroid treatment.

Our data also reveal that there may be considerable variations in response whilst treatment is maintained unaltered (*e.g.* patient E.H., Fig. 2). This individual variability has also been observed in our investigations of patients receiving continuous daily corticotrophin therapy (Carter and James, 1970a).

One obvious explanation for such variation could be irregularity of adherence to the prescribed regime. As far as it is possible to be certain, we have complete confidence that all the patients concerned were entirely conscientious throughout the study. A small number who reported failure for various good reasons were excluded because of an inadequate follow-up period.

Using this method of administration, there are steep rises in plasma prednisolone levels once every 48 hours, and we are not in a position to assess the effect of this on any parameter other than pituitary-adrenal stress responsiveness. It is open to speculation whether this regime is associated with other advantages, or whether it may incur some disadvantages. Ackerman and Nolan (1968), Soyka and Saxena (1965), and Soyka (1967) have indicated that, when much larger doses of steroids are administered in this way to patients with other diseases such as the nephrotic syndrome, there is a diminution of certain other side-effects—notably the Cushingoid appearance and the inhibition of growth in juveniles.

Preservation of pituitary-adrenal function by this regime would be of purely academic interest if therapeutic efficacy was impaired, and some mention of our clinical experience is therefore important. We have been able to study relatively few patients, but the period of maintenance in some of them is now over 2 years, and we have the advantage that all patients are seen regularly and assessed by one physician to whom they are well known.

Some difficulties were encountered: two patients, both of whom could tolerate divided doses of steroids, were unable to tolerate 20 or 25 mg. prednisolone in one dose taken after food, as instructed. They experienced severe dyspepsia, giddiness, and faintness and had to lie down for the rest of the day. One very conscientious patient was worried especially about this, because she was unable to perform her daily exercises without which she could not maintain her muscle strength and mobility. Both patients renewed attempts to take this dose, but were unable to continue. This was surprising in view of the much larger single doses (up to 120 mg.) that some patients take as treatment for other diseases.

Several patients whose treatment was converted from daily steroids experienced intolerable rheumatoid symptoms of pain and stiffness when the regime was altered. The majority, however, whom it must be emphasized were carefully selected for this pilot study for their stability of temperament and their stoical and sensible attitude to their disease, managed very well. The rationale for choosing this regime was explained and their full co-operation was ensured. They were advised to mark on a card calendar the days on which they had taken the steroids, and they were given instructions for dealing with any moderate exacerbation of symptoms.

It is obviously easier to establish treatment under the regime in question when steroids are introduced

for the first time, as the patient then appreciates the gain of the equivalent of 10 or 12·5 mg. prednisolone daily (albeit receiving it as 20 or 25 mg. every 48 hours). If, on the other hand, daily dosage is changed to alternate-day dosage—notwithstanding no change in total dosage, a loss may be felt on the non-steroid day. It is also obvious that this system of treatment is more appropriate to patients with moderate rather than severe disease activity; patients with only mild activity would not be given steroids at all, unless for some special associated reasons.

The purpose of this study was to make an assessment of the usefulness of alternate-day corticosteroid therapy in the preservation of HPA function. Although our series has not been large enough to make a meaningful assessment of the proportion of patients who are able to tolerate this regime, it is in our opinion a feasible and useful procedure in carefully selected patients.

Summary

The effect of alternate-day corticosteroid (prednisolone) therapy on pituitary-adrenal function has been studied in two groups of patients with active chronic polyarthritis. Doses of 20 to 30 mg. prednisolone every 48 hours were used, and responsiveness to the stress of insulin hypoglycaemia was tested at intervals in each patient during treatment.

The first group of patients had not received any previous treatment with corticosteroids. Six of seven patients retained pituitary-adrenal responsiveness at, or near, the lower limit of normal; one patient showed a considerable degree of depression of response.

The second group of patients were receiving corticosteroids daily and were converted to alternate-day treatment. A slight reduction in dose was tolerated and improved pituitary-adrenal responses were observed. However, considerable variation was noted and, in some patients, several weeks elapsed before any marked improvement occurred.

It is concluded that, when patients can tolerate alternate-day corticosteroid therapy, this is advantageous in producing less pituitary-adrenal suppression than does daily treatment. Clinical management with this regime is satisfactory in selected patients.

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References

ACKERMAN, G. L., AND NOLAN, C. M. (1968) *New Engl. J. Med.*, **278**, 405 (Adrenocortical responsiveness after alternate-day corticosteroid therapy)

CARTER, M. E., AND JAMES, V. H. T. (1970a) *Ann. rheum. Dis.*, **29**, 73 (Effect of corticotrophin on pituitary-adrenal function)

——, —— (1970b) *Lancet*, **1**, 328 (Pituitary-adrenal response to surgical stress in patients receiving corticotrophin treatment)

——, —— (1970c) *Ann. rheum. Dis.*, **29**, 409 (An attempt at combining corticotrophin with long-term corticosteroid therapy with a view to preserving hypothalamic-pituitary-adrenal function)

FLEISHER, D. S. (1967) *J. Pediat.*, **70**, 54 (Pituitary-adrenal responsiveness after corticosteroid therapy in children with nephrosis)

GREENWOOD, F. C., LANDON, J., AND STAMP, T. C. B. (1966) *J. clin. Invest.*, **45**, 429 (The plasma sugar, free fatty acid, cortisol and growth hormone response to insulin. I. In control subjects)

MYLES, A. B., BACON, P. A., AND DALY, J. R. (1971) *Ann. rheum. Dis.*, **30**, 149 (Single daily dose corticosteroid treatment)

ROPES, M. W., BENNETT, G. A., COBB, S. JACOX, R., AND JESSAR, R. A. (1959) *Ibid.*, **18**, 49 (Diagnostic criteria for rheumatoid arthritis)

SADEGHI-NEJAD, A., AND SENIOR, B. (1969) *Pediatrics*, **43**, 277 (Adrenal function, growth, and insulin in patients treated with corticoids on alternate days)

SOYKA, L. F. (1967) *Amer. J. Dis. Child.*, **113**, 693 (Treatment of the nephrotic syndrome in childhood)

—— AND SAXENA, K. M. (1965) *J. Amer. med. Ass.*, **192**, 225 (Alternate-day steroid therapy for nephrotic children)

TOWNSEND, J., AND JAMES, V. H. T. (1968) *Steroids*, **11**, 497 (A semi-automated fluorimetric procedure for the determination of plasma corticosteroids)