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suppression, i.e. adrenal suppression which does not spontaneously recover when the administered corticosteroid is withdrawn, and which carries the risk of failure to respond to stress.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
Table  Clinical particulars of 18 cases

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<th>Case No.</th>
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<th>Duration of therapy (wks)</th>
<th>Grip strength</th>
<th>Peak flow rate (l./min.)</th>
<th>Synacthen test</th>
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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.

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.
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 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,
McCay, Bakoul, 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 inter-
preting 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 (dose
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.

We wish to thank Dr. Oswald Savage, Dr. J. T. Scott, and
Dr. Eric Hudson for allowing us to investigate patients
in their care. The skilled technical assistance of Mrs. Jean
Turner is gratefully acknowledged.

References

(Adrenocortical function during intermittent corticosteroid therapy).
stimulated and basal ACTH secretion phases in man and their response to corticoid inhibition).
(Pituitary adrenal function during corticosteroid withdrawal in rheumatoid arthritis).


