PLASMA “CORTISOL” RESPONSE TO SYNACTHEN IN PATIENTS ON LONG-TERM SMALL-DOSE PREDNISONE THERAPY

BY

J. A. HICKLIN AND M. R. WILLS

From the Departments of Rheumatology and Chemical Pathology, Royal Free Hospital, London

In view of the uncertainty about safe limits of steroid dosage and of the particular interest in the 5 mg. per day dose level (de Andrade, McCormick, and Hill, 1964), we studied adrenal cortical responsiveness in a series of patients with rheumatoid arthritis, who had been on this dose of prednisone for varying periods, by the Synacthen test (Wood, Frankland, James, and Landon, 1965).

Material

Patients.—39 patients were studied, all but one of whom had taken prednisone 5 mg./day for periods of from 8 weeks to 8 years. One patient (Case 31) had her dose increased from 5 to 7 mg./day 8 months before the test. With the exception of two who had polymyalgia rheumatica, all had rheumatoid arthritis. Of these 39 patients, nineteen were selected at random and studied again after a year to discover the effects of continued or altered prednisone dosage upon adrenal function.

Control.—Twenty normal hospitalized controls of comparable age range were studied under the same test conditions as the patients.

Methods

Plasma “cortisol” was estimated by a modification of the technique of Mattingly (1962) for free 11-hydroxycorticoids. In this technique both cortisol and corticosterone are measured. The amounts of circulating corticosterone are small and since the present study is essentially comparative, the result is referred to as plasma “cortisol”. Prednisone does not interfere with the estimated result by more than 1 per cent.

Synacthen Test.—All tests were carried out on non-fasting subjects starting between 9 and 10 a.m. None of the patients had taken any steroid for at least 12 hours before the test. Between 9 and 10 a.m. samples of venous blood were collected for the estimation of resting levels of plasma cortisol. 250 μg. Synacthen in 0·5 ml. sterile water were then injected intramuscularly. A sample of blood was collected at 30 and 60 minutes after the injection of Synacthen. The 60-minute samples were estimated in all cases. Although these latter values are not given in the Tables of results they were used to confirm the 30-minute values in order to exclude the possibility of a delay in absorption as being the cause of an abnormal response.

Results

In the twenty normal control subjects, the resting level of plasma “cortisol” at 9 a.m. varied between 7·0 and 22·7 μg./100 ml. (mean 14·9 μg.); 30 minutes after the injection of Synacthen values varied between 25·5 and 36·5 μg./100 ml. (mean 31 μg.). Our criteria for a normal Synacthen test were the finding of both:

1. A baseline plasma “cortisol” value of 7 μg./100 ml. or more.
2. An increment at 30 minutes of 10 μg./100 ml. or more on the baseline value.

These criteria are in accordance with those of other workers (Wood and others, 1965; Greig, Browning, Boyle, and Maxwell, 1966).

Table 1 (overleaf) shows the results in 39 patients, whose total dose of steroid varied from 0·3 to 14·2 g. prednisone, and whose period of treatment varied from 8 weeks to 8 years. They are arranged in order of total dosage which corresponds closely to the number of weeks of treatment.

No patient was found to have evidence of lack of adrenal responsiveness during the first year of treatment, but Case 21 showed an abnormal response at one year. This patient had been previously treated with steroids at another hospital, but had been on 5 mg./day for 52 weeks at this hospital. The other three patients (Cases 31, 37, 39) with a lack of adrenal response had all received large doses of steroid. Three patients (Cases 6, 16, 22) showed low baseline values but a normal increment after the Synacthen, whereas six others (Cases 1, 8, 20, 25, 26, 34) with normal baseline
values showed a subnormal increment after Synacthen after variable doses of steroids. The four patients with clear evidence of lack of adrenal response (21, 31, 37, 39) are scattered in a random fashion in the Table, suggesting that individual variation in sensitivity to the 5 mg. dose is of more importance than total dose or total time. The plasma "cortisol" at 60 minutes in these four patients was still poor, suggesting that poor absorption of Synacthen was not the basis of their poor response.

Table IIA compares the results of the first and second tests after one year, on ten patients who remained on the same dose of prednisone. Two (34 and 35) showed an increased resting level and increment after Synacthen despite a further 76 and 44 weeks treatment respectively. The other eight patients showed a decrease in either the baseline plasma "cortisol" level or the increment after Synacthen. One previously abnormal patient (21) remained abnormal, and one further patient (32) who had previously shown a normal response became abnormal; the latter had an abnormal low baseline level at the first test. Two patients (22 and 23), although showing a normal increment after Synacthen, showed low baseline values after further steroid therapy.

Table IIB compares the results of first and second tests of five patients whose dose was in some way reduced between the first and second tests. One patient (39), who had had the largest amount of steroid of all, became normal on reducing the daily dose from 5 to 4 mg./day. In contrast, patient 8, in whom the steroid had been reduced to 4 mg./day for several months after a relatively small total initial dose, had become abnormal by the time of the second test. Patient 37 remained abnormal despite a reduction in the daily dose of steroid from 7 to 5 mg. prednisone.

Table IIC shows that three patients whose prednisone was stopped between the first and second tests all had normal tests on the second occasion, including one (31) who had an abnormal response previously.

Table IID shows that, in one patient whose dose was increased (29), the test on the second occasion was markedly abnormal.
PLASMA “CORTISOL” RESPONSE TO SYNACTHEN

TABLE II
RESULTS OF REPEAT SYNACTHEN TESTS

<table>
<thead>
<tr>
<th>Group</th>
<th>Patient No.</th>
<th>Total Dose (mg.)</th>
<th>Total Time (days)</th>
<th>First Test</th>
<th>Plasma “Cortisol” (µg./100 ml.)</th>
<th>Total Dose (mg.)</th>
<th>Total Time (days)</th>
<th>Second Test</th>
<th>Plasma “Cortisol” (µg./100 ml.)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Total Dose</td>
<td></td>
<td>Resting</td>
<td>30’ Increment</td>
<td>Total Dose</td>
<td></td>
<td>Resting</td>
<td>30’ Increment</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Time</td>
<td></td>
<td></td>
<td></td>
<td>Time</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(A) Same Dose</td>
<td>19</td>
<td>1945</td>
<td>47</td>
<td>15</td>
<td>26</td>
<td>11</td>
<td></td>
<td>3220</td>
<td>93</td>
</tr>
<tr>
<td>(B) Dose Reduced</td>
<td>38</td>
<td>3700</td>
<td>88</td>
<td>14</td>
<td>24</td>
<td>9</td>
<td></td>
<td>4955</td>
<td>146</td>
</tr>
<tr>
<td>(C) Dose continued</td>
<td>31</td>
<td>2535</td>
<td>71</td>
<td>10</td>
<td>20</td>
<td>10</td>
<td></td>
<td>3306</td>
<td>95</td>
</tr>
<tr>
<td>(D) Dose Increased</td>
<td>29</td>
<td>2300</td>
<td>70</td>
<td>14</td>
<td>29</td>
<td>15</td>
<td></td>
<td>5895</td>
<td>144</td>
</tr>
</tbody>
</table>

*Indicates abnormal value. Patients with adrenal suppression in bold type.

Discussion

It has been suggested that there is a relationship between the incidence of adrenal cortical suppression and the dose and duration of treatment of steroid therapy (Savage, 1966; de Andrade and others, 1964), but this relationship is not universally confirmed (Livanou, Ferriman, and James, 1965). The differing numerical values that have been suggested as safe limits of prednisone dosage are shown in Table III. These figures imply that the product of the dose given multiplied by the duration of treatment can be used to calculate either a safe total dose or a safe duration of treatment.

TABLE III
SUGGESTED SAFE LIMITS OF PREDNISONE DOSAGE

<table>
<thead>
<tr>
<th>Reference</th>
<th>Total Dose (g.)</th>
<th>Total Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treadwell and others 1963</td>
<td>4.6</td>
<td>30 mths at 7 mg./day</td>
</tr>
<tr>
<td>Jørgensen, 1965</td>
<td>5.8</td>
<td></td>
</tr>
<tr>
<td>Goth, Görgényi, Fövényi, and Szántó 1964</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Hamaty 1966</td>
<td>18.2</td>
<td>10 yrs at 5 mg./day</td>
</tr>
</tbody>
</table>

5 mg. prednisone is the equivalent of the daily adrenal glucocorticoid output (Peterson and Wyngaard, 1956). Shuster and Williams (1961) found no evidence that 5 mg. exogenous prednisone suppressed endogenous cortisol production during the period they studied. Jørgensen (1965) found no abnormality in the ACTH response until a total dose of 5-8 mg. prednisone had been given. Hamaty (1966) suggested that 18-2 g. prednisone could be tolerated as 5 mg./day for 10 years. In contrast Goth, Görgényi, Fövényi, and Szántó (1964) found abnormalities to the ACTH test developing between a total dose 1 and 2 g. of prednisone.

These earlier series consist of patients on a variety of doses for a variety of times. It is therefore necessary, in using their results, to predict the progress of adrenal suppression in other patients, to assume that the figure given by multiplying the total dose by the total time can be applied equally to calculate a safe total dose or time in another patient. There is very little evidence to support this. It may well be that 5 mg./day can be tolerated for much longer than twice the time which the same patient can tolerate 10 mg./day, and very probably for much longer than four times the same patient’s endurance at 20 mg./day.

Therefore the kind of study reported here, in which the patients are all taking the same daily dose for various times, is more likely to produce a clear picture of at least a segment of what may be a three
dimensional graph. The study shows that the daily dose of 5 mg./day prednisone is not free of the danger of adrenal suppression; moreover, even from a study concentrated on only one aspect of the time/dose relationship, it is not possible to predict the onset of adrenal suppression. Individual testing is therefore necessary. The results from these patients whose adrenal function was tested on a second occasion suggest that, while the onset of adrenal suppression is so greatly influenced by the individual sensitivity as to appear random, the progress of each patients adrenal function seems to follow simple pharmacological concepts, tending to deteriorate where prednisone is continued at the same daily level or increased, and tending to improve where the daily dose is adequately reduced or discontinued.

Summary

39 patients on prolonged low doses of steroids were studied by the Synacthen test for evidence of adrenal suppression. Four had unequivocally abnormal tests. No abnormality occurred before the end of one year, but thereafter there was no relationship between total dose, total time, and onset of suppression.

Nineteen of the patients were re-tested after an interval of one year to assess the effects of altered or continued steroid therapy.

The dose level of 5 mg./day prednisone is not free of the danger of adrenal suppression. The variation in individual sensitivity is so great that predictions cannot be made, and each patient must be treated separately. Adrenal function proceeded as might be expected from a simple dose-response relationship when studied over a period of time, but individual variability is still evident.

We should like to thank Dr. A. T. Richardson, Dr. E. D. R. Campbell, and Dr. J. H. Jacobs, whose patients took part in the study.

We are grateful to Dr. T. B. Binns and Cities Laboratories Ltd. for their gift of Synacthen and financial support of part of this project.

REFERENCES


La réponse du cortisol plasmatique au Synacthène chez des malades traités longtemps par de petites doses de prednisone

RÉSUMÉ

Chez 39 malades soumis à un traitement prolongé par de petites doses de stéroïdes on rechercha des signes de dépression de la fonction surrenale par le test au Synacthène. Chez quatre malades les résultats de ce test furent indubitablement anormaux. Aucune anomalie n’apparut avant la fin de la première année, mais après cela il n’y eut pas de relation entre la dose totale, la durée totale et le début de la dépression.

On répète le test après un intervalle d’un an chez 19 malades pour déterminer les effets du traitement stéroïdien modifié ou non.

La dose quotidienne de 5 mg. de prednisone n’est pas exempte du danger de dépression surrenale. La variation de la sensibilité individuelle est si grande que des prédictions ne peuvent pas être faites, et que chaque malade doit être traité comme un cas particulier. La fonction surrenale suit son cours prévu, compte tenu simplement de la relation entre dose et réponse pendant une certaine période, mais la labilité individuelle est encore présente.

La respuesta del cortisol plasmático al Synacthen en enfermos tratados durante un tiempo prolongado con dosis pequeñas de prednisona

SUMARIO

En 39 enfermos sometidos a un tratamiento prolongado con pequeñas dosis de esteroides se buscaron pruebas de depresión de la función suprarrenal por el test de Synacthen. En cuatro enfermos los resultados de este test fueron inequívocamente anormales. No anomalías ocurrieron durante el primer año del tratamiento, pero a partir del segundo año no hubo relación alguna entre la dosis total, la duración total y el principio de la depresión.

En 19 enfermos el test fue repetido después de un intervalo de un año para determinar los efectos del tratamiento esteroide continuo o alterado.

La dosis diaria de 5 mg. de prednisona no se ve exenta del peligro de depresión suprarrenal. La variación de la sensibilidad individual es tal que el resultado no se puede anticipar y cada paciente debe tratarse separadamente. La función suprarrenal sigue un curso que se puede prever al estudiar la simple relación entre la dosis y la respuesta durante un período de tiempo, pero la variabilidad individual queda en evidencia.