ADRENAL CORTICAL FUNCTION IN PATIENTS WITH TETANUS

BY

M. J. LEVELL, S. R. STITCH, J. R. W. DYKES AND J. J. L. ABLETT

SUMMARY

Plasma cortisol concentrations have been measured in fifteen patients with tetanus at 2-3-day intervals throughout the period of treatment. The concentration at 9 a.m. was usually within the normal range, whereas the concentration at 11 p.m. was usually elevated above the normal range for that time of day. The patients with frequent episodes of hypertension showed the greatest elevation of the 11 p.m. concentration. Episodes of hypotension occurred in four patients, but were not associated with evidence of adrenal cortical exhaustion.

Selye (1946) proposed that stress stimulated the adrenal cortex and that failure of the cortex, either as a result of primary disease or as a result of exhaustion, would impair the ability to withstand stress. In man the adrenal cortex is stimulated by a variety of physical and emotional traumata and adverse environmental conditions but there has been little or no direct evidence of adrenal exhaustion (Cope, 1965).

If adrenocortical exhaustion occurs in man, evidence for it should be sought in situations of unusually prolonged stress, such as tetanus, in which a patient is likely to be severely ill for 2-3 weeks. In this disease several authors have reported the occurrences of marked cardiovascular instability (Ablett, 1967; Keilty et al., 1968; Kerr et al., 1968) and periods of hypotension (Clifton, 1964). We have examined plasma cortisol concentrations in patients with tetanus during treatment in order to assess the degree of adrenocortical response to this disease, and in particular to see whether episodes of hypotension were preceded by evidence of adrenocortical failure.

PATIENTS AND METHODS

Fifteen consecutive patients were treated for tetanus in the intensive care ward of the Leeds General Infirmary, fourteen of them on a regime of curarization and intermittent positive pressure ventilation (IPPV) for periods varying from 12 to 25 days. All were given barbiturates, phenothiazines and analgesics at some stage of their illness. In all cases, the patients had suffered only trivial injuries at the time of infection, so that the trauma of the original accident was unlikely still to be affecting the adrenal cortex. None gave a history of recent steroid therapy.

During periods of cardiovascular lability, blood pressure readings were made half-hourly and a score was counted, based on the number of spikes of systolic pressure of at least 40 mm Hg above the modal value for a particular 12-hour period. A systolic pressure of less than 80 mm Hg sustained for at least half an hour has been regarded as an episode of hypotension.

Plasma 11-OH corticosteroid (cortisol) concentrations were determined by the fluorimetric method of Mattingly (1962) with the modification of Spencer-Peet, Daly and Smith (1965). None of the patients was being given drugs known to interfere with this method. Recoveries of cortisol added to pooled plasma from tetanus patients were carried out, as were analyses on mixtures of plasma from tetanus patients and pooled normal plasma. Neither type of experiment indicated interference with the analytical method.

RESULTS

The 9 a.m. plasma cortisol values during the severe phase of the illness were either within the normal range (5-25 µg/100 ml in this laboratory) or were slightly elevated, only one value being over 40 µg/100 ml. The 11 p.m. values ranged from 3 to 53 µg/100 ml, most of them being abnormally high for this time of day. Comparison of the mean values for 9 a.m. and 11 p.m.

PLASMA CORTISOL CONCENTRATION (µg/100 ml) IN RELATION TO EPISODES OF HYPERTENSION.

Data from 15 patients under treatment for tetanus.

<table>
<thead>
<tr>
<th>Episodes of Hypertension</th>
<th>Plasma taken at 9 a.m.</th>
<th>Plasma taken at 11 p.m.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean  n  SEM  P</td>
<td>Mean  n  SEM  P</td>
</tr>
<tr>
<td>None within +24 hr.</td>
<td>21.2 47 1.3 &gt;0.1</td>
<td>18.8 41 1.2</td>
</tr>
<tr>
<td>At least one during previous 24 hr.</td>
<td>19.6 7 2.1</td>
<td></td>
</tr>
<tr>
<td>None on day of samples</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 on day of sample</td>
<td>24.4 9 1.9 0.05-0.1</td>
<td>29.2 9 3.3 &lt;0.001</td>
</tr>
<tr>
<td>2 on day of sample</td>
<td>23.1 8 2.3 &gt;0.1</td>
<td>22.7 7 3.0 0.05-0.1</td>
</tr>
<tr>
<td>3 on day of sample</td>
<td>26.6 5 5.6 0.02-0.05</td>
<td>24.4 5 5.6 0.02-0.05</td>
</tr>
<tr>
<td>4 on day of sample</td>
<td>26.0 3 4.5 0.05-0.1</td>
<td>27.0 3 1.4 &lt;0.001</td>
</tr>
</tbody>
</table>

P = Probability derived from t test against first group.

cortisols suggested that the normal diurnal rhythm had been lost. The elevation of the 11 p.m. values was particularly marked during periods of cardiovascular instability (see Table I). Because the hypertensive episodes were scored in 24-hour periods beginning at 9 a.m., the 9 a.m. cortisol was also related to episodes of hypertension occurring during the previous 24 hours (see table). Figure 1 shows the results from the four patients who had episodes of hypotension. In general these were not preceded by an irreversible fall of plasma cortisol concentration though there is the possibility of an association between the fall of plasma cortisol between days 11 and 13 and the third bout of hypotensive episodes in patient 1.

Fig. 1
Plasma cortisol [O-O 9 a.m.; ●-● 11 p.m.], episodes of hypertension (▲-▲) and episodes of hypotension (bars), against the number of days since the first symptom. The days of IPPV were for patient No. 1, 4–16; No. 2, 1–25; No. 3, 2–13; No. 4, 10–35.
DISCUSSION

Although the plasma cortisol concentration was raised in the majority of patients, at least in the evening, the values were lower than those we have often encountered in Cushing's syndrome or in patients on prolonged corticotropin therapy in which adrenal over-activity lasts for considerably longer than the acute phase of tetanus. Thus the degree of adrenal cortical stimulation in these patients should have been well within the capacity of the gland; indeed, none of the patients (with the doubtful exception of patient 1) showed changes which we could interpret as impending adrenocortical exhaustion.

The elevation of plasma cortisol was surprisingly modest. Bertrand, Lauras and Cautenet (1958) found values of 30–100 µg/100 ml in children with meningitis and, in a miscellaneous group of infections, noted that the plasma concentrations varied with the severity of the disease. Melby and Spink (1958) also found elevated values (40–78 µg/100 ml) in patients with shock due to infection and even higher concentrations in patients who died of the infection. Jacobs and Nabarro (1969) noted a wider range of values (13–72 µg/100 ml) in patients with acute infection. However, Perkoff and associates (1959) reported that, whereas pyrexial patients with no loss of consciousness had a mean plasma cortisol value of 35 µg/100 ml, those with a reduced level of consciousness had a mean of 22 µg/100 ml. This latter figure is of the order found in our tetanus cases in whom the level of consciousness had been reduced by sedatives. The normal ranges of the three groups of workers cited were in each case similar to, or slightly lower than our own. Two explanations may be offered for our failure to obtain greater rises. First, the spasms of tetanus when controlled by drug therapy may be a lesser stress situation than the clinical impression would lead one to believe, and in support of this is the suggestion that the adrenocortical response in other situations depends on the degree of shock (Einerth, Hedner and Wiklander, 1965). The highest levels (43 and 53 µg/100 ml) noted for the 11 p.m. plasma cortisol values were in two patients in whom tubocurarine had been withdrawn but in whom it was subsequently restarted.

Alternatively, the drugs which these patients were receiving may have interfered with the response. In particular chlorpromazine, barbiturates and narcotics have been shown to affect adrenal cortical function, at least in experimental animals. The position in man is less clear. Chlorpromazine has been shown to block the adrenal response to hypoglycaemia (Christy et al., 1956) and to metyrapone (Saarimaa, Sourander and Rinne, 1963). Patients 1, 2 and 4 (fig. 1) received chlorpromazine throughout, patient 3 on days 1–6 only. Barbiturates have little effect on the adrenal response to stress (Siker, Lipschitz and Klein, 1956) although they may suppress resting adrenal output. The blocking effect of narcotics has been demonstrated in rats and appears to depend upon the magnitude of the stress; in a study in man pethidine failed to block the response to surgical stress (Oyama et al., 1969).

Four of the patients had periods of hypotension. Patient 3 had recurrent episodes during the first 3 days following her transfer from another hospital, associated with fluid depletion and previous over-indulgent drug therapy. Her plasma cortisol values at the end of this period were not low. Patients 2 and 4 also did not show evidence of decreased plasma cortisol concentrations, nor did patient 1 on two of three occasions. However, our observations do not exclude a possible contributory role of the adrenal cortex: for example, hypotensive episodes following withdrawal of steroid therapy may be associated with a normal plasma cortisol concentration but may still be due to a relative adrenocortical insufficiency (Robinson, Mattingly and Cope, 1962).

The patients exhibited a loss of normal diurnal rhythm of plasma cortisol concentration with a mean value of about 1.1 for the ratio 11 p.m./9 a.m. compared with about 0.5 in normals (calculated by interpolation from the data of Perkoff et al., 1959). The diurnal rhythm of cortisol is related to the pattern of sleeping (Perkoff et al., 1959; Orth, Island and Liddle, 1967). Our tetanus cases were in a permanently hypnotic state for 2–3 weeks with abolition of a normal sleep pattern and this may have caused the loss of diurnal rhythm.

An alternative mechanism for this loss is suggested by the observations of Clayton and associates (1963) that the response to lysine vasopressin, which stimulates ACTH release, was
greater at midnight than at 9 a.m. Our observation that the 11 p.m. values showed a closer association with the severity of the disease (as judged by cardiovascular instability) than the 9 a.m. values, supports the suggestion of Clayton and associates that the response of the pituitary to stress may be greater at night than in the morning.

REFERENCES


FONCTION CORTICOSURRENALE DE PATIENTS TETANIQUES

SOMMAIRE

Les concentrations plasmatiques de cortisol ont été mesurées chez quinze patients avec tétanie à des intervalles de 3 à 5 jours durant l’équipe période de traitement. La concentration à 9 h du matin était en général normale, mais celle du 11 h du soir habituellement plus grande normallement à cette heure de la journée. Les patients avec des épisodes fréquents d’hypertension manifestèrent la plus forte augmentation de la concentration de 11 h du soir. Des épisodes d’hypotension manifestés chez quatre patients mais elles n’étaient pas associées à des signes d’épuisement corticosurréal.

NEBENNIERENRINDENFUNKTION BEI PATIENTEN MIT TETANUS

ZUSAMMENFASSUNG

Die Plasmakonzentration von Cortisol wurde bei 15 Patienten mit Tetanus in Abständen von 2-3 Tagen während der gesamten Behandlungszeit gemessen. Die Konzentration war um 9 Uhr morgens gewöhnlich innerhalb des Normalbereiches, wogegen die Konzentration um elf Uhr abends gewöhnlich über die Normalwerte dieser Tageszeit erhöht war. Die Patienten mit häufigen Perioden von Hypertonie zeigten um elf Uhr abends die größte Konzentrations erhöhung. Perioden von Hypotension traten bei vier Patienten auf, waren jedoch von keinem Hinweis auf eine Nebennierenrindentheskopfung begleitet.

* Available on request from the General Infirmary at Leeds.