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Plasma Cortisol Levels in Mania: Associated Clinical Ratings and Changes during Treatment with Haloperidol

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Summary: Plasma cortisol levels were elevated in a large proportion of samples from manic patients. Although a correlation was found between clinical ratings of the severity of mania and the degree of elevation of daytime cortisol levels, some patients with low clinical ratings had elevated cortisol levels. During treatment with haloperidol, cortisol levels returned to normal earlier that the clinical state. The underlying mechanisms are discussed.

There have been few studies of circulating corticosteroids in mania, as opposed to depression (Butler & Besser, 1968; Besser & Edwards, 1972; Carroll, 1979). Frequent sampling over 24 hours has revealed raised mean levels of plasma cortisol in severe but not mild cases, in the few manic patients investigated (Sachar, 1975; Akesode *et al*, 1976). Levels are raised above normal more often in samples taken at midnight than in the morning samples (Platman & Fieve, 1968; Carpenter & Bunney, 1971).

The present study concerns the relationship between circulating cortisol levels and clinical ratings of mania, as well as the effects of treatment upon these variables. If the increase in plasma cortisol was a direct consequence of the manic state, there should be a relationship between the severity of mania and the increase in circulating cortisol. Alternatively, if the increase arises indirectly, for instance through the depressive or dysphoric symptoms or through the non-specific stresses associated with mania, the relationship to ratings of clinical severity of mania might be less obvious.

We have previously reported that during treatment of mania with pimozide, plasma cortisol levels fell gradually over two weeks, as the clinical state improved (Cookson *et al*, 1980). The changes in plasma cortisol and in clinical state have now been assessed during treatment with haloperidol. This drug is of particular interest because it differs from pimozide, a selective dopamine-receptor-blocking drug, by having in addition a blocking effect at alpha-one adrenoceptors (Anden *et al*, 1970, Szabadi *et al*, 1981). Alpha-one receptors are involved in the normal control of secretion of pituitary corticotrophin by promoting neurosecretion of corticotrophin-releasing hormone from the median eminence of the hypothalmus (Grossman & Besser, 1982).

Method

Patients

The 31 in-patients (18 female, 13 male) who were studied met diagnostic criteria for mania according to the American Diagnostic and Statistical Manual (DSM-III); patients with mood-incongruent psychotic features were excluded. Although DSM-III allows the diagnosis of mania in patients showing irritability without elation, no patients in the series showed this. Twenty one patients had irritability combined with elation. Patients with intercurrent physical illness were excluded, as were patients on medication for chronic illness, with the exception of one on thyroxine, and one on a diuretic for hypertension. Twenty one patients were known to have had previous episodes of both depression and mania, three had only manic episodes, and three had only depression in the past. For four patients, this was their first known episode of affective illness, while six patients were studied during two separate manic episodes. The age-range was 18-78 (mean, 51) years. Whenever possible, patients were observed without anti-psychotic medication, before entry to the study; this was for two days or more in 16 patients. While under observation, four patients received nitrazepam (5-10 mg) at night. In the week preceding entry to the study, the number of patients known to have received medication was as follows: benzodiazepines (2), anti-psychotics (4), antidepressants (1), lithium (4).

Clinical ratings and blood sampling

Blood samples were taken at 0900, 1800, and 2400 hours; the patients were assessed using the rating scale of Petterson *et al*, (1973). This contains eight items, rated with anchor points; as a measure of severity the sum score minus eight was used, so that normal subjects would score zero. The eight items are: motor activity, pressure of speech, flight of ideas, noisiness, aggressiveness, orientation, elevated mood, and a global rating (inclusion of which allows the rater to take account of features such as disinhibition and gradiosity that are not specifically rated). Of 37 manic episodes studied, three-point cortisol levels were obtained in 30 cases (Figures 1 & 2); for the remainder, only two points were obtained, owing to the urgency for treatment.

Fourteen patients who had been studied during mania were re-examined when they were fully recovered and had been off psychotropic medication (except lithium in six cases) for at least one week; three patients were in-patients, while the remainder attended the ward as out-patients for venepuncture at 0900 and 1800 hrs.

Seven patients had blood samples taken on two separate days during their in-patient stay for mania, with an intervening drug-free observation period of one to 14 days (mean 4.2 days).

Eight manic patients were re-examined, both three days after commencement of medication with intravenous and/or oral haloperidol (12–40 mg/day in divided doses) and after full recovery (Figure 3). Five of these were receiving procyclidine orally (up to 30 mg daily) while on haloperidol. Intravenous haloperidol (2.5–10 mg) was used to initiate treatment in nine patients. Blood samples were taken at intervals before and after the injection as part of a previously reported study (Cookson *et al*, 1983); in four of these, samples were taken from an indwelling heparinised venous cannula, but the injection was given in the other arm.

The responses of six of these patients to treatment with pimozide have been previously reported (Cookson *et al*, 1980).

Plasma samples were stored at −20°C and assayed fluorimetrically by the Mattingly method for corticosteroids. The assay was performed in the setting of a clinical endocrinology department with long experience of its use in endocrine patients and normal volunteers (Besser & Edwards, 1972).

Non-parametric statistics were used (Fisher, Wilcoxon, and Mann-Whitney tests, and Spearman rank correlation).

Results

Pre-treatment

Figures 1 and 2 show the three-point plasma cortisol levels found during 30 episodes of mania, divided according to whether the day-time levels were in the normal range or above it. Raised levels of circulating cortisol were found in

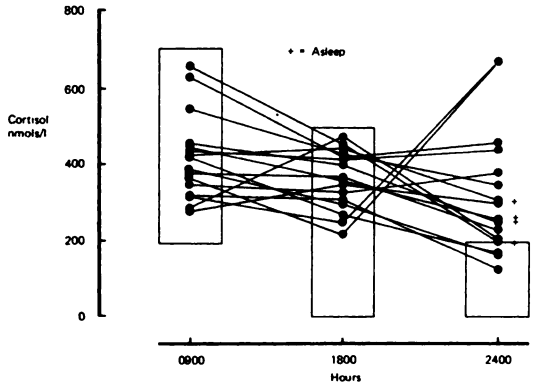

FIG. 1 Plasma cortisol levels in sixteen manic patients with daytime levels in the normal range (boxed area).

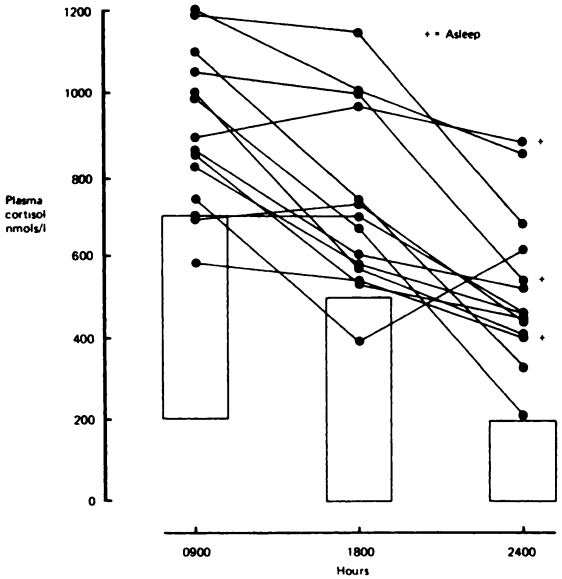

FIG. 2 Plasma cortisol levels in fourteen manic patients with a raised daytime level.

half of the samples taken at 0900 or 1800 hrs, but in 26 taken at 2400 hours. Raised levels were found in midnight samples in six patients, despite them being asleep at the time of the sampling.

Clinical ratings of severity were higher in patients with raised day-time levels of cortisol (median = 17; range 8–24) than those with normal levels (median = 12; range 6–21) (n = 37, u = 84, P <0.01).

Of 14 episodes with a clinical rating above 15, only one was accompanied by normal day-time levels of plasma cortisol, but of 23 episodes with ratings lower than 15, six were accompanied by raised levels of cortisol. Cortisol levels in the day-time correlated with clinical ratings of mania (r = 0.47, n = 37, P <0.01). The correlation between clinical ratings and midnight levels of cortisol was not significant (r_s = 0.2, n = 33). Irritability was detected in all patients with clinical ratings above 15, and in eight of the 23 with lower ratings. Among the latter group, the detection of irritability did not distinguish those with raised day-time cortisol levels from those with normal levels.

Plasma levels of cortisol did not alter significantly during a drug-free observation period. Levels (mean±SEM) before and after observation were as follows: at 0900 hrs (732±127 nM/L 'v' 763±139, n = 6), at 1800 hrs (556±75 'v' 609±91, n = 7) and at 2400 hrs (486±64 'v' 484±35, n = 7). Levels in individual patients before and after drug-free observation were significantly correlated by rank order at 0900 hrs(r_s = 0.94, P <0.01) and at 1800 hrs (r_s = 0.83, P <0.01), not at 2400 hrs (r_s = 0.07).

In fully recovered patients, cortisol levels were all within the normal range. Patients whose day-time levels

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had been above the normal range during mania had significantly lower levels ($P \leq .01$) on recovery at 0900 hrs (905±46 nM/L 'v' 467±30), at 1800 hours (714±63 'v' 276±31) and at 2400 hrs (578±65 'v' 120±21); $n = 10$, except for midnight after recovery when $n = 3$. In patients whose day-time cortisol levels were within the normal range during mania, the levels after recovery were lower at 1800 hrs (383±22 'v' 254±32, $n = 7$, $P < .05$), but not at 0900 hrs (426±43 'v' 390±23, $n = 7$); no patient in this group was studied at 2400 hrs, after recovery.

Effects of haloperidol

After two or three days treatment with haloperidol, the levels of cortisol had fallen significantly at 0900 hrs ($P < 0.02$), 1800 hrs $P < 0.02$), and 2400 hrs ($P < 0.05$). All values were then within normal limits, and were not significantly different from those in the same patients after full recovery, although the patients were still clinically manic (Figure 3).

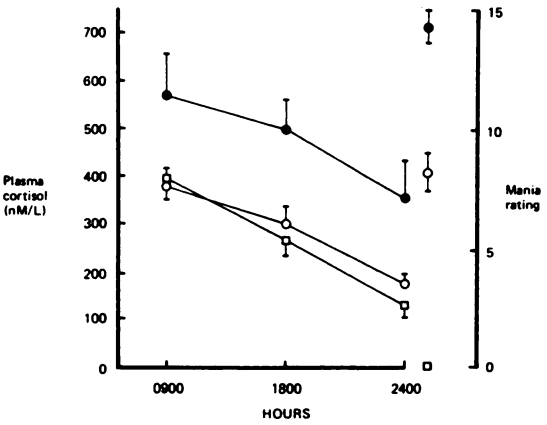

FIG. 3 Cortisol levels (mean±SEM) and clinical ratings in eight manic patients before treatment (●), after three days of treatment with haloperidol (o) and at full recovery (□). Only 2 patients were sampled at midnight after recovery.

In nine patients whose initial medication was intravenous haloperidol, a fall in plasma cortisol level after 60 minutes, compared to the pre-injection level, was seen in only two cases, and these were the only two who were asleep at the time of sampling ($P < 0.5$).

Discussion

In this series of manic patients, plasma cortisol levels were consistently raised in about half, but abnormal at some time in all but five patients. The elevation was more evident in the evening and at midnight than in the morning; the midnight levels were elevated in 26 of the 31 patients, often markedly so and into the range seen in severe Cushing's syndrome. Raised levels of plasma cortisol occur in patients hospitalised for a variety of psychiatric disorders (Swigar *et al*, 1979); nevertheless, an explanation of the neurochemical mechanisms leading to the high levels of circulating cortisol that were observed might help in understanding the pathogenesis of mania.

Part of the variation in plasma cortisol levels was attributable to differing severity of mania between patients, but raised levels were found in some patients with relatively low clinical ratings. Levels of cortisol in CSF tend to be raised in mania, without correlation to the ratings of clinical severity (Gerner & Wilkins, 1983). Factors other than mania *per se* may therefore underly part of the rise in cortisol levels.

A proportion of manic patients show a resistance to suppression of plasma cortisol by dexamethasone in the dexamethasone suppression test (DST), although no relationship with the severity of mania has been found (Graham *et al*, 1982). It was claimed that an abnormal DST occurs when there is an admixture of depressive symptoms in mania (Carroll, 1979), and this has been confirmed (Evans & Nemeroff, 1983; Krishnan *et al*, 1983). An abnormal DST may also be found a few days before a switch from mania to depression in rapidly cycling manic-depressives (Greden *et al*, 1982). An earlier study had found normal DST in a large series of manic patients during treatment (Schlesser *et al*, 1980).

Thus, both the severity of mania and the admixture of depressive symptoms may contribute to the increase of circulating cortisol. However, depressive symptoms are common during mania and can be difficult to assess.

Another factor to be considered is that ventricular enlargement is seen in CT scans in some manic-depressives, and that this correlated with increased urinary free cortisol levels (Kellner *et al*, 1983).

Non-specific 'stress' related to the duration of mania and to accompanying weight loss, insomnia, overactivity, anxiety and irritability may also be relevant, but elevation of two other 'stress hormones', prolactin and growth hormone, does not occur, making this hypothesis unlikely (Cookson *et al*, 1982). A different clinical rating instrument would be required to assess the role of these separate items.

The manic state has been likened to the effect of amphetamines (Schildkraut, 1965). It is therefore interesting to note that the elevation of plasma cortisol produced by amphetamine shows a circadian variation, being greater later in the day (Besser *et al*, 1969); also, a small dose of amphetamine

given in the evening delays the normal circadian fall in cortisol levels (Butler *et al*, 1968). Amphetamine is thought to stimulate cortisol secretion by indirect activation of central alpha-one adrenoceptors (Rees *et al*, 1970). The same receptors might therefore be activated in mania, and the findings with haloperidol may be related to this, since this drug blocks alpha-one receptors as well as dopamine receptors at clinically relevant doses (Szabadi *et al*, 1981).

Although drug-free observation did not affect the levels, treatment with haloperidol lowered plasma cortisol to approximately normal levels within three days, in a sub-group of these manic patients. There appeared to be a dissociation during treatment between the early normalisation of cortisol levels and the more gradual improvement in clinical ratings which is known to continue for two weeks and is paralleled by a rise in prolactin levels (Cookson *et al*, 1983). In contrast to the present findings with haloperidol, in a previous study with pimozide, the fall in cortisol levels occured in parallel with clinical improvement (Cookson *et al*, 1982).

Though this difference between pimozide and haloperidol requires confirmation in matched series of patients, it might be related to the different pharmacology of the two drugs. Pimozide, is also a dopamine-receptor-blocking drug, but lacks activity at alpha adrenoceptors (Anden *et al*, 1970). An alpha-one adrenoceptor blocking drug, thymoxamine, has been shown to antagonise the rise in plasma cortisol induced in normal subjects by methylamphetamine (Rees *et al*, 1970). Interacting noradrenergic and opiate pathways in the hypothalamus are thought to be involved in the control of the pituitary-adrenocortical axis, through modulation of neurosecretion of corticotrophin-releasing hormone from the median eminence (Grossman & Besser, 1982). Haloperidol might lower cortisol levels by blockade of these alpha-one adrenoceptors in the hypothalamus.

However, the potency of anti-psychotic drugs in binding central alpha receptors is correlated also with their sedative properties (Peroutka & Snyder, 1980). Therefore the cortisol-normalising effect of haloperidol in mania might be mediated indirectly through the sedative properties of the drug, rather than through a direct effect on the hypothalamic control of the pituitary-adrenocortical axis.

Sedative drugs, whatever their mechanisms of action, may lower cortisol levels. For example, benzodiazepines and barbiturates lower circulating cortisol levels in normal subjects and exaggerate the normal circadian fall-off in ACTH secretion; this action is opposed by amphetamines (Butler *et al*, 1968). Our finding that intravenous haloperidol led to an early reduction of cortisol level only in patients who were obviously sedated seems in keeping with the idea that the sedative effect of haloperidol is involved; but this finding should be interpreted with caution since no placebo control was used and the stress of venepuncture can raise cortisol levels.

The levels of noradrenaline and its metabolite MHPG in the cerebrospinal fluid are elevated in mania (Post *et al*, 1978; Swann *et al*, 1983). The elevation is thought to result from increased activity in noradrenaline pathways in the brain, but it is unclear to what extent such overactivity precedes or is secondary to the changes in activity of other neuro-transmitters including dopamine (Silverstone & Cookson, 1982). Our present findings suggest that the activation of the pituitary-adrenocortical axis in some cases of mania may involve noradrenergic pathways and may be dissociable, by sedative alpha-one receptor-blocking drugs, from other aspects of mania. Another example of a dissociation between behavioural and noradrenergic measures which have been reported is that during the treatment of mania with lithium, CSF levels of MHPG are lowered, even in patients whose manic state ratings do not improve; however, the changes in ratings of anxiety do correlate with the lowering of MHPG levels (Swann *et al*, 1984).

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