Effect of meclastine, an H₁-antihistamine, on plasma ACTH in adrenal insufficiency

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Abstract. In order to evaluate the possible role of endogenous histamine in ACTH secretion we investigated the effect of the H₁ antagonist meclastine on plasma ACTH in patients with ACTH hypersecretion. Seven patients with primary adrenal insufficiency (group 1) and 5 patients with ACTH dependent Cushing's syndrome (group 2) were given an iv infusion of meclastine (4.8 mg/90 min). In patients of group 2 plasma ACTH was unaffected by meclastine infusion. However, in patients of group 1 with intact steroid feedback meclastine was followed by a significant drop in plasma ACTH as compared with ACTH levels after saline infusion (46.0 ± 4.6% vs 85.0 ± 7.0%, P < 0.01). These results suggest that histamine is involved in the control of ACTH secretion, possibly by stimulation of CRF release.

Histamine is a biogenic amine with neurotransmitter properties (Snyder & Taylor 1972) and is widely distributed in brain (Schwartz 1975). Highest concentrations are found in the median eminence of the hypothalamus and smaller concentrations are present in the suprachiasmatic, pre-mamillary, and arcuate nuclei (Brownstein et al. 1974), suggesting that histamine plays a role in CNS control of pituitary hormone secretion. In animals, histamine is suggested to be involved in the regulation of prolactin (Arakelian & Libertun 1977), LH (Libertun & McCann 1976), and ADH release (Bhargava et al. 1973), respectively. In man it has been reported that the antihistaminergic agents meclastine and dexchlorpheniramine inhibit the arginine-induced increase of hGH (Pontiroli et al. 1976). Administration of cimetidin, reacting antagonistic at H₂ receptor sites, is followed by a rise in serum prolactin in healthy man (Carlson & Ippoliti 1977).

Recently Rudolph et al. (1979) have shown that in pentobarbital-anaesthetized dogs small doses of intraventricularly administered histamine produce an increase in ACTH secretion without any detectable systemic effects. In a previous study on healthy volunteers we have shown that the administration of the H₁ antagonist meclastine is followed by a decrease in basal plasma cortisol concentration (Winkelmann et al. 1979). To further define the role of histamine in the regulation of the hypothalamus-pituitary-adrenal axis we studied the effect of meclastine in patients with elevated plasma ACTH levels due to primary adrenal insufficiency or ACTH dependent Cushing's syndrome.

Materials and Methods

Seven patients (3 males and 4 females) suffering from primary adrenal insufficiency were studied (group 1): 5 patients with Addison's disease and 2 patients with congenital adrenal hyperplasia. In addition 5 patients with ACTH dependent Cushing's syndrome (1 male and 4 females) were tested (group 2). Four of these patients had undergone bilateral or unilateral adrenalectomy. Written informed consent was obtained from all patients. Remarkable side effects of meclastine have not been observed except for a slight fatigue in some cases. The blood pressure remained unchanged during the infusion. Hypertensive values were measured in two patients with Cushing's syndrome only, while the blood pressure
was normal in all other cases (clinical data are given in Table 1).

Substitution therapy was withdrawn for at least 16 h before starting the tests. All tests were done following an overnight fast and were started between 8 and 9 a.m. An indwelling needle was placed into a forearm and kept open by a slow saline infusion. Before starting meclastine infusion 3 baseline blood samples were taken at −30 min, −15 min and at zero time. Meclastine was given in a total dose of 4.8 mg/90 min, starting with 2.4 mg for the first 30 min and followed by 2.4 mg for the remaining 60 min. Additional blood samples were taken at 15, 30, 45, 60, 75, 90 and 120 min. In patients with primary adrenal insufficiency control infusions with saline were done after an interval of at least on week.

ACTH was determined by radioimmunoassay after extraction of ACTH from plasma using QUSO G2 according to Voigt et al. (1974). After a five day incubation period in the cold (+4°C) separation of free and bound ACTH was performed by the method of Donald (1968) using Dextran coated charcoal.

\[ ^{251} \text{ACTH} \] was purchased from Isotopendienst West (Frankfurt/M, FRG). The antibody used is directed against the N-terminal part of the molecule and shows full cross-reactivity to 1-24 ACTH, 11-24 ACTH and 1-39 hACTH. No cross-reactivity was found to 1-10 ACTH, 27-39 hACTH, \( \alpha \)-MSH, or \( \beta \)-MSH. We used a preparation of 1-39 hACTH of the Medical Research Council (74/555) as standard, and found a physiological range of 2–50 pg/ml at 9 a.m.

Cortisol was measured by RIA using commercially available reagents (NEN Chemicals, Dreieich 4, FRG). Statistical evaluation of the data was performed using Student's t-test.

### Results

Patients with primary adrenal insufficiency (group 1) exhibited elevated plasma ACTH levels, from 105 to as much as 3490 pg/ml (Fig. 1). After starting the meclastine infusion all patients showed a progressive decrease in plasma ACTH which lasted throughout the infusion period. The extent of ACTH decrease was not related to either the primary cause of hypersecretion or to sex or plasma cortisol values of the patients (Fig. 1). During meclastine infusion plasma cortisol also dropped in patients with congenital adrenal hyper-

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**Table 1.**

Clinical data of patients with ACTH hypersecretion.

<table>
<thead>
<tr>
<th>Patients</th>
<th>Sex</th>
<th>Age (years)</th>
<th>Body weight (kg)</th>
<th>Blood pressure (mmHg)</th>
<th>Diagnosis</th>
<th>Surgical treatment</th>
<th>Plasma cortisol (9 a.m.) (( \mu g/100 \text{ml} ))</th>
<th>Plasma ACTH (9 a.m.) (pg/ml)</th>
</tr>
</thead>
</table>
| I. Intact steroid feedback
| 1 C. H. | F   | 35          | 50.9             | 115/60                | Addison's disease | –                   | 0.2                                       | 3490                          |
| 2 K.-H. W. | M  | 30          | 64.0             | 105/60                | Addison's disease | –                   | 2.0                                       | 1980                          |
| 3 K.-H. S. | M  | 35          | 57.0             | 110/60                | Addison's disease | –                   | 2.8                                       | 820                           |
| 4 H. W. | M   | 57          | 87.2             | 130/80                | Addison's disease | –                   | 2.8                                       | 607                           |
| 5 A. B. | F   | 53          | 53.4             | 130/85                | Addison's disease | –                   | 0.1                                       | 990                           |
| 6 T. V. | M   | 20          | 48.5             | 120/80                | congenital adrenal hyperplasia | –                   | 8.4                                       | 2900                          |
| 7 B. R. | F   | 33          | 50.8             | 105/80                | congenital adrenal hyperplasia | –                   | 7.4                                       | 105                           |

II. Altered steroid feedback

| 1 A. K. | F   | 45          | 76.0             | 135/90                | Cushing's disease | bilateral adrenalectomy | 0.4                                       | 2430                          |
| 2 M. M. | F   | 46          | 73.6             | 170/70                | Cushing's disease | –                   | 32.1                                      | 63                            |
| 3 H. T. | M   | 40          | 70.4             | 180/100               | Cushing's disease | unilateral adrenalectomy | 48.8                                      | 152                           |
| 4 M. G. | F   | 37          | 75.7             | 110/90                | Cushing's disease | bilateral adrenalectomy* | 15.8                                      | 595                           |
| 5 A. W. | F   | 51          | 72.5             | 140/70                | Cushing's disease | bilateral adrenalectomy** | 11.6                                      | 1430                          |

* Local remnant. ** Ectopic remnant.

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plasia from 8.4 to 5.1 and from 7.4 to 5.2 µg/100 ml, respectively.

When depicted on a logarithmic scale, the slope of ACTH was found to be similar in all patients, irrespective of basal ACTH values. Therefore the mean ACTH levels of all patients are given in per cent of the mean of the 3 baseline values (Fig. 2). During meclastine infusion a significant inhibition of ACTH release was observed as compared to saline infusion: ACTH levels were 65.3 ± 5.7 vs 89.0 ± 3.0% at 30 min (P < 0.02), 49.0 ± 4.8 vs 83.0 ± 5.0% at 60 min (P < 0.01) and 46.0 ± 4.6 vs 85.0 ± 7.0% at the end of the infusion (P < 0.01), respectively. After cessation of meclastine administration plasma ACTH levels evidently increased but still remained below starting values. There was no correlation between body weight and meclastine-induced ACTH decrease.

An effect of meclastine on plasma ACTH in patients with ACTH dependent Cushing’s syndrome (group 2) was not obvious. In one patient only (M.G.) a decrease of ACTH from 595 pg/ml to 390 pg/ml was observed (Fig. 3). The decrease might be due to spontaneous fluctuations.

Fig. 2.
Plasma ACTH levels in 7 patients with primary adrenal insufficiency during administration of meclastine (●) and saline (◆) and in 5 patients with Cushing’s disease receiving meclastine (×). ACTH values are given as per cent of the means of three basal values.

Discussion
At present histamine is suggested to be a putative neurotransmitter in the brain (Schwartz 1975). The general distribution pattern is similar to other biogenic amines such as norepinephrine and 5-hydroxytryptamine (Snyder & Taylor 1972). It is well established that systemic administration of histamine stimulates ACTH secretion in rats (Dallman & Yates 1968) and dogs (Cowan 1975). However, this effect is mediated by an unspecific stress response due to pain or changes in blood pressure (Meyer & Knobil 1967). Thus, in humans a very promising approach in elucidating the role of histamine receptors in the regulation of pituitary hormone secretion consists in the evaluation of the effects of specific antagonists. It now appears that, for this amine, the H₂ antagonist meclastine is a particular suitable probe since it lacks antiserotonergic, antiadrenergic or anticholinergic effects (Römer & Weidmann 1966). The results presented here indicate that meclastine is a potent inhibitor of
ACTH secretion in patients with elevated ACTH levels that are due to primary adrenal insufficiency.

These studies with meclastine may reflect a stimulatory effect of histamine on ACTH release. This would be in agreement with the findings of Rudolph et al. (1979), who have reported a rise in ACTH secretion in dogs after intraventricular administration of histamine, possibly by stimulation of H1 receptors. In humans similar studies are so far lacking. In recent years, various investigators have shown the antihistaminergic agent cyproheptadine to inhibit ACTH secretion under a number of conditions (Plonk et al. 1974; Delitala et al. 1975; Krieger et al. 1975). These effects, however, have been thought to be related to the antiserotonergic properties of the compound.

There are several possible sites at which histaminergic neurons could act, thus affecting secretion of ACTH and/or CRF. While in vitro no direct effects of histamine on anterior pituitary cells have been found, the most likely explanation would be an action via release of hypophysiotrophic hormones like CRF (Weiner & Ganong 1978). Other pharmacological actions of meclastine, which are unrelated to its antihistaminergic properties, cannot fully be excluded. In rhesus monkeys cardiovascular or sedative effects have been reported (Römer & Weidmann 1966). However, meclastine concentrations 25 times in excess of those in our studies were used. – In a previous study (Winkelmann et al. 1979) we have shown that meclastine leads to a decrease in basal plasma cortisol levels in healthy volunteers, probably by inhibition of ACTH release. These findings suggest that the suppressive action of meclastine on plasma ACTH is not only present in a steroid depleted state, but also in normal subjects with intact pituitary-adrenal axis. Preliminary data from our laboratory on the effect of meclastine on hypoglycaemia-induced ACTH increase support this notion.

In all patients with ACTH dependent Cushing’s syndrome no inhibitory effect of meclastine on plasma ACTH was detected. Thus different from the effects observed with somatostatin (Fehm et al. 1976) an intact steroid feedback control seems to be a prerequisite for the effect of acute meclastine administration on plasma ACTH concentrations.

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References


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