EFFECTS OF ADMINISTRATION OF METOPIRON
AND OF DELIVERY ON HUMAN PLASMA
CORTICOTROPHIN

By
Tore H:son Holmdahl

ABSTRACT

The ACTH activity of human peripheral blood was assayed during two
types of stimuli: 1) administration of SU-4885 (Metopiron® CIBA),
2) normal delivery. Metopiron produced an increase of plasma ACTH
activity in 3 normal subjects but failed to do so in 1 case of pituitary
tumour. Of the 7 cases of normal delivery studied, 4 showed a significant
increase in plasma ACTH activity at the time of delivery.

The quantitative assay of the corticotrophic activity of human peripheral blood
plays an important part in the clinical investigation of cases of endocrinological
disorders. Not only can it be used for the determination of the normal
("resting") level of ACTH, but it can also be used for estimating the pituitary
ACTH-reserve.

The reports on human plasma ACTH are, however, conflicting. Some
authors have found high values of ACTH (Bornstein & Trehwhella 1950; Montanari et al. 1951; Parrott 1951; Rossi et al. 1952; Gray & Parrott 1953; Moruzzi et al. 1954), others low or non detectable levels of blood ACTH (Taylor et al. 1949; Sydnor & Sayers 1952; Sydnor et al. 1953; Salassa & Albert 1954). Sayers (1955) claims that the normal level of blood ACTH is
less than 0.5 mU per 100 ml of blood.

Assay of the resting level of plasma ACTH can be of importance in
establishing the diagnosis of Cushing's syndrome. Davies (1964) found that in
this condition the mean blood ACTH values were three to four times those
of normal subjects.

Several attempts have been made to develop tests of pituitary function in-
volving ACTH assays. Vernikos-Danellis & Marks (1962) used the epinephrine induced release of ACTH as a pituitary function test.

In the last few years the use of SU-4885 (Metopiron CIBA) for testing pituitary function has found widespread acceptance. This is an indirect test of the pituitary function and the outcome of the test is influenced by the adrenal cortex. Attempts have been made to use the Metopiron test as a »direct« test of the pituitary function by measuring the plasma ACTH level after Metopiron administration (Meakin et al. 1960; Liddle et al. 1962; Vance et al. 1962). The published results are, however, conflicting. In animal experiments Cushman et al. (1963) have found evidence supporting the view that plasma ACTH-like activity increases after intravenous Metopiron administration in the dog.

This report presents some evidence in favour of the view that blood ACTH assays during Metopiron administration can be of value in testing pituitary function. It also deals with ACTH release due to obstetrical stress.

METHODS AND MATERIALS

In the present report, plasma ACTH has been assayed by using a modification of Sayers' test (Sayers et al. 1948). In order to block the endogenous ACTH release in the test animals, prednisolone has been administered prior to the assay. This acts as a substitute for hypophysectomy in the original Sayers' test (Hamburger 1960). The method for ascorbic acid determination in the original test has been replaced with the method of Dekanski & Harvie (1960). ACTH was extracted from plasma using an acid-acetone extraction procedure (Gemzell et al. 1951).

Two different types of stimuli for increased ACTH release were studied: 1) administration of Metopiron, 2) normal delivery. Metopiron inhibits the 11β-hydroxylase in the adrenal cortex. This results in a depression or even complete arrest of the synthesis of cortisol (compound F), aldosterone and corticosterone. The cortisol level of peripheral plasma falls to low or not detectable levels. Plasma cortisol normally regulates the output of ACTH from the pituitary by feed-back inhibition. The Metopiron induced fall of plasma cortisol results in an increased ACTH release. The high level of ACTH stimulates the adrenal cortex: due to the inhibition of the 11β-hydroxylase, however, only the precursors of cortisol and corticosterone are synthesized. These precursors, 11-deoxycortisol (substance S) and 11-deoxycorticosterone, are found to be increased in the peripheral plasma, and are excreted as 17-OHCS and as 17-ketogenic steroids in the urine. The blood level of substance S has little or no effect on ACTH release from the pituitary. In the Metopiron cases in this report, the patients were given 750 mg of the drug orally. Blood samples were withdrawn at intervals of 10 minutes starting 10 minutes after the administration of Metopiron. The blood was rapidly transported in ice to the laboratory and the plasma withdrawn and put into the deep-freeze within 30 minutes. For the study of the obstetrical stress, blood samples were taken as follows: 1) during the final stage of labour, approximately half an hour prior to the expected time of delivery; 2) at the time of delivery; and 3) half an hour after delivery. The deliveries were normal (no surgical intervention, blood loss less than 600 ml).
Adrenal ascorbic acid depletion (AAAD) due to normal saline and to normal saline containing known amounts of ACTH. Vertical lines indicate standard errors, numbers of test animals are given in brackets.

Since the primary aim of this report has been to show relative changes in ACTH activity, no attempt has been made to express the ACTH concentration in blood in terms of mU/ml. A dose-response curve based on bioassay of known amounts of ACTH is given in Fig. 1.

RESULTS

The effect of Metopiron on plasma ACTH has been studied in 4 patients (Fig. 2). Case A was a 78 year old man admitted to the hospital because of bilateral atrophy of the optic nerves. X-ray showed a sagittally expanded sella turcica with decalcification of the dorsal part. The left eye was amaurotic, vision in the right eye was 0.4. Surgery later showed a chromophobic adenoma of the pituitary gland. Cases B, C and D were women aged 27, 30 and 31 years respectively. They were admitted to the hospital because of infertility of non-hormonal origin. Urinary excretion of 17-OHCS, 17-ketosteroids, and total gonadotrophins were within normal limits. X-rays of the sella turcica were normal. These 3 cases were consequently regarded as »normal pituitary cases«.

Blood ACTH in the 3 normal cases showed a marked rise, 20 and 30 minutes after the Metopiron administration. In the case of the pituitary tumour no rise in ACTH above the resting level occurred. The ACTH level in the 3 normal cases were all significantly elevated 20 minutes after Metopiron.
Adrenal ascorbic acid depleting activity of human peripheral blood at intervals of 10 minutes following Metopiron administration to 4 subjects. A is a case of pituitary tumour; B, C and D are normal cases. Vertical lines indicate standard errors.

**Fig. 2.**

Adrenal ascorbic acid depleting activity of human peripheral blood before, during and after delivery.

Of the 7 cases of normal deliveries studied, 4 showed a significant rise in blood ACTH at the time of delivery (Fig. 3). Two of the cases showed resting levels of ACTH at the time of delivery. The postpartum levels of ACTH were elevated in some of the cases, in 1 of the cases the postpartum level was significantly above the normal resting level of blood ACTH.

584
DISCUSSION

The clinical use of Metopiron for the detection of pituitary disorders usually involves determination of the urinary secretion of 17-OHCS and 17-ketogenic steroids. This preliminary study suggests that blood ACTH assays may also be of importance in establishing a diagnosis of pituitary insufficiency. Reports of plasma ACTH activity following Metopiron have been conflicting. Meakin et al. (1960) found that blood ACTH assays after Metopiron administration was a useful tool in estimating the pituitary secretory capacity in patients with unresponsive adrenal glands. Liddle et al. (1962) found elevated ACTH levels in blood after administration of Metopiron in normal subjects. Vance et al. (1962), however, did not find detectable levels of ACTH after Metopiron in normal subjects. In one patient with Addison's disease they found lower ACTH value after Metopiron. In none of these reports, however, was an attempt made to measure plasma ACTH within the first hour after the Metopiron administration. Vance et al. (1962) infused Metopiron intravenously for two hours and started ACTH assays when the infusion was discontinued, that is two hours after the first dose. In none of the normal cases described in this report was any elevation of plasma ACTH level found.

In the study of Vernikos-Danellis & Marks (1962) it was shown that ACTH release due to epinephrine infusion in normal subjects occurred very rapidly reaching a peak activity as soon as 2.5 minutes after the start of the infusion.

These earlier findings suggest that changes in plasma ACTH due to pituitary stimulation, either produced by stress or by an enzyme block in the adrenal cortex, occur very rapidly, hence, blood ACTH assays aimed at showing alterations in the plasma ACTH level should be performed within minutes rather than hours after the stimulation.

Studies of blood ACTH during delivery might be of clinical interest in cases subject to excessive bleeding and leading to pituitary ischaemic necrosis and subsequent insufficiency (Sheehan's syndrome). In two of the obstetric cases no ACTH increase at the time of delivery occurred. This might be due to prolonged exposure of the blood samples at room temperature. It is of vital importance to transport the blood in ice as rapidly as possible to the laboratory. The plasma should be separated and put into the deep-freeze within 30 minutes. All 7 cases studied were normal deliveries. The postpartum course in all cases was normal and uneventful.

REFERENCES


585
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