IMITATION OF THE ADRENO-CORTICAL RESPONSE TO SURGERY BY INTRAVENOUS INFUSION OF SYNTHETIC HUMAN ACTH

By

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ABSTRACT

The concentration of plasma corticosteroids was followed during major surgery and during the infusion of synthetic human ACTH at dose rates varying from 2400 ng to 15,000 ng per hour. The results showed that the time course of plasma corticosteroids during major surgery was intermediate between that obtained during the infusion of 7500 and 15,000 ng synthetic human ACTH per hour. This gives an estimated ACTH secretion rate during major surgery of between 7500 ng and 15,000 ng per hour.

During major surgery the plasma concentration of cortisol increases steeply reflecting an increase in the production of cortisol (Plumpton et al. 1969; Engell et al. 1960).

This event presumably is caused by a release of ACTH from the pituitary gland. The lack of suitable methods for direct determinations of ACTH secretion makes it difficult to evaluate the amount of ACTH secreted during a «stress» situation.

The purpose of the present study was to obtain an estimate of the endogenous secretion of ACTH during major abdominal surgery by reproducing the adreno-cortical response to surgery by the intravenous infusion of synthetic human ACTH.
MATERIAL AND METHOD

Forty seven patients without any signs or symptoms of endocrine, liver or renal disease were studied. None of them received any hormonal preparations.

Thirty seven patients were given an infusion of synthetic human ACTH (supplied by Dr. Mulder, AB Ferring, Malmö, Sweden) dissolved in 0.15 N hydrochloride acid (pH = 2.1) made isotonic with sodium chloride. The biological activity of the synthetic human ACTH was 100 IU per mg. The infusion was started at 8 a.m. through an indwelling cannula placed in a brachial vein. The ACTH infusion rate remained constant for the following 3 hours by using a Braun perfuser. The infused volume was always 30 ml per hour. Blood was sampled every 30 minutes through another indwelling cannula placed in the contralateral brachial vein.

Twenty eight patients were studied during non-acute major abdominal surgery. Surgery was initiated between 8 a.m. and 10 a.m. In those patients who were subjected to both ACTH infusion and surgery, the surgical procedure was performed one to five days after the ACTH infusion. All the patients were anaesthetized in the same manner (thiomebumalsodium, suxamethonichloride, N₂O + O₂ and halothane). Blood was sampled at the time of skin incision and then every 30 minutes until closure of the skin. The plasma concentration of corticosteroids (11-OHCS) was determined using a fluorimetical method (Mattingly 1962) slightly modified (Binder 1972).

RESULTS

The mean plasma concentrations of corticosteroids during major abdominal surgery in 28 patients are given in Table 1. Zero time was the time of skin incision. The adreno-cortical response showed a great variation between patients. No relation to the type or duration of surgery was found.

In order to mimic the adreno-cortical response to surgery, synthetic human ACTH was infused in 37 patients at dose rates from 2400 ng per hour to 15 000 ng per hour. The mean plasma concentration of corticosteroids during ACTH infusions are also given in Table 1.

The average time course of plasma corticosteroids during the ACTH infusions and during surgery is shown in Fig. 1. It is seen that the mean concentration of corticosteroids in plasma during the infusion of 15 000 ng of synthetic human ACTH per hour reached levels of about those obtained during major abdominal surgery. The mean response to the infusion of 7500 ng ACTH per hour was clearly less than the mean response to surgery.

Due to the great interpatient variation in the adreno-cortical response to ACTH infusion and surgery, 18 of the patients were studied during both procedures using dose rates of 4200 ng (4 patients), 7500 ng (5 patients) and 15 000 ng (9 patients) synthetic human ACTH per hour.

The average course of plasma corticosteroids during infusion and surgery for each dose rate group is illustrated in Fig. 2. It is seen that in the same patients the plasma corticosteroid levels obtained during surgery were inter-
Table 1.
The mean and standard error of the mean plasma concentrations of plasma corticosteroids (µg/100 ml) during major abdominal surgery and during ACTH infusions.

<table>
<thead>
<tr>
<th>Minutes</th>
<th>Surgery</th>
<th>ACTH infusion rate (ng per hour)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>2400</td>
</tr>
<tr>
<td>0</td>
<td>21.0 ± 1.4</td>
<td>19.4 ± 1.7</td>
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<tr>
<td>30</td>
<td>35.0 ± 1.4</td>
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<td>60</td>
<td>40.7 ± 1.6</td>
<td>25.4 ± 2.5</td>
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<tr>
<td>90</td>
<td>41.4 ± 1.5</td>
<td>23.8 ± 2.3</td>
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<tr>
<td>120</td>
<td>43.6 ± 1.7</td>
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<td>n</td>
<td>28</td>
<td>5</td>
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</table>
The average concentration of corticosteroids in plasma (µg/100 ml) during major abdominal surgery and during infusion of synthetic human ACTH at different dose rates.

mediate between those obtained during the infusion of synthetic human ACTH at a dose rate of 7500 ng and 15 000 ng per hour.

**DISCUSSION**

The plasma concentration of corticosteroids during major abdominal surgery and during infusion with synthetic human ACTH at different dose rates was measured. The adreno-cortical response to surgery was in accordance with other reports (Plumpton et al. 1969; Engell et al. 1960).

The average plasma concentration of corticosteroids during infusion with 7500 ng or less per hour of synthetic human ACTH did not reach the level obtained during major abdominal surgery. The average plasma concentration of corticosteroids during infusion with 15 000 ng synthetic human ACTH per hour reached a higher level than that obtained during major abdominal surgery. This thus gives an estimate of the endogenous ACTH secretion of between 7500 ng and 15 000 ng per hour during major abdominal surgery.

The great interpatient variability in adreno-cortical response to infusion with synthetic human ACTH and to major abdominal surgery makes this statement of doubtful significance. However, within the same patients, the average response to major abdominal surgery was intermediate between that obtained during infusion with 7500 ng and with 15 000 ng synthetic human ACTH per hour.
The average concentration of corticosteroids in plasma (μg/100 ml) during major abdominal surgery (dotted line) and during infusion of synthetic human ACTH (full line) at different dose rates, in the same patients.

The possibility of an endogenous production of ACTH during the ACTH infusion cannot be excluded. However, during the infusion of 600 ng synthetic human ACTH per hour no adreno-cortical response was observed.

An altered metabolism of cortisol during surgery would invalidate the estimate of ACTH secretion. Previous studies, using large doses of cortisol, showed an impaired cortisol metabolism during surgery (Tyler et al. 1954; Murray et al. 1958). However, Estep et al. (1966) using physiological amounts of labelled cortisol, found no alteration in the metabolism of cortisol before and during surgery.

Similarly a different metabolism of endogenous human ACTH as against exogenous human ACTH would invalidate our results. At present this problem is unsolved.
Ney et al. (1963) found an average ACTH concentration (bioassay) of 0.74 mU per 100 ml based on one plasma sample from patients undergoing major surgery. Berson & Yalow (1968), Yalow et al. (1969), Newsome & Rose (1971) and Ichikawa et al. (1971) found an ACTH concentration (immunoassay) of 200 – 1000 pg per ml both during and after major surgery.

Besser et al. (1971) have recently demonstrated that immunoreactive ACTH disappeared at a slower rate from the plasma than bioactive ACTH. The half time for disappearance of plasma ACTH varied from 5 minutes (bioassay) to 28 minutes (immunoassay).

Furthermore, the ACTH secretion rate determinations presupposes knowledge of the distribution volume of ACTH, which is at present unknown.

These results show therefore that there are at present considerable objections to direct determination of ACTH secretion in vivo and argue in favour of the indirect methods as used in the present study.

Based on our results we suggest that the «physiological» capacity of the adrenal cortex should be tested by the infusion of ACTH at a dose rate of about 12 500 ng per hour.

REFERENCES


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