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Papers

Plasma 11-Hydroxycorticoid Levels in Surgical Stress

by D Mattingly MRCP
and Christine Tyler BSc PhD
(Postgraduate Medical Institute,
University of Exeter)

The increased adrenocortical activity which accompanies surgical stress has been extensively investigated during the past twelve years (Franksson & Gemzell 1954, Sandberg *et al.* 1954, Steenburg *et al.* 1956, Hume *et al.* 1962). The plasma cortisol level rises sharply during surgery and provides a useful index of the timing and intensity of the adrenal response. Little practical use has been made of this knowledge, however, for most of the methods for estimating cortisol in plasma are too laborious for routine clinical use.

This is unfortunate, for the diagnosis of adrenal failure in surgical patients has become increasingly important with the widespread use of corticosteroid drugs. Hypotension during surgery is frequently thought to be a sign of adrenal failure but the diagnosis is rarely based on biochemical evidence. The rapid estimation of the plasma cortisol level in these patients is the only way of assessing adrenocortical activity at the time of collapse.

This is now possible with the development of a simple and rapid fluorimetric method for the estimation of free plasma 11-hydroxycorticoids (Mattingly 1962). This method is sufficiently accurate and reliable for routine clinical use (Mattingly 1963). The main free 11-hydroxycorticoid in human plasma is cortisol (hydrocortisone), but small amounts of corticosterone are present as well (Bush & Sandberg 1953). Only 2.0 ml of plasma is required for each estimation and the diagnosis of adrenal failure can, if necessary, be confirmed within an hour of taking blood from the patient. Plasma 11-hydroxycorticoid levels in normal subjects range from 6 to 24 $\mu\text{g}/100\text{ ml}$ between 9 a.m. and 10 a.m., and fall during the day to reach levels ranging from 0 to 6 $\mu\text{g}/100\text{ ml}$ at midnight.

The interpretation of random plasma 11-hydroxycorticoid levels (11-OHCS) in surgical patients requires a knowledge of the usual pattern of response to anaesthesia and surgery, and we have therefore followed the plasma 11-OHCS levels in a number of surgical patients.

Four patients undergoing abdominal surgery were premedicated with Omnopon and scopolamine, and anaesthetized with thiopentone, nitrous oxide and *d*-tubocurarine. Three patients had a total hysterectomy and one had a partial gastrectomy. The pattern of response was very similar in all 4 patients and is illustrated by the levels found in the patient described below.

Case 1 Woman, aged 48

This patient had a total hysterectomy for fibroids. Her plasma 11-OHCS level on the morning of operation was 7.6 $\mu\text{g}/100\text{ ml}$. The level had fallen to 1.2 $\mu\text{g}/100\text{ ml}$ one hour after premedication with 20 mg Omnopon and 0.45 mg scopolamine. It remained at this level during induction of anaesthesia with 0.5 g of 2.5% thiopentone, nitrous oxide and *d*-tubocurarine. There was a negligible rise in the plasma 11-OHCS level at the time of incision of the abdominal wall, but it rose to 24.7 $\mu\text{g}/100\text{ ml}$ when the fallopian tubes and round ligaments were cut some twenty-six minutes after the skin incision had been made.

When the operation was completed the plasma 11-OHCS level was 38 $\mu\text{g}/100\text{ ml}$, and it rose to 70 $\mu\text{g}/100\text{ ml}$ six hours later. By 10 a.m. the next morning it was down to 25 $\mu\text{g}/100\text{ ml}$ and had fallen to 15.5 $\mu\text{g}/100\text{ ml}$ at 10 a.m. on the second post-operative day (Fig 1). Her post-operative recovery was uneventful.

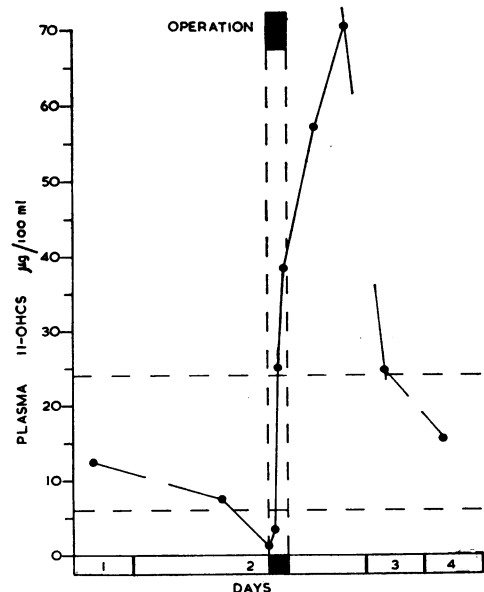


Fig 1 Case 1 Normal adrenocortical response to surgical stress. The horizontal broken lines show the normal range between 9 a.m. and 10 a.m.

The pattern of response seen in these patients can be divided into three phases: (1) The response to premedication and anaesthesia. (2) The response to surgery. (3) The response in the post-operative period. These will be discussed separately.

Premedication and Anaesthesia

The plasma 11-OHCS levels on the morning of operation were all within the normal limits and ranged from 7.6 to 19.2 $\mu\text{g}/100\text{ ml}$. One hour after premedication with Omnopon and scopolamine they had fallen and now ranged from 1.2 to 10.1 $\mu\text{g}/100\text{ ml}$. A further fall was seen in one patient after induction with thiopentone, nitrous oxide and *d*-tubocurarine. The levels at the end of induction ranged from 1.1 to 4.9 $\mu\text{g}/100\text{ ml}$.

Viikari & Thomasson (1957) followed the plasma 17-hydroxycorticoid levels in a group of patients undergoing thoracic operations. Their patients were heavily sedated with pethidine and anaesthetized with thiopentone and nitrous oxide. They also found a fall in the plasma corticosteroid levels after induction.

It is important to realize that very low plasma 11-OHCS levels may be found in normal patients at this stage of an operation and are not necessarily indicative of adrenal failure. This apparent inactivity on the part of the adrenals is presumably due to the depressive effect of these drugs on the central nervous system.

Response to Surgery

The plasma 11-OHCS levels in our patients showed a negligible rise during the incision of the abdominal wall and the initial handling of the viscera. Levels at this time ranged from 3.5 to 8.8 $\mu\text{g}/100\text{ ml}$.

The exact timing of the subsequent adrenal response was difficult to determine with certainty, but in one patient the plasma 11-OHCS level had risen from 4.0 to 26 $\mu\text{g}/100\text{ ml}$ sixteen minutes after the skin incision. All 4 patients had levels greater than 24 $\mu\text{g}/100\text{ ml}$ within half an hour of the start of the operation. The plasma levels continued to rise throughout the rest of the operation, and ranged from 38 to 49 $\mu\text{g}/100\text{ ml}$ when the patients left the theatre.

These observations would suggest that a low plasma 11-OHCS level during the first half hour of an abdominal operation should be interpreted with caution. It may not necessarily signify a failure on the part of the adrenals to respond to surgical stress. On the other hand, a low level later in the operation, or during the immediate post-operative period, would be indicative of adrenal failure.

Post-operative Levels

The highest plasma 11-OHCS levels in our patients were found in the first six hours after the operation. They ranged from 45 to 70 $\mu\text{g}/100\text{ ml}$. The levels at 10 a.m. on the following morning varied between 19.8 and 26.0 $\mu\text{g}/100\text{ ml}$, and were between 15.0 and 20.6 $\mu\text{g}/100\text{ ml}$ at 10 a.m. on the second post-operative day. All 4 patients had an uneventful recovery.

Effect of Spinal Analgesia

Hume *et al.* (1962) have shown that complete transection of the spinal cord at T4 abolished the adrenocortical response to a major abdominal operation. Spinal analgesia, on the other hand, has not been found to block the adrenal response to surgery (Johnson 1964). We have followed the plasma 11-OHCS levels in one patient who was given a general anaesthetic followed by a spinal analgesic to produce a bloodless field:

Case 2 Man, aged 45

This patient had a complete colectomy and ileorectal anastomosis for polyposis coli. His pre-operative plasma 11-OHCS level fell from 12.9 to 4.3 $\mu\text{g}/100\text{ ml}$ one hour after premedication with 20 mg Omnopon

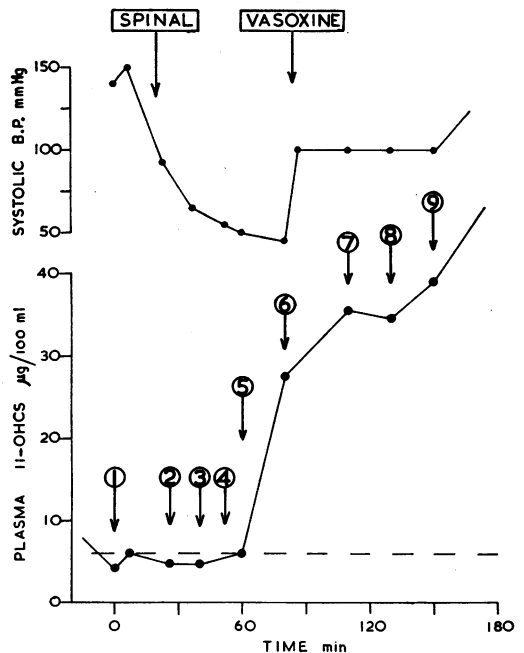


Fig 2 Case 2 Delay in adrenocortical response due to spinal analgesia. 1, after premedication. 2, before skin incision. 3, incision of abdominal wall. 4, handling viscera. 5, mobilizing colon. 6, resection of colon. 7, ileorectal anastomosis completed. 8, skin closure. 9, operation completed. The horizontal broken line shows the lower limit of the normal range between 9 a.m. and 10 a.m.

and 0.45 mg scopolamine. It remained at this level after induction with 2.5% thiopentone, suxamethonium and endotracheal intubation. Halothane 1% was given until spinal analgesia was produced with 2.5 ml of 0.5% heavy Nupercaine injected into the third lumbar space. The systolic blood pressure fell rapidly from 150 to 65 mmHg six minutes after the injection.

The plasma 11-OHCS level remained low, and forty minutes later, when the colon was being mobilized, it was still only 6.1 $\mu\text{g}/100\text{ ml}$. One hour after the skin incision it had risen to 27.3 $\mu\text{g}/100\text{ ml}$. The systolic pressure at this time was down to 45 mmHg but it rose to 100 mmHg after an intravenous injection of 10 mg methoxamine (Vasoxine). The plasma 11-OHCS level continued to rise and reached a level of 58 $\mu\text{g}/100\text{ ml}$ five hours after the operation had been completed (Fig 2).

It was still elevated at 54 $\mu\text{g}/100\text{ ml}$ at 10 a.m. on the following day and had only fallen to 36 $\mu\text{g}/100\text{ ml}$ at 10 a.m. on the second post-operative day. These elevated levels were accompanied by a fever which was due to a wound infection.

Spinal analgesia in this patient did not prevent the normal adrenal response to surgery but appeared to delay its onset. A random low plasma 11-OHCS level during the first forty minutes of the operation might have been misinterpreted as evidence of adrenal failure had the subsequent response not been observed.

Levels in Shocked Patients

The mean morning plasma 11-OHCS level in 23 patients suffering from acute adrenal insufficiency was 2.2 $\mu\text{g}/100\text{ ml}$, the range being 0 to 5.4 $\mu\text{g}/100\text{ ml}$. Only 7 of these patients were hypotensive at the time the blood was taken (systolic blood pressure <100 mmHg).

No levels as low as this were found in a group of 14 surgical patients and 23 medical patients who developed hypotension and were suspected of adrenal failure. None had a level below 20 $\mu\text{g}/100\text{ ml}$ and the levels were markedly elevated in the majority (Fig 3). Most of the surgical patients developed hypotension in the post-operative period and the blood pressure in some of these patients rose after the intravenous injection of 100 mg of hydrocortisone succinate.

There are many causes for a falling blood pressure in these sick patients and the rapid estimation of the plasma 11-OHCS level will enable the diagnosis of adrenal failure to be excluded in the majority of them. A response to intravenous hydrocortisone does not necessarily confirm the diagnosis of hypo-adrenalism (Robinson *et al.* 1962).

Summary

Plasma 11-hydroxycorticoid levels reflect the adrenocortical response to surgical stress and can be determined quickly and accurately by a simple

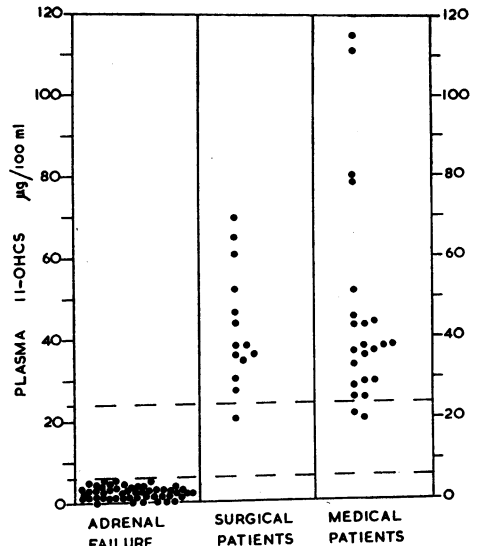


Fig 3 Plasma 11-OHCS levels in shocked patients (see text). Horizontal broken lines show the limits of the normal range between 9 a.m. and 10 a.m. Fifty-one separate estimations were made on the 23 patients with adrenal failure and all these results are shown in this diagram

fluorimetric technique. The interpretation of random plasma 11-hydroxycorticoid levels must take into account the relative inactivity of the adrenals during premedication, induction of anaesthesia with barbiturates, and the first half hour of surgery. Spinal analgesia does not appear to prevent the normal response to surgery but may delay its onset. Prolonged hypotension in surgical patients is an unreliable guide to the prevailing level of adrenocortical activity.

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