PLASMA CATECHOLAMINE CONCENTRATIONS DURING SURGERY IN UNSUPPLEMENTED GLUCOCORTICOID-TREATED PATIENTS

H. KEHLET, P. NIKKI, A. JAÄTTELÄ AND S. TAKKI

SUMMARY

Plasma catecholamine (CA) concentrations, mean arterial pressure (MAP) and plasma corticosteroids were measured in fifteen unsupplemented glucocorticoid-treated patients undergoing major surgery. Eight patients had normal and seven patients had reduced plasma corticosteroid concentrations. Changes in plasma CA and MAP during surgery were not related to adrenocortical function. Two patients developed hypotension during the operation, but had normal plasma CA and corticosteroid concentrations.

Since the first report of collapse during surgery in a patient receiving glucocorticoid treatment (Fraser, Preuss and Bigford, 1952) numerous similar reports have followed. However, biochemical evidence of this postulated adrenocortical failure is very limited (Sampson, Brooke and Winstone, 1961). Thus Kehlet and Binder (1973a), in a study of 104 glucocorticoid-treated patients undergoing surgery without supplementary glucocorticoids, concluded that the plasma concentration of cortisol is not the prime determinant of changes in arterial pressure during stress in these patients. Therefore, other possible explanations for the observed hypotensive periods merit investigation.

Glucocorticoids have been reported to influence catecholamine synthesis (Wurtman and Axelrod, 1966) and secretion (Luft and von Euler, 1952; Morris, De Roche and Earle, 1973; Kelsch et al., 1971) and the peripheral response to catecholamines (Fritz and Levine, 1951; Reis, 1960). The purpose of this study was to investigate the catecholamine and circulatory responses during surgery in glucocorticoid-treated patients who were not given supplementary doses.

PATIENTS AND METHODS

Fifteen patients under treatment with glucocorticoids were studied during elective major surgery (for example, splenectomy or colectomy). Age, sex, and the duration and dose of glucocorticoid treatment, are given in table I. In order to ensure complete metabolism of the exogenous glucocorticoid present, glucocorticoid treatment was stopped 36 hours before operation.

The patients were premedicated with pethidine 1 mg/kg and atropine 0.01 mg/kg. Anaesthesia was induced with thiopentone 3-5 mg/kg followed by suxamethonium 1 mg/kg. Tubocurarine 0.5 mg/kg, fentanyl and N₂O+O₂ (2:1) were given for maintenance of anaesthesia. All patients had an endotracheal tube inserted and ventilation was assisted or controlled throughout the procedure. Blood-gas tensions were not measured. Arterial pressure and heart rate were measured at intervals of 1-5 min during the total period of anaesthesia. The surgical procedure always exceeded 60 min in duration.

Blood samples were collected from a cannula inserted in a cubital vein at least 15 min before induction. The details of the technique used for sampling were described previously (Nikki et al., 1972): samples 1 and 2 were withdrawn before induction, sample 3 after induction but before the skin incision, sample 4 during the presumed maximal operative stimulus from traction and palpation of the abdominal organs, sample 5 after minimizing the response with tubocurarine (5-10 mg) and fentanyl (0.05-0.2 mg), and sample 6 shortly after extubation.

The concentrations of noradrenaline (NA) and adrenaline (A) in plasma were determined fluorimetrically as described previously (Tammisto et al., 1971), with differential determination of NA and A. Total catecholamines are expressed as the sum of NA and A.

Plasma cortisol was measured fluorimetrically (Binder, 1972) as "plasma corticosteroids". Samples...
were taken at the time of the skin incision and 1 hour later.

The changes in plasma levels of total catecholamines, NA, A (Nikki et al., 1972), and corticosteroids (Kehlet, Binder and Engbæk, 1973) which occur in normal patients undergoing surgery, have been described previously.

RESULTS

Table I shows the individual and average values of the initial resting mean arterial pressure (MAP), and the total catecholamine (CA), noradrenaline (NA), and adrenaline (A) concentrations in plasma. The results were assessed on the basis of the adrenocortical response to surgery (table I). The criterion of normality was a concentration of corticosteroids in plasma of at least 30 µg/100 ml 1 hour after the skin incision (Kehlet, Binder and Engbaek, 1973; Kehlet and Binder, 1973b). Eight (1–8) patients showed a normal adrenocortical response to surgery and seven (9–15) patients showed an impaired response. Initial mean values of MAP, CA, NA and A were of the same order in the two subgroups (table I).

The mean changes in MAP, CA, NA and A during surgery are shown in figure 1. MAP increased about 8 mm Hg during supposed maximal surgical stimulation and after extubation. Plasma catecholamines were unchanged during induction and surgical stimulation, but increased by about 20% shortly after stimulation and by about 50% after extubation, predominantly the result of an increase in NA.

No differences between the two subgroups were found.

In two patients hypotension occurred during surgery. In one (No. 6 in table I), the arterial pressure fell to 80/40 mm Hg during traction of the vagus nerves, and in another (No. 5) there was a fall to 80/50 mm Hg as a result of haemorrhage during a splenectomy. Plasma corticosteroids and catecholamines were normal during the operation in these two patients.

DISCUSSION

This study was undertaken to investigate whether the high frequency of hypotension during operation in unsupplemented glucocorticoid-treated patients, shown to be unrelated to the measured corticosteroid levels (Kehlet and Binder, 1973a), could be

| Table I. Clinical data, plasma corticosteroids, total plasma catecholamines (CA), noradrenaline (NA), adrenaline (A) concentrations and mean arterial pressure (MAP) in 15 glucocorticoid-treated patients undergoing major surgery without supplementary glucocorticoid. |
|---|---|---|---|---|---|
| Glucocorticoid treatment (prednisone or equivalent) | Plasma corticosteroids (µg/100 ml) | Hours after skin incision | Initial mean arterial pressure (mm Hg) | Plasma catecholamines (µg/l) before anaesthesia |
| Normal plasma corticosteroid level | | | | |
| Patients | Age and sex | mg/day | Duration (months) | 0 | 1 | 76 | 101 | 85 | 115 | 90 | 80 | 99 | 95 | 1.01 | 1.98 | 1.87 | 0.92 | 0.42 | 0.79 | 1.24 | 0.46 | 0.38 | 0.08 |
| 1 | 28/M | 10 | 12 | 27 | 46 | 76 | 1.01 | 0.65 | 0.36 |
| 2 | 61/F | 5 | 6 | 22 | 45 | 101 | 1.98 | 1.95 | 0.03 |
| 3 | 24/F | 15 | 4 | 19 | 42 | 85 | 1.87 | 1.53 | 0.34 |
| 4 | 69/F | 15 | 3 | 26 | 41 | 115 | 0.92 | 0.41 | 0.51 |
| 5 | 68/F | 74 | 30 | 26 | 37 | 90 | 0.42 | 0.39 | 0.03 |
| 6 | 62/F | 15 | 7 | 17 | 37 | 90 | 0.79 | 0.32 | 0.47 |
| 7 | 76/F | 15 | 12 | 27 | 34 | 99 | 1.24 | 1.14 | 0.10 |
| 8 | 32/M | 80 | 1 | 19 | 34 | 95 | 0.46 | 0.38 | 0.08 |
| Mean ± SE | | | | 23 ± 1 | 40 ± 2 | 93 ± 4 | 1.09 ± 0.19 | 0.85 ± 0.21 | 0.24 ± 0.07 |
| Abnormal plasma corticosteroid level | | | | | | | |
| Patients | Age and sex | 124 | 7 | 16 | 26 | 107 | 1.29 | 0.40 | 0.89 |
| 10 | 79/F | 12 | 7 | 16 | 26 | 107 | 1.29 | 0.40 | 0.89 |
| 11 | 55/F | 40 | 2 | 12 | 25 | 91 | 0.83 | 0.43 | 0.40 |
| 12 | 42/F | 15 | 3 | 14 | 23 | 83 | 0.82 | 0.60 | 0.22 |
| 13 | 65/F | 15 | 24 | 8 | 21 | 130 | 1.16 | 1.08 | 0.08 |
| 14 | 82/M | 124 | 36 | 13 | 15 | 92 | 1.31 | 1.31 | 0.00 |
| 15 | 27/F | 20 | 3 | 9 | 13 | 88 | 1.00 | 0.62 | 0.38 |
| Mean ± SE | | | | 11 ± 2 | 18 ± 3 | 97 ± 6 | 1.05 ± 0.07 | 0.70 ± 0.12 | 0.34 ± 0.10 |
| All patients mean ± SE | | | | 95 ± 4 | 1.07 ± 0.11 | 0.78 ± 0.13 | 0.29 ± 0.06 |
PLASMA CATECHOLAMINES DURING SURGERY

Adrenocortical glucocorticoid secretion has been shown to be necessary for the conversion of noradrenaline (NA) to adrenaline (A) (Wurtman and Axelrod, 1966). NA urinary excretion is normal during glucocorticoid deficiency (Parvez and Parvez, 1972). Inhibition of adrenocortical glucocorticoid secretion by administration of physiological maintenance doses of glucocorticoids for at least 9 days results in decreased A synthesis in rats (Wurtman, Noble and Axelrod, 1967) and urinary A excretion in man (Noble et al., 1968), but unchanged NA excretion (Noble et al., 1968). After the administration of pharmacological doses of glucocorticoids to rats A synthesis is preserved (Wurtman, Noble and Axelrod, 1967), while glucocorticoid administration has been associated with a reduced plasma NA (Kelsch et al., 1971) and urinary NA excretion in both clinical and experimental studies (Luft and von Euler, 1952; Kelsch et al., 1971; Parvez and Parvez, 1972).

In the present study of fifteen unsupplemented glucocorticoid-treated patients, the resting plasma concentrations of total catecholamines (CA), NA and A were unchanged compared with a normal control group (Nikki et al., 1972) and showed no relationship to the actual plasma corticosteroid concentration. This is not contradictory, as the patients...
had been without exogenous glucocorticoids for only 36 hours. Similarly, Morris, DeRoche and Earle (1973) found that the basal urinary A excretion was unrelated to the plasma cortisol concentration in glucocorticoid-treated children who had been deprived of exogenous glucocorticoid for 12 hours.

The effect of surgical stimulation on plasma catecholamine concentrations in normal subjects during similar types of anaesthesia and operation has been reported previously (Nikki et al., 1972). The changes in CA, NA and A during surgery in the fifteen unsupplemented glucocorticoid-treated patients in the present study are similar to those found in normal subjects. No significant difference in catecholamine concentrations could be demonstrated between glucocorticoid-treated patients with normal and impaired adrenocortical function. In contrast, Morris, DeRoche and Earle (1973) found lower urinary A excretion during insulin-induced hypoglycaemia in glucocorticoid-treated children with reduced adrenocortical function, compared with those who had normal function. However, the hypoglycaemia was more pronounced in the group with normal adrenocortical function, possibly explaining their higher A values.

Data on cardiovascular reactivity to catecholamines during glucocorticoid deficiency are conflicting. Thus, an impaired peripheral reactivity to catecholamines has been described in the mesenteric vessels in rats (Fritz and Levine, 1951; Zweifach, Shorr and Black, 1953) and in the conjunctival vessels in man (DeFilippis, del Guercio and Mattioli, 1965). However, others have demonstrated normal reactivity in dogs (Brown and Remington, 1955; Webb et al., 1965) and man (Birke et al., 1960). Cardiac contractility is normal (Birke et al., 1960) or decreased (Webb et al., 1965). In contrast, administration of pharmacological doses of glucocorticoid potentiates the peripheral vascular reactivity to catecholamines (Reis, 1960; Yard and Kadowitz, 1972). The results of the present study in unsupplemented glucocorticoid-treated patients are not contradictory to these reports. Thus, initial values and operative changes in mean arterial pressure (MAP), possibly related to plasma catecholamines, were parallel to and of the same magnitude as those in normal patients (Nikki et al., 1972). The MAP changes in patients with reduced plasma corticosteroid responses were the same as in those with normal function, indicating that an impaired glucocorticoid stress-response seems to be without major influence on catecholamine effects.

In conclusion, the results of this study suggest that the secretion of catecholamines and their cardiovascular effects during surgery are normal in unsupplemented glucocorticoid-treated patients, even when the plasma corticosteroid levels are reduced. Therefore there must be other factors contributing to hypotension during surgical stimulation in these patients.

ACKNOWLEDGEMENT

This work was supported by a grant from Statens Lægevidenskabelige Forskningsråd.

REFERENCES


---

**FIRST WORLD CONGRESS ON INTENSIVE CARE**

**LONDON: JUNE 24-27, 1974**

**INTERIM PROGRAMME**

The Scientific Programme will include major symposia, seminars and “meet the expert” sessions to encourage discussion, free papers and films. Specialized contributions on a variety of renal, paediatric, neurosurgical, traumatic and coronary care problems will be given at appropriate points in the programme. The main topics will be as follows:

**Tuesday, June 25**

**INTENSIVE THERAPY** (including Coronary Care): Roles in Community Care; Organisation; Design; Staffing and Training.

**MONITORING:** Basic Requirements; Methods and Equipment; Specialised Areas.

**Wednesday, June 26**

**TRAUMA AND RESUSCITATION:** Ambulance and on-site Services; Primary Care; Immediate Problems.

**POISONING:** Diagnosis; Biochemical Assay; Metabolic and Other Problems; Therapy.

**SHOCK AND RELATED PROBLEMS**

**RESPIRATORY FAILURE:** Acute and Chronic Types; Management and Problems.

**Thursday, June 27**

**ASSESSMENT OF TISSUE HYPOXIA:** Electrophysiological; Biochemical; Immunological; Histochemical.

**BRAIN DEATH**

**METABOLISM AND NUTRITION IN THE CRITICALLY ILL**

**INFECTION:** Prevention and Treatment.

**Congress Office:** First World Congress on Intensive Care, National Heart Hospital, Westmoreland Street, London W1M 8BA. Telephone 01-935 2314.

**Enquiries:** Scientific Programme to: Dr I. McA. Ledingham, Department of Surgery, Western Infirmary, Glasgow G11 6NT, Scotland.

All other matters to: Dr Alan Gilston, National Heart Hospital, Westmoreland Street, London W1M 8BA.