EFFECTS OF ANAESTHESIA AND SURGERY ON PLASMA ALDOSTERONE CONCENTRATION AND RENIN ACTIVITY IN MAN

T. OYAMA, K. TANIGUCHI, T. JIN, T. SATONE AND T. KUDO

SUMMARY

The effects of various anaesthetic agents and surgery on the plasma concentrations of aldosterone and on renin activity were investigated in 76 patients. The plasma concentration of aldosterone was increased markedly by 2.5 times the control value during 45 min of ether anaesthesia. It was increased also during halothane, methoxyflurane and enflurane anaesthesia. Spinal anaesthesia did not alter significantly the plasma concentration of aldosterone. Plasma renin activity and ACTH concentration were increased slightly during general anaesthesia.

The present study was undertaken to investigate the effects of various anaesthetic agents and surgery on the plasma concentrations of aldosterone and the renin activity in man.

The renin-angiotensin-aldosterone system plays an important role in the maintenance of electrolyte balance, fluid volume and arterial pressure. Anaesthetics have been reported to cause the release of renin in rats as measured by plasma renin activity (Pettinger et al., 1975; Miller, Ackerly and Peach, 1978). However, such increases have not been observed in man (Robertson and Michelakis, 1972; Bailey et al., 1975; Miller et al., 1975). Furthermore, no extensive study has reported on the effect of anaesthetics on the plasma concentrations of aldosterone in man apart from our previous study which featured a small number of patients (Oyama et al., 1973).

MATERIALS AND METHODS

Seventy-six patients, in the age range 10–58 yr, were studied after giving informed consent. None had a history of endocrine disease, or of hepatic or renal malfunction. The patients were all in good general health. Premedication consisted of pentobarbitone 100 mg given orally, and pethidine 35 mg i.m. plus atropine 0.5 mg i.m. No food or water was given for at least 10 h before the start of anaesthesia.

The effects of ether–nitrous oxide anaesthesia (16 patients), halothane–nitrous oxide (15 patients), methoxyflurane–nitrous oxide (15 patients), enflurane–nitrous oxide (15 patients), spinal anaesthesia (15 patients) and of surgery on the plasma concentrations of aldosterone were determined in 76 surgical patients. With the exception of the spinal anaesthesia group (10–15 min) the patients were anaesthetized for 45 min before the start of surgery. Hysterectomy was performed in the majority of patients except for those in the spinal anaesthesia group, who underwent appendicectomy or haemorrhoidectomy.

The plasma renin activity (PRA), serum and urinary concentrations of sodium and potassium, urinary Na/K ratios and urine volume were determined simultaneously in all groups. Plasma concentrations of ACTH were measured in 33 patients who underwent halothane–nitrous oxide, enflurane–nitrous oxide anaesthesia and spinal anaesthesia.

Anaesthesia was induced and maintained with methoxyflurane 0.3–1% or diethyl ether 5–15%, or enflurane 1.0–3.0% combined with nitrous oxide 3.5 litre min\(^{-1}\) in oxygen 1.5 litre min\(^{-1}\), and tubocurarine was given to produce neuromuscular blockade when required. Thiopentone was not used as an induction agent in any patient. Intubation of the trachea was performed following the injection of suxamethonium 40 mg i.v. Ventilation of the lungs was assisted manually throughout the procedure.

To produce spinal anaesthesia amethocaine 10–12 mg diluted with 10% glucose 2 ml was injected into the subarachnoid space at either L3–4 or L4–5. The level of anaesthesia, determined with pinprick, was T10–6 and its duration was 90–120 min (mean 105.3 ± 3.1 SEM). The duration of surgery was 12–30 min (mean 22.2 ± SEM 1.7).

Low molecular weight dextran 500 ml was infused throughout the procedure in each group, and whole blood was transfused when blood loss exceeded 300 ml.

© Macmillan Journals Ltd 1979
Four 6-ml samples of venous blood were drawn into heparinized syringes in the general anaesthesia groups: (1) at 8.30 a.m., immediately before induction of anaesthesia; (2) 45 min after anaesthesia but before surgery; (3) 1 h after the start of the operation; (4) in the recovery room when the patient was fully awake. The plasma was separated within 30 min, frozen at —20 °C for storage and thawed within 1 month for radioimmunoassay for aldosterone by the method of Mayes and colleagues (1970) using 1.2-3H-aldosterone (New England Nuclear Corporation) and antisera provided by Dr C. A. Nugent. The mean recovery rate for utilized 1.2-3H-aldosterone by our method was 77% and the coefficient of variation (c.v.) was 6%.

Plasma renin activity was measured according to the method of Haber and colleagues (1969), using an angiotensin I radioimmunoassay kit utilizing 125I-angiotensin I produced by CEA-IRE-SORIN Co. Ltd. Two millilitre of venous blood was mixed well in an iced test-tube which contained EDTA-2 Na 2 mg. The plasma was separated by frozen-centrifugation, and was kept at —20 °C for storage. The mean recovery rate was 72% and c.v. was 7%. The plasma concentrations of ACTH were determined by radioimmunoassay as described by Berson and Yalow (1968). The 125I-ACTH kit was produced by Radiochemical Center Co. Ltd; the recovery rate was 40% and c.v. was 12%.

RESULTS

The plasma concentrations of aldosterone were increased markedly, being 2.5 times the control values during ether-nitrous oxide anaesthesia, 1.5 times during halothane-nitrous oxide or 1.6 times during methoxyflurane-nitrous oxide anaesthesia and two times during enflurane-nitrous oxide anaesthesia. There was a further increase to about three times greater than the control values at 0.5–2 h after the start of the surgery. Increased plasma concentrations of aldosterone were observed on the first day after operation (fig. 1). Spinal anaesthesia did not alter significantly the plasma concentrations of aldosterone or serum sodium or potassium.

The renin activity in the plasma was increased slightly during ether-nitrous oxide, halothane-nitrous oxide, enflurane-nitrous oxide anaesthesia and surgery (fig. 2). However, there were no significant changes in serum sodium or potassium concentrations in these groups. A significant decrease in urinary Na/K ratio with all the inhalation agents was
associated with the increase in the plasma concentrations of aldosterone (fig. 3).

Although the plasma concentrations of ACTH increased slightly during halothane–nitrous oxide and enflurane–nitrous oxide anaesthesia, and were increased markedly during surgery, they had decreased by the 1st day after operation (fig. 4). The plasma concentrations of ACTH were not altered significantly during spinal anaesthesia, although they did increase slightly after surgery (fig. 4).

**DISCUSSION**

The renin–angiotensin–aldosterone system is important in the maintenance of the fluid and electrolyte...
Plasma concentrations of aldosterone are influenced by many factors, such as its secretion from the zona glomerulosa of the adrenal cortex, metabolism in the liver, peripheral utilization, and renal excretion. However, the adrenal secretion appears to play the main role during stress. Hume, Bell and Barter (1962) found that the secretion rate of aldosterone in the adrenal vein was increased after surgical stress. Aldosterone secretion is increased by ACTH, a decrease in the plasma concentration of sodium, an increase in potassium concentration, a decrease in the plasma sodium to potassium ratio and by a reduction in the extracellular fluid or blood volume.

A decrease in blood volume or in arterial pressure or vasoconstriction of the renal arteries decreases pressure in the afferent arteriole leading to a release of renin from the juxtaglomerular cells of the kidney. The renin converts angiotensinogen which is manufactured in the liver to angiotensin I. This substance is converted further in the blood stream by an enzyme to angiotensin II which stimulates the adrenal cortex to release aldosterone. As neither pregnant patients, nor any taking oral contraceptives, nor any suffering from the nephrotic syndrome were included in the study, the plasma renin activity represents plasma concentration of angiotensin. Aldosterone, in turn, leads to sodium retention and an increase in arterial pressure, which acts as a feedback mechanism to shut off the further release of renin.

It is not certain, however, whether this feedback mechanism operates during stress. In our present study the plasma renin activity did not increase significantly during anaesthesia, but it did increase significantly during surgery in man. According to Naruse (1970), plasma renin activity was not changed during the early part of the surgical procedure and increased only in the later part of the operation. Our findings accord with others which reported that neither halothane (Robertson and Michelakis, 1972) nor ketamine (Miller et al., 1975) caused any significant change in plasma renin activity. Therefore, the participation of the renin-angiotensin system in the increase in the concentrations of plasma aldosterone during anaesthesia appears to be minor. However, during surgery it may play a role.

The secretion of aldosterone is enhanced by the decreases in sodium and the increases in potassium concentrations. However, the variation in plasma electrolytes was small during anaesthesia and surgery. Therefore, it seems unlikely that changes in plasma
electrolyte concentrations are a major regulatory mechanism during anaesthesia and surgery. According to Ganong (1973), in the dog the plasma potassium concentration must increase at least 1 mmol litre$^{-1}$ or the plasma sodium decrease by about 20 mmol litre$^{-1}$ before a stimulating effect is seen.

The authors’ findings indicate that, although general anaesthesia with ether, halothane, methoxyflurane or enflurane stimulates the secretion of aldosterone from the adrenal cortex, spinal anaesthesia does not stimulate aldosterone secretion in man. The marked increase in ACTH secretion or the increased plasma renin activity, or both, appeared to play an important role in the increase in the concentration of aldosterone during the procedure. The magnitude of the surgical stress and the duration of spinal anaesthesia alone was less than those in the other inhalation anaesthetic groups. Therefore, it cannot be denied that this might contribute to the smaller response in aldosterone secretion in the spinal anaesthesia group.

An excess of aldosterone leads to an increase in extracellular fluid, sodium retention, potassium depletion and hypertension, while aldosterone deficiency leads to sodium depletion, potassium retention, hypovolaemia and hypotension. Therefore, aldosterone appears to play some role in homeostasis and serum electrolyte balance during anaesthesia and surgery (Miller, Ackerly and Peach, 1978).

Since there were no substantial differences in the plasma concentrations of aldosterone among the inhalation agents, any of these agents or techniques can be used for adrenalectomy in patients with primary hyperaldosteronism, except for methoxyflurane, which is nephrotoxic. From the theoretical point of view, spinal anaesthesia could become the anaesthetic of choice for these patients.


REFERENCES


La concentración de aldosterona en la plasma aumentó notablemente a un valor 2,5 veces superior al de control durante 45 min de anestesia con éter. Aumentó también durante la anestesia de halotano, metoxiflurano y enfurano. La anestesia espinal no alteró significativamente la concentración de aldosterona en la plasma. La actividad de renina en la plasma y la concentración de ACTH aumentaron ligeramente durante anestesia general.