ANAESTHESIA AND DISORDERS OF THE ADRENAL CORTEX

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The physiological significance of the adrenal cortex in the ability of the individual to withstand "stress" has long been recognized: Selye (1950) provided a detailed description of the role of the cortex in the responses to a variety of stresses, including surgical trauma. In the 1950's postoperative collapse in patients receiving corticosteroid therapy was attributed to adrenocortical insufficiency and there followed considerable interest in the role of the adrenocorticoids, particularly the glucocorticoids, in the responses to anaesthesia and surgery. More recently, there has been interest in the role of the mineralocorticoids, stimulated largely by research into the aetiology of hypertension.

Improvement of diagnostic techniques in endocrinology has led to an increase in the number of patients presenting for surgical treatment of disorders of the adrenal cortex. Lately, attention has been directed to the significance of adrenocortical function and corticosteroid therapy in critical care.

The aim of this article is to provide a brief description of the adrenocortical responses to anaesthesia and surgery and to review aspects of some of the more commonly occurring disorders of the adrenal cortex of relevance to the anaesthetist.

ADRENOCORTICAL RESPONSE TO ANAESTHESIA AND SURGERY

The endocrine and metabolic responses to anaesthesia and surgery have received much attention during the past 25 years and have been reviewed recently (Traynor and Hall, 1981). The early demonstration of an increase in plasma concentration of corticosteroids during anaesthesia and surgery (Franksson and Gemzell, 1953; Sandberg et al., 1954) was later shown to involve an increase in the rate of adrenal secretion of cortisol in response to surgery (Hardy and Turner, 1957; Hume, Bell and Bartter, 1962). The plasma cortisol concentration increases rapidly after induction of anaesthesia and commenced of surgery and remains increased for a variable period after operation; the magnitude and duration of the response are related to the severity of the surgical stress (Sandberg et al., 1954; Plumpton, Besser and Cole, 1969a; Foster et al., 1979). The increase in secretion of cortisol is associated with the release of large amounts of ACTH (Hume, Bell and Bartter, 1962; Oyama and Takiguchi, 1970).

There is evidence that both anaesthesia and surgical stress are involved in the stimulation of the cortisol response. Preoperative apprehension is associated with an increase in the plasma cortisol concentration and this may be reduced by premedication (Oyama et al., 1969). The i.v. induction agents thiopentone, propanidid, Althesin and etomidate are not associated with an increase in plasma cortisol, although a variety of other anaesthetic agents—diethyl ether, halothane and cyclopropane—may cause an increase in the plasma cortisol concentration (Oyama, 1980). Surgical stimulation elicits a further increase in plasma cortisol, the magnitude of the response being related to the severity of the surgical stimulus. This adrenocortical response has been observed during surgery within the pelvis (Engquist et al., 1977), upper abdomen (Traynor et al., 1982), thorax (Bromage, Shibata and Willoughby, 1971) and heart (Taylor et al., 1976).

During anaesthesia and surgery there is also an increase in the rate of secretion of aldosterone (Hume, Bell and Bartter, 1962) and in the plasma aldosterone concentration (Cochrane, 1978; Engquist et al., 1978; Menzies Gow and Cochrane, 1979; Oyama et al., 1979). Oyama and others (1979) showed that nitrous oxide anaesthesia supplemented by a variety of volatile anaesthetic agents including halothane and enflurane causes an increase in the plasma aldosterone concentration, that the concentration increases further after the commencement of surgical stimulation, and that the overall increase persists for about 24 h after lower abdominal surgery. This response may be dependent on increases in the concentrations of ACTH or
renin (Robertson and Michelakis, 1972; Brandt, Olgaard and Kehlet, 1979; Oyama et al., 1979) and may possibly be influenced by changes in blood volume (Engquist et al., 1978).

The metabolic consequences of these adrenocortical responses to anaesthesia and surgery are largely unknown. Metabolic responses to surgery such as hyperglycaemia, increased protein breakdown and sodium and water retention, may be produced in normal patients by the administration of cortisol; however, it has been shown, using extradural blockade, that the hyperglycaemic response to upper abdominal surgery may be inhibited in the presence of a normal cortisol response (Bromage, Shibata and Willoughby, 1971; Buckley et al., 1982) and this dissociation of endocrine and metabolic responses casts doubt on the exact role of the cortisol response in relation to the metabolic changes; the role of increases in cortisol in relation to the metabolic changes may be permissive rather than directly causative (Johnston, 1973; Traynor and Hall, 1981). Similarly, whilst anaesthesia and surgery are accompanied by sodium and water retention, these responses are not dependent on an increase in plasma aldosterone concentration (Cochrane, 1978; Brandt, Olgaard and Kehlet, 1979) and therefore the role of the aldosterone response in peroperative changes in fluid and electrolyte balance remains unknown.

There is a relationship between adrenocortical insufficiency and hypotension, and it has been postulated that the adrenocorticoïds have a role in the maintenance of cardiovascular homeostasis. Influences of corticosteroids on catecholamine synthesis and secretion and on the cardiovascular responses to catecholamines have been described (Kehlet et al., 1974). An involvement of corticosteroids in the fluid-shift responses to haemorrhage has also been sought (Gann and Pirkle, 1975; Barton and Passingham, 1982), and a recent review has examined a suspected role of the adrenal cortex in the pathogenesis of essential hypertension (Gomez-Sanchez, 1982).

Whilst it is possible that the corticosteroids may be important in both cardiovascular and metabolic responses to anaesthesia and surgery, their role remains obscure, particularly in view of the finding that patients may withstand surgery after the adrenocortical responses have been inhibited, for example by extradural blockade (Gordon, Scott and Percy Robb, 1973; Engquist et al., 1977; Brandt, Olgaard and Kehlet, 1979) or by high-dose opioid anaesthesia (Hall et al., 1978; Bovill et al., 1983), apparently without clinically detectable ill-effect. Traynor and Hall (1981) concluded that the adrenocortical response to anaesthesia and surgery should be safely prevented rather than left unaltered.

**ADRENOCORTICAL INSUFFICIENCY**

Addison (1855) described a clinical syndrome characterized by asthenia, gastrointestinal symptoms, hypotension, weight loss and pigmentation, associated with a "diseased condition of the suprarenal capsules", thus providing the first description of primary adrenocortical insufficiency (Addison's disease). Early in this century the commonest cause of Addison's disease was bilateral destruction of the adrenal glands by tuberculous infection. Today tuberculosis accounts for probably less than 20% of cases (Irvine and Barnes, 1972) the majority of cases now involving an auto-immune adrenitis (idiopathic Addison's disease). Rarer causes of destruction of the adrenal glands include infiltration from malignancy and amyloidosis, and infarction from atheroma, polyarteritis nodosa and systemic lupus erythematosus. Destruction as a consequence of haemorrhage into the adrenal gland may be caused by septicemia, anticoagulant therapy or toxemia of pregnancy.

Secondary adrenocortical insufficiency occurs as a result of inadequate secretion of ACTH and may be caused by tumours or vascular lesions in the region of the hypothalamus and pituitary. The commonest cause of adrenocortical insufficiency now occurs in patients receiving corticosteroid therapy with consequent hypothalmo-pituitary suppression of ACTH secretion and atrophy of the adrenal cortices. Topical, aerosol, oral or parenteral administration of steroids may all cause adrenocortical insufficiency (Feiwel, James and Barnett, 1969; Choo-Kang et al., 1972).

The clinical features of adrenocortical insufficiency depend on the aetiology and vary from the chronic condition, described by Addison, to acute adrenal failure with weakness, hypotension, dehydration and electrolyte disturbances (hyponatraemia and hyperkalaemia). The anaesthetic management of a patient showing features of acute adrenal failure has been described recently (Smith and Byrne, 1981). Laboratory diagnostic techniques have been devised to determine the nature of the pathology; medical treatment is directed to restoring normal fluid and electrolyte balance, thereafter maintaining corticosteroid concentrations with both glucocor-
Steroid therapy and surgical patients

Reports of early postoperative “collapse” and death in patients receiving steroid therapy (Fraser, Preuss and Bigford, 1952; Lewis et al., 1953) were attributed, with little evidence, to adrenocortical insufficiency and, as a result, high-dose corticosteroid regimens were recommended for the perioperative management of patients receiving or having received steroid therapy (Bayliss, 1958). Only relatively few reports of perioperative collapse in patients receiving steroid therapy showed an association with low plasma steroid concentrations (Sampson, Brooke and Winstone, 1961; Sampson, Winstone and Brooke, 1962; Jasani et al., 1968); consequently, doubt has been cast on an adrenocortical aetiology in many of the reports of perioperative collapse (Mattingly and Tyler, 1965; Cope, 1966; Plumpton, Besser and Cole, 1969a). Kehlet (1976; cited by Symreng et al., 1981) has failed to find evidence for involvement of adrenocortical insufficiency in a majority of reports reviewed. In addition, the observation that patients may withstand at least some types of major surgery after inhibition of the normal cortisol response to surgery (Gordon, Scott and Percy Robb, 1973; Engquist et al., 1977) casts further doubt on the importance of the possible role of adrenocorticoids during surgery. However, it is still claimed that there is an occurrence of intraoperative hypotension in steroid-treated patients not receiving adequate steroid supplementation therapy (Black and Montgomery, 1982) and therefore there remains a rationale for providing steroid supplementation to these patients. A variety of steroid supplementation regimens have been proposed (Plumpton, Besser and Cole, 1969b; Kehlet, 1975; Diethelm, 1977; Black and Montgomery, 1982; Liddle, 1982; Williams and Dluhy, 1983); the recommended total dose of hydrocortisone on the day of surgical operation varies from 25 mg to 600 mg. In view of possible adverse influences of corticosteroids on the metabolic responses to anaesthesia and surgery and other sequelae of corticosteroid therapy (retardation of healing, increased susceptibility to infection, gastrointestinal haemorrhage (Diethelm, 1977)), attempts have been made to rationalize steroid supplementation for surgical patients at risk of developing adrenocortical insufficiency and to define appropriate (minimal) steroid dosage.

The increase in plasma cortisol concentration in response to anaesthesia and surgery may be diminished or absent in some patients receiving steroid therapy, whilst patients who have ceased steroid therapy 3 days to 24 months before surgery and others still receiving steroid therapy may show quantitatively normal plasma cortisol responses (Plumpton, Besser and Cole, 1969a; Kehlet and Binder, 1973). Preoperative tests have been used to identify those patients who show normal plasma cortisol responses during surgery—the insulin–hypoglycaemia test of hypotalamo–pituitary–adrenal function (Plumpton, Besser and Cole, 1969a) and the ACTH–stimulation test of adrenal function (Symreng et al., 1981). However, despite an impaired plasma cortisol response, patients receiving steroid therapy may withstand major surgery without steroid supplementation; Kehlet and Binder (1973) found, in a group of 104 patients, a relatively high frequency of perioperative hypotension, but considered that this was only attributable to low plasma cortisol concentration in one patient. It is not possible to identify patients requiring steroid supplementation, without biochemical testing of adrenal function.

Steroid supplementation regimens have attempted to imitate the normal plasma cortisol response to anaesthesia and surgery. Plumpton, Besser and Cole (1969b) showed that appropriate plasma cortisol concentrations could be achieved by administering hydrocortisone 100 mg i.m. every 6 h for 3 days for major surgery, and only hydrocortisone 100 mg i.v. during induction of anaesthesia for minor surgery. Based on estimations of daily secretion rates of cortisol, Kehlet (1975) has suggested a lower dose schedule namely, for major surgery, hydrocortisone 25 mg i.v. during induction of anaesthesia and thereafter an i.v. infusion of hydrocortisone 100 mg/24 h until resumption of gastrointestinal function and, for minor surgery, only hydrocortisone 25 mg i.v. during induction of anaesthesia. Symreng and others (1981) have demonstrated the efficacy of this low–dose schedule in a small group of patients.
during the first 24 h after major surgery.

On available evidence, therefore, a low-dose steroid regimen provides plasma cortisol concentrations similar to those seen in the normal adrenocortical response to anaesthesia and surgery. However, steroid-treated patients with diminished adrenocortical responses may withstand surgery without steroid supplementation and this emphasizes the need for further study of the role of the adrenocortical responses in relation to the plasma concentrations of corticosteroids and greater precision in the identification of patients who may require steroid supplementation during anaesthesia and surgery.

**Steroid therapy and critically ill patients**

The experimental examination of a relationship between adrenocortical function and responses to haemorrhage and trauma (Swingle et al., 1942; Swingle et al., 1944; Knapp and Howard, 1957) aroused interest in the role of adrenocorticos in the management of critically ill patients; steroids have been used as part of the therapy in such patients. However, the frequency of occurrence of adrenocortical insufficiency in critically ill patients has been questioned; in a recent investigation no evidence of adrenocortical insufficiency was found amongst a high-mortality group of patients (Sainsbury, Stoddart and Watson, 1981). Specific roles have been proposed for steroids in the treatment of critically ill patients; thus it has been claimed that the administration of steroids may increase the stability of lysosomal membranes in certain types of shock and that steroids may have useful therapeutic effects in relation to the cardiovascular system. However, the evidence supporting these claims is inconclusive (Stoddart, 1975) and the value of steroid therapy in this context has been questioned (Sainsbury, Stoddart and Wilson, 1981).

Evidence has been provided that the plasma cortisol concentration in critically ill patients may have a prognostic value (Finlay and McKee, 1982; McKee and Finlay, 1983); also, in a small number of patients, increase in low plasma cortisol concentrations by administering hydrocortisone was associated with a reduced mortality rate (McKee and Finlay, 1983). It has been proposed that one factor contributing to adrenocortical suppression in the patients studied by Finlay and McKee (1982) could be an i.v. sedative technique using etomidate (Ledingham and Watt, 1983; Ledingham et al., 1983). There is some evidence for a direct suppressive effect of etomidate on adrenocortical secretion of cortisol (Preziosi and Vacca, 1982; Ledingham et al., 1983), and in critically ill patients not receiving an etomidate infusion the frequency of reduced plasma cortisol concentration is low (Sainsbury, Stoddart and Wilson, 1981; Stoddart and Watson, 1983). These findings indicate the need for further investigation of adrenocortical function in critically ill patients, to determine the significance of sedative techniques in critically ill patients, and to determine the efficacy of maintenance of plasma cortisol concentrations by corticosteroid therapy.

**HYPERSECRETION OF GLUCOCORTICOIDS—CUSHING’S SYNDROME**

Cushing’s syndrome arises from prolonged increase of the plasma concentration of glucocorticoids and may be caused by excessive secretion or administration of steroid therapy. The causes of abnormally increased secretion of glucocorticoids are divided into those involving an excess of ACTH (ACTH-dependent) and those involving primary disease of the adrenal cortex with hypersecretion of glucocorticoids and corresponding depression of ACTH concentrations (non-ACTH dependent). Of the ACTH-dependent variety the majority involve excessive release of ACTH from the anterior pituitary, causing bilateral adrenocortical hyperplasia (Cushing’s disease); a smaller number arise from ectopic secretion of ACTH, for example in association with bronchial carcinoma. The non-ACTH dependent pathologies include adrenocortical adenoma and carcinoma. The commonest cause of Cushing’s syndrome arising from excessive adrenocortical secretion is pituitary hypersecretion of ACTH (60–70%); primary adrenal disease accounts for 20–30% (Orth and Liddle, 1971).

The clinical manifestations of Cushing’s syndrome—central obesity, muscle wasting, osteoporosis, thinning and bruising of the skin, hirsutism, psychiatric disturbances, glucose intolerance and hypertension—are directly attributable to increased concentrations of corticosteroids. Glucose intolerance is common, but 20–30% of patients exhibit overt diabetes mellitus (Soffer, Iannaccone and Gabrilove, 1961; Ross, Marshall-Jones and Friedman, 1966; Welbourne, Montgomery and Kennedy, 1971; Ernest and Ekman, 1972). Hypertension is usually benign but often severe (Ernest and Ekman, 1972) and, in untreated patients, may enter a malignant phase and may be associated with congestive cardiac failure. The hypertension has been related to sodium retention, increased an-
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Giotensin formation and increased vascular responsiveness to pressor agents (Cullen, Reckless and McLaren, 1980). In addition many patients exhibit hypokalaemia (Welbourne, Montgomery and Kennedy, 1971).

Biochemical and radiological investigations have been devised to determine the diagnosis and to identify the site of the underlying disease (Cullen, Reckless and McLaren, 1980; Nelson, 1980). Therapy of Cushing's syndrome is dictated by the site of the underlying pathological cause. The appropriate therapy for patients with pituitary-dependent disease has been debated and treatments directed at the pituitary (irradiation or hypophysectomy) and the adrenals (bilateral adrenalectomy) have been compared (Montgomery and Welbourne, 1978; Gold, 1979; Krieger, 1982; Burch, 1983; Pelkonen et al., 1983). Thus, patients with Cushing's syndrome may present for a variety of surgical procedures: trans-sphenoidal hypophysectomy, bilateral adrenalectomy, or removal of primary adrenal tumours.

Preoperative management of patients presenting for surgery may require treatment of hypertension and congestive cardiac failure, stabilization of diabetes mellitus and reversal of hypokalaemia (Black and Montgomery, 1982). In addition, Montgomery and Welbourne (1978) recommended the use of chemotherapy (metyrapone, cyproheptadine, bromocriptine) in patients with a florid syndrome to reduce the rate of adrenal secretion of steroids before surgery.

Descriptions of the anaesthetic management of patients with Cushing's syndrome reflect a wide choice of anaesthetic agents (Stephen, 1977; Maddi and Gabel, 1980; Black and Montgomery, 1982). Specific problems likely to be encountered in patients undergoing adrenal surgery include difficulty in tracheal intubation associated with obesity, the need for careful positioning of patients who have a high frequency of osteoporosis, cardiovascular fluctuations as a consequence of caval compression, direct manipulation of the adrenals or surgical haemorrhage, and pneumothorax resulting from damage to the pleura. A relatively high frequency of thromboembolic sequelae has been reported in patients following adrenal surgery (Blichert-Toft et al., 1972; Ernst andEkman, 1972).

Irrespective of the cause of the syndrome and type of remedial surgery, patients with Cushing's syndrome require steroid supplementation therapy during and after operation; this requirement has been claimed to be greater than in other conditions (James, 1970; Black and Montgomery, 1982). A variety of glucocorticoid schedules have been used for both adrenalectomy and hypophysectomy (Besser and Edwards, 1972; Ernest and Ekman, 1972; Tyrell et al., 1978; Black and Montgomery, 1982); a total dose of hydrocortisone 300 mg given throughout the day of operation is probably adequate for both pituitary and adrenal operations (Tyrell et al., 1978; Black and Montgomery, 1982). Subsequent postoperative steroid replacement therapy, involving titration against the plasma cortisol concentration and assessment of mineralocorticoid requirement, has been described in detail (Besser and Edwards, 1972; Kehlet, Binder and Blichert-Toft, 1976; Tyrell et al., 1978; Bigos et al., 1980; Chalmers, Mashiter and Joplin, 1981; Urbanic and George, 1981).

Hypersecretion of Mineralocorticoids—Conn's Syndrome

A syndrome associated with hypersecretion of aldosterone was first described by Conn (1955). The increased secretion arises either from a benign adenoma of the adrenal cortex (approximately 75%) or from bilateral adrenocortical hyperplasia (25%); rarely, an adrenocortical carcinoma is the cause (Brown et al., 1972; Nelson, 1980). Conn's syndrome is characterized by hypertension, hypokalaemia and metabolic alkalosis associated with low plasma concentrations of renin and angiotensin II.

Arterial hypertension in Conn's syndrome is usually mild (Conn, Cohen and Rovner, 1964) and it has been estimated that the frequency of the syndrome in the hypertensive population is approximately 1% (Brown et al., 1972). The causative mechanism is not known; it has been proposed that, in some patients, hypertension may be attributable to an unidentified agent (New et al., 1976). Of the other features of the syndrome, potassium depletion and hypokalaemia may be severe and cause muscle weakness; an associated metabolic alkalosis is in part a consequence of potassium depletion (Williams, 1976) and may cause tetany and paraesthesiae. An impairment of glucose tolerance occurs in approximately 50% of patients (Streeter et al., 1973) and has been related to the effect of potassium depletion on insulin secretion (Conn, 1965). Renal dysfunction causing polyuria may be associated with chronic potassium depletion and hypertension. A number of biochemical and radiological techniques have been
used to distinguish between unilateral tumours and bilateral hyperplasia: adrenal arteriography and venography, estimation of aldosterone in adrenal venous blood, adrenal computerized axial tomography, and quadric analysis of biochemical and clinical data (Nelson, 1980). The specific nature of the lesion is of importance in defining appropriate therapy; thus, the treatment of choice for adrenocortical adenoma is surgical removal, whilst bilateral adrenocortical hyperplasia may be managed medically using spironolactone or amiloride to avoid bilateral adrenalectomy (Ferriss et al., 1975; Weinberger et al., 1979).

The anaesthetic management of patients with primary hyperaldosteronism has been reported frequently (Garlington and Bailey, 1958; Gangat et al., 1976; Matsuki et al., 1976; Shipton and Hugo, 1982a) and has been reviewed by Finch (1969) and Shipton and Hugo (1982b). Spironolactone has been given before operation to reverse the metabolic effects of hyperaldosteronism (Brown et al., 1972) and to aid in correction of hypokalaemia and metabolic alkalosis. Hypertension may respond to this treatment, although specific antihypertensive therapy may also be required (Biglieri, 1976). Despite the use of a wide variety of anaesthetic agents, few anaesthetic problems have been reported in these patients (Finch, 1969; Shipton and Hugo, 1982b). It has been recommended that these patients should be managed with the usual precautions for hypertensive patients; other recommendations include cautious use of muscle relaxants in patients with persisting potassium depletion, avoidance of hyperventilation and a subsequent aggravation of a metabolic alkalosis and hypokalaemia, and perioperative monitoring of the plasma glucose concentration. Glucocorticoid maintenance therapy should only be required if both adrenal glands are mobilized or removed. In addition, as with all adrenal surgery, there are specific intraoperative problems that may be encountered, as discussed under the management of patients with Cushing's syndrome. Postoperative care demands attention to fluid and electrolyte balance, particularly in view of an increased frequency of renal dysfunction; negative sodium and potassium balances may necessitate potassium supplementation therapy and mineralocorticoid replacement may be required temporarily (Shipton and Hugo, 1982b).

Other syndromes associated with abnormal rates of secretion of aldosterone may be encountered that show at least some of the features of primary hyperaldosteronism, for example some patients with secondary hyperaldosteronism and hyperaldosteronism associated with renin-secreting tumours. The anaesthetic management of a patient with Bartters syndrome (hyperaldosteronism associated with juxtaglomerular hyperplasia, hypokalaemic alkalosis, hyperreninaemia and without hypertension) has been described (Abston and Priano, 1981).

CONCLUSIONS

There is little evidence available to influence the choice of particular anaesthetic agents in the management of patients with either hypo- or hyper-secreting dysfunction of the adrenal cortex. The management of patients undergoing anaesthesia and surgery should be directed to treatment of the individual, metabolic and cardiovascular, component disorders of these syndromes.

The role of the adrenocortical hormones in the physiological responses to the "stress" of anaesthesia and surgery and critical illness has not been elucidated. Whilst it remains difficult to identify those patients at risk of developing adrenocortical insufficiency, the available evidence indicates that, in patients undergoing anaesthesia and surgery, corticosteroid therapy in lower doses than previously used provides sufficient protection during the imposition of these insults; the value of corticosteroid therapy in critical care remains unknown. It is possible that further investigations directed to specific physiological and pharmacological actions of particular adrenocortical hormones may yield more information than studies confined by the conventional classification of adrenocortical activity as either glucocorticoid or mineralocorticoid.

REFERENCES


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