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Acute Adrenal Insufficiency in a Patient with Appendicitis during Anesthesia

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The perioperative management of patients taking steroids is controversial.¹⁻⁴ Intraoperative and postoperative hypotension as a consequence of inadequate steroid coverage is rare and even in steroid-dependent patients is due to more common problems of hypovolemia, anesthetic overdose, cardiopulmonary disease, or mechanical disorders.^{1,5-8,10} We report a case in which intraoperative steroid administration appeared to be very important in the successful resuscitation of a patient with intractable hypotension and the subsequent diagnosis of Addison's disease.

REPORT OF A CASE

A 28-year-old, 68-kg man presented to the emergency room with a 2-day history of periumbilical abdominal pain, nausea, vomiting, diarrhea, and fever. The patient had a medical history of aseptic meningitis at age 14 yr, with a reported serum sodium of 128 mEq/l and a serum potassium of 5.1 mEq/l. Recently there was a history of two hospital admissions and several emergency room visits over the past 3 years for dehydration and hypotension associated with gastrointestinal complaints. These episodes had always responded to conservative therapy with iv hydration. No electrolyte abnormalities were noted at any time. The most recent hospital admission for gastroenteritis and dehydration occurred 3 months earlier and was associated with his running in a marathon. He was otherwise healthy and took no medication. There was a history of three operations for hypospadias repair, without any reported surgical or anesthetic complications.

Upon arrival in the emergency room, the patient was lethargic but arousable. Arterial blood pressure was not obtainable, heart rate was 118 bpm, and temperature 38.6° C. He had decreased bowel sounds, with guarding and rebound tenderness in the right lower quadrant. No abnormal pigmentation was noted. Initial laboratory values included white blood count 25.2 bil/l, hemoglobin 14.7 g/dl, serum sodium 134 mEq/l, serum potassium 4.4 mEq/l, serum chloride 97 mEq/l, CO₂ 18 mEq/l, blood glucose 74 mg/dl, creatinine 6.2 mg/dl, blood urea nitrogen 34 mg/dl, and calcium 8.8 mg/dl. Analysis of arterial blood gases with FI_{O₂} of 0.21 revealed a pH of 7.40, PaCO₂ 32 mmHg, PaO₂ 53 mmHg, and HCO₃ 19.1 mEq/l. The eosinophil count was not elevated. An iv and central venous catheter were inserted, and 12 l of crystalloid were given over a 4-h period. Initial central venous pressure during the fluid resuscitation was 6.5 cmH₂O. A dopamine infusion was started at 4 μg · kg⁻¹ · min⁻¹. Arterial blood pressure gradually increased to 80-

100 mmHg systolic. A barium enema was done, which showed a mass in the area of the cecum thought to be compatible with a periappendiceal abscess. A diagnosis of acute appendicitis with probably rupture leading to septic shock was made, and an abdominal exploration was planned.

On arrival in the operating room, the patient had a systolic blood pressure of 90 mmHg and a central venous pressure of 8 cmH₂O. After insertion of a radial artery catheter, anesthesia was induced with ketamine 75 mg and succinylcholine 100 mg iv. Anesthesia was maintained during the 1 h case with 100% oxygen and diazepam 10 mg, fentanyl 250 μg, ketamine 100 mg, and metocurine 30 mg iv. Shortly after the surgical incision was made, hypotension to 60 mmHg systolic occurred. Arterial blood pressure remained low, despite the iv infusion of 3 liters of crystalloid, 3 units of packed erythrocytes, 100 mEq of sodium bicarbonate, 0.3 mg of epinephrine, and epinephrine and dopamine infusions. Throughout the procedure, analysis of arterial blood gases indicated adequate ventilation. At surgery an unruptured acutely inflamed appendix was found, and a Gram's stain of peritoneal fluid revealed a few polymorphonuclear leukocytes and no bacteria. At the termination of surgery the heart rate was 122 bpm, systolic blood pressure 80 mmHg, and central venous pressure 15 cmH₂O. Hydrocortisone 300 mg iv was given iv, for the surgical picture was not consistent with septic shock. After giving the patient hydrocortisone, he immediately was transferred to the ICU. In this interval, there was no apparent change in anesthetic depth. The arterial blood pressure on arrival in the ICU was 148/70 mmHg and the central venous pressure was 11 cmH₂O. The infusion of epinephrine was decreased and ultimately discontinued.

Postoperatively his course was complicated by a perioperative myocardial infarction with EKG changes of ST segment elevation in leads 1, 2, 3, AVF and V₃ through V₆ and a maximum CPK of 3960 IU/l with 8% fraction 2. The patient also developed pericarditis and required pericardiectomy and drainage of a small amount of pericardial fluid on the first postoperative day. This second operation was done with supplemental steroid administration and was uneventful. The etiology of the myocardial infarction was felt to be secondary to the long period of hypotension while in adrenal crisis.

The remainder of the hospital course was unremarkable, and the patient made a complete recovery. Throughout his hospital stay, the patient was maintained on iv and oral steroids. All blood cultures were negative, and the Gram's stain of pericardial fluid revealed no organisms. Since the diagnosis of adrenal insufficiency was doubtful, a myocardial biopsy was performed, which also proved negative. An evaluation for adrenal insufficiency then was pursued. Both a 1-h and 3-day adrenocorticotropin hormone (ACTH) stimulation test were done. The 1-h test showed an increase of the serum cortisol from 4 μg/dl to 8 μg/dl. The normal AM cortisol is 5-25 μg/dl, and the usual response to ACTH is a rise of at least 11 μg/dl after 1 h.¹² The 3-day test revealed an initial serum cortisol of 2 μg/dl, which rose only to 12 μg/dl 7 h after the final ACTH infusion. The normal response is a rise in serum cortisol to greater than 25 μg/dl.¹³ Thyroid function tests and measurements of testosterone levels were normal. These results were deemed consistent with a diagnosis of Addison's disease. The patient ultimately did well and was discharged on the twelfth hospital day, continuing to take hydrocortisone and fludrocortisone orally.

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Further studies have shown an ACTH level of 402 pg/ml (normal 20–200 pg/ml) while not taking steroids, a lack of antiadrenal antibodies, and ACTH stimulation tests with results comparable to those noted previously. The diagnosis of primary Addison's disease was confirmed with these laboratory results. The patient continues to do well on 30 mg hydrocortisone and 0.1 mg fludrocortisone daily.

DISCUSSION

Addison's disease is an extremely rare entity with a reported incidence of up to 60/1,000,000 population. It is found more often in women than men and usually is diagnosed between the ages of 20 and 50 years. Addison's disease is usually idiopathic in origin, with 60% of these cases having antiadrenal antibodies. In the past a large number of cases were caused by tuberculosis; today this cause is responsible for only 20% of cases. Much less common causes include hemorrhage into the adrenal glands, neoplasia, sepsis, and trauma. In the autoimmune form, other endocrine deficiencies usually related to antibody formation may occur.¹³

The clinical manifestations of Addison's disease are related to the failure of function of adrenal cortical tissue. Hence, both glucocorticoid and mineralocorticoid functions are affected. Generally, loss of more than 90% of adrenal cortical tissue is necessary before the disease becomes clinically apparent. In the chronic form of primary adrenal insufficiency, the usual presenting symptoms are, in order of decreasing frequency, weakness and fatigue, weight loss, anorexia, hyperpigmentation, hypotension, gastrointestinal complaints, salt craving, and postural changes. In patients with undiagnosed or inadequately treated Addison's disease, any stress such as surgery and anesthesia, infection, trauma, or dehydration can precipitate an adrenal crisis. This is a medical emergency that can lead to complete cardiovascular collapse and death if undiagnosed and untreated. Adrenal crisis is characterized by hypotension and shock, leading to vascular collapse, hypovolemia and dehydration, nausea and vomiting, abdominal pain, and weakness. Laboratory manifestations include hyponatremia, hyperkalemia, azotemia, hypoglycemia, normochromic normocytic anemia, lymphocytosis, eosinophilia, and hypercalcemia.

If acute adrenal insufficiency is suspected, treatment should be instituted immediately and be aimed at correcting the underlying metabolic abnormalities. Intravascular volume should be replaced rapidly with intravenous glucose, saline, and plasma expanders. Hydrocortisone hemisuccinate 100 mg iv should be given immediately and continued with 100 mg iv every 6 h. The precipitating causes must be sought and treated. Hemodynamic support with vasopressors should be undertaken if the other measures described prove inade-

quate. Appropriately treated, adrenal crisis is self-limited after restoration of volume, administration of adrenal cortical hormones, and correction of electrolyte abnormalities. Following initial treatment the dose of hydrocortisone should be decreased after the first 24 h to 50 mg iv every 6 h. Steroids then may be tapered and switched over several days to oral cortisone 15–20 mg qAM, 10–15 mg qPM, and for mineralocorticoid effect, fludrocortisone 0.05–0.1 mg qAM.¹²

There are several features of the case presented here that bear discussion. In retrospect, our patient had several episodes of dehydration and hypotension without any laboratory abnormalities prior to his admission for appendectomy. Yet he was able to train for, run in, and complete a marathon without a serious adrenal crisis. On the present admission it was only the severity, duration, and lack of responsiveness of his vascular collapse to the usual therapeutic maneuvers that led us to entertain the diagnosis of acute adrenal insufficiency. The response to the infusion of the hydrocortisone after all other measures had been ineffective was quite dramatic.

The chance of cardiovascular collapse of this nature during anesthesia and surgery leading to a diagnosis of Addison's disease is small. Vandam and Moore, without giving details, cite three cases out of 60,000 operations where this may have occurred.¹ There has been only one other case report where Addison's disease was diagnosed as the consequence of cardiovascular collapse during surgery.¹¹ Even in that case, however, the diagnosis was made only in retrospect when laboratory abnormalities became apparent 3 weeks postoperatively on the day of the patient's hospital discharge.

Intraoperative hypotension and cardiovascular instability, even in patients who may be steroid dependent, is unlikely to be caused by hypoadrenalism.^{3,10} Addisonian crisis is a sufficiently uncommon entity that a recent review chapter on the "Failure of the Peripheral Circulation During Anesthesia" neglected to mention it.¹⁴ The diagnosis of acute adrenal insufficiency should be considered only if the more usual causes of hemodynamic instability such as hypovolemia, anesthetic or drug overdose, cardiopulmonary disorders, or mechanical problems have been searched for and treated, and general supportive measures undertaken without clinical response. Patients who are receiving steroids chronically, have a recent history of steroid use, or are known to be hypoadrenal obviously are the most likely to suffer under the stress of anesthesia and surgery. Thus, one's relative index of suspicion should be tempered to the given clinical situation. Even so, in this particular case, the use of steroids in conjunction with appropriate hemodynamic support was dramatic and ultimately led to the correct diagnosis of primary Addison's disease.

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Postoperative Pain Relief for Circumcision in Children: Comparison among Morphine, Nerve Block, and Topical Analgesia

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Circumcision in children usually is followed by pain that may produce crying, restlessness, and agitation in the postoperative period. Several techniques of pain relief, including caudal block,¹⁻⁷ blockade of the dorsal nerve of penis⁸⁻¹¹ and narcotic administration^{6,7} have been used. The use of topical analgesia has not been described in this kind of surgery. Because of the simplicity of application, we investigated the efficacy of topical analgesia in relief of postcircumcision pain in comparison with blockade of the dorsal nerve of penis, narcotic administration, and a control group in whom no analgesic treatment was given.

METHODS

Seventy-seven healthy boys, ages ranging from 1 to 13 years admitted for circumcision as outpatients were studied. They were divided randomly into one control group and five study groups (table 1). No premedication was given. All circumcisions were done under general anesthesia. Induction of anesthesia was with thiopental 4 mg/kg iv or by inhalation of nitrous oxide and halothane, according to the child's stated preference. Anesthesia was maintained with inhalation of 70% nitrous oxide and 1-1.5% halothane through a face mask.

The first group (control) received general anesthesia alone; no supplemental drug was given neither during nor after surgery. In the second group, morphine (0.2 mg/kg) was given im after the children had been anesthetized. In the third group, after anesthesia had been induced, the dorsal nerves of the penis were blocked by single injection of 1-1.5 ml 0.5% bupivacaine at the root of the penis.⁸ In the fourth, fifth, and sixth groups, after the surgery had been accomplished but before the children were awake, a thin film of lidocaine spray (10-20 mg of 10% solution), lidocaine ointment (0.5-1 ml of 5% preparation), or lidocaine jelly (0.5-1

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