Anesthetic implications for patients receiving exogenous corticosteroids

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Opposing views exist about perioperative replacement of corticosteroids and appropriate replacement dosages. Anesthesia providers must be aware of the need for corticosteroid replacement not only in patients who have primary adrenal insufficiency but also in patients who have adrenal insufficiency resulting from long-term corticosteroid therapy. Without adequate knowledge, the anesthesia provider may fail to prepare the patient to withstand the stress of surgery and may open the way for life-threatening hemodynamic abnormalities that accompany inadequate amounts of corticosteroids.

The purpose of this article is to review the literature explaining the rationale and the proper perioperative dosing with corticosteroids for patients with long-standing asthma, rheumatoid arthritis, or Crohn disease.

The review of literature reflects articles on endogenous hormones, exogenous hormones, diseases that require long-term corticosteroid therapy, the hypothalamus-pituitary-adrenal axis, and corticosteroid replacement therapy.

Key words: **Anesthesia, exogenous corticosteroids, perioperative implications.**

For many years, differing opinions have existed regarding corticosteroid replacement in patients receiving long-term corticosteroid therapy. Anesthesia providers are responsible for recognizing this need in certain patient populations and choosing the correct dose of corticosteroid. To recognize this need, providers must understand the functions of certain glands in the body and the hormones produced by these glands.

The function of the anterior pituitary is to synthesize, store, and secrete hormones such as adrenocorticotrophic hormone (ACTH), prolactin, human growth hormone, thyroid-stimulating hormone, lutenizing hormone, and follicle-stimulating hormone. Adrenocorticotropic hormone is essential for the growth, development, and continued function of the adrenal cortex, the outer portion of the adrenal glands. It also stimulates the formation of cholesterol, the initial building block for the synthesis of corticosteroids, a group of adrenal cortical hormones that include glucocorticoids, mineralocorticoids, and androgens. The major stimulus for the secretion of ACTH is stress. The stimulus for the release of the hormone is under the control of a substance known as corticotropin-releasing hormone (CRH), which itself originates in the hypothalamus. Certain stress-inducing factors such as hypoglycemia, septicemia, trauma, and stress from anesthesia and surgery may increase the release of ACTH. Through an innate negative feedback mechanism, adrenal glucocorticoids regulate the release of CRH and ACTH.[1]

Glucocorticoids, a general classification of adrenal cortical hormones, protect against stress and produce an anti-inflammatory response in the body. Cortisol, also known as hydrocortisone, is the most potent glucocorticoid. Functions of cortisol include maintenance of cardiac function, systemic blood pressure, and normal responses to catecholamines. Cortisol also regulates the metabolism of fats, carbohydrates, and proteins and balances sodium and potassium levels.[1]

When stress occurs and the hypothalamus is stimulated, CRH is released. Corticotropin, in turn, stimulates ACTH release from the anterior pituitary, causing the increased synthesis of glucocorticoids in the adrenal cortex. This negative feedback system is known as the hypothalamic-pituitary-adrenal (HPA) axis. Exogenous steroids inhibit the HPA axis, causing atrophy of the adrenal glands. The glands are incapable of producing the basal rate of cortisol needed for the body to maintain homeostasis. Patients receiving long-term corticosteroid therapy, therefore, have suppression of the HPA axis and develop a relative adrenal insufficiency that partially reduces the capacity of the adrenal cortex to produce cortisol.[2] If intravenous corticosteroids are not administered during times of acute stress such as surgery and anesthesia, circulatory collapse may occur. The dilemma facing anesthesia providers is recognition of patients who need corticosteroid replacement and administration of appropriate dosages. The patients include not just those with total adrenal insufficiency, but people who have been receiving oral corticosteroid therapy for conditions such as rheumatoid arthritis, asthma, and Crohn disease.

The treatment of rheumatoid arthritis includes efforts to relieve pain, preserve joint strength and function, prevent deformities, and attenuate systemic complications. Treatment includes a combination of

drugs, physical therapy, and surgery. Corticosteroids are the drugs of choice and are used extensively for the management of rheumatoid arthritis itself and to provide symptomatic relief. The treatment for bronchial asthma includes anti-inflammatory corticosteroids and bronchodilators. Treatment for Crohn disease includes antidiarrheal drugs, antimicrobial drugs, and corticosteroids, which produce a quick remission. Patients with rheumatoid arthritis or Crohn disease often undergo surgical procedures for palliative measures or as short-term cures. Patients with bronchial asthma may undergo surgical procedures related to other disease processes.

Surgery requires that a patient have nothing to eat or drink for approximately 6 hours before anesthesia, with an exception being medication. Patients taking long-term corticosteroids should take their usual medication up until the time of surgery. The added stress of surgery, anesthesia, and the underlying disease require additional intravenous corticosteroids. When the major stress of the perioperative period is resolved, and the patient is in stable condition and free of complications, cortisol (hydrocortisone) administration can be gradually reduced over a few days to the usual maintenance dose.[3]

Anesthesia providers must be aware of the need for corticosteroid replacement in patients receiving corticosteroid therapy. To understand the need for perioperative corticosteroid replacement, knowledge is required of the functions of corticosteroids in the human body. Without adequate knowledge, patients are at risk of receiving a higher- or lower-than-required dose of corticosteroids, thus compromising their anesthesia management.

Endogenous hormones

The body produces many endogenous hormones to maintain daily living. Without these hormones, a person would be unable to function. Three of the many hormones are glucocorticoids, ACTH, and CRH.

A healthy adult secretes cortisol, the most important glucocorticoid, in the absence of stress, at a rate of 10 to 20 mg/d. In response to stress, cortisol secretion increases to approximately 150 mg/d.[1] Cortisol, also known as hydrocortisone, regulates metabolism, cardiovascular function, growth, and immunity.[4] Cortisol increases the rate of production of glucose; stimulates protein breakdown, thus decreasing stores of protein; mobilizes fatty acids from adipose tissue and increases oxidation of fatty acids; and regulates cardiovascular function, growth, and immunity.

The anti-inflammatory effect of cortisol stems from its ability to stabilize lysosome membranes to prevent the migration of leukocytes into inflamed areas where they would cause further inflammation.[1] Glucosteroids also reduce the ability of the body to respond to antigens by inhibiting the ability of tissue macrophages to kill microorganisms.[4] Exogenous cortisol can depress the immune system by decreasing the production of antibodies, causing the body to be more susceptible to bacterial and viral infections.

Circulating cortisol has a direct negative feedback effect on the hypothalamus, which produces CRH. The hypothalamus alerts the anterior pituitary to stop the production of ACTH, which is responsible for stimulating the adrenal cortex to produce cortisol. Increased stress to the body can override the negative feedback loop, and circulating levels of cortisol can be increased. This effect is beneficial because it mobilizes fats and proteins to be used as energy and also produces glucose. Patients receiving exogenous corticosteroid therapy, however, react differently because of adrenal suppression.

A patient who has received prolonged corticosteroid therapy may develop a functional atrophy of the HPA axis.[5] A suppressed HPA axis prevents the release of cortisol during stressful stimuli.[3] This suppression could cause a variety of hemodynamic abnormalities, such as hypovolemic or circulatory shock. The administration of exogenous corticosteroid has, therefore, been recommended before, during, and, sometimes, after the stress of surgery.[3,5]

Exogenous hormones that replace cortisol

Many synthetic corticosteroids (exogenous hormones) have become important in treating inflammatory and allergic disorders. Two frequently prescribed short- to medium-acting glucosteroids are prednisone and methylprednisone, each prescribed for the treatment of rheumatoid arthritis, Crohn disease, and asthma.

Prednisone is a synthetic corticosteroid given orally to suppress the immune system and inflammation. Prednisone is converted rapidly to prednisolone in the body. It mimics the mechanism of action of cortisol but is 4 times as potent. The starting dose of prednisone depends on the extent of the disease and the age of the patient.[5] The dose usually is increased and adjusted until the desired effect is produced, and then the dose is decreased in small amounts until the lowest dose necessary to maintain functional improvement is reached. The dose should be increased during stressful events such as surgery.[6] When prednisone is taken on a long-term basis, the adrenal glands begin to atrophy and no longer produce essential corticosteroids. In some cases, alternate-day therapy is recommended to minimize this secondary adrenal insufficiency. If the exogenous corticosteroid is to be discontinued, a tapering regimen must be prescribed

to facilitate recovery of the adrenal glands and adequate cortisol production.

Methylprednisolone (Medrol), is another exogenous corticosteroid developed for its anti-inflammatory and immunosuppressive effects. Methylprednisolone can be administered orally, topically, or by injection.[4] Dosage requirements depend on the disease being treated. Side effects of methylprednisolone are similar to those of prednisone. Methylprednisolone, along with other corticosteroids, can mask the signs of infection and impair the body's natural immune response, so people taking corticosteroids can acquire serious, life-threatening infections. The suppression that methylprednisolone confers on the immune system also makes vaccinations ineffective and reduces the effect of antibiotics.

Side effects of methylprednisolone and other corticosteroid therapy vary from mild to severe, with higher dosage and longer duration showing an increase in adverse effects. The most common side effects are fluid retention, weight gain, high blood pressure, potassium loss, headache, and muscle weakness. Other side effects are puffiness of the face (moon face), growth of facial hair, thinning and easily bruised skin, impaired wound healing, ulcers, exacerbation of diabetes, rounding of the upper back, obesity, growth retardation in children, menstrual changes, visual disturbances (cataracts), mood swings, personality changes, and psychosis.[7] Major adverse effects can be avoided if patients are monitored closely. Also, if patients are prescribed corticosteroids topically (by inhalation, intranasally, transdermally, or rectally) or if they received them intra-articularly or intrasynovially, they rarely experience major systemic effects.[2,7]

Disease states requiring long-term corticosteroid therapy

There are many conditions that require exogenous steroid replacement. Rheumatoid arthritis, Crohn disease, and bronchial asthma are 3 of the most common diseases for which exogenous corticosteroid administration is the treatment of choice and a possible cause of HPA suppression.

Rheumatoid arthritis is an autoimmune disease primarily occurring in the synovial tissues. Rheumatoid arthritis can occur at any age but is diagnosed most frequently in the fourth to sixth decade of life. This disease causes chronic inflammation of the joints, tissues around the joints, and other organs of the body.[8,9] The cause of rheumatoid arthritis is unknown. There is no known cure for rheumatoid arthritis despite worldwide research.

When the disease is in the active state, inflammation is present. When the joints and other organs are inflammation-free, the disease is in remission. Symptoms in the active state are fatigue, lack of appetite, low-grade temperature, muscle and joint aches, and stiffness. Stiffness is usually exacerbated in the early morning hours or after periods of inactivity. During the active phase of the disease, joints become red, hot, swollen, painful, and not easily moved. With rheumatoid arthritis, joints usually are affected symmetrically, progressing from small joints of the wrist, hands, and feet to the knees, shoulders, hips, elbows, ankles, and cervical spine. The chronic inflammation often causes joint deformity, destruction, and loss of function.[8-10]

The goals for treatment of rheumatoid arthritis are to reduce joint inflammation and pain, to maximize joint function, and to prevent joint destruction and deformity. The optimal treatment for these patients consists of medication, rest, joint exercises, joint protection, and education. There are 2 lines of medication for this disease: fast-acting, first-line drugs and slow-acting, second-line drugs. First-line drugs, such as aspirin and corticosteroids, are used to treat the inflammation and pain. They neither cure the arthritis nor prevent joint damage. Slow-acting drugs, such as gold, methotrexate, and hydroxychloroquine, promote remission and help prevent joint destruction.

Patients with less destructive forms of rheumatoid arthritis may be treated with rest and anti-inflammatory drugs. People with severe disease usually are treated with a combination of first- and second-line drugs. For the lowest effective dose of corticosteroids, alternate-day or single-day doses and the shortest possible duration should be used.[6,8] Surgery is an option for patients with severe joint deformities.

Rheumatologists recommend corticosteroid replacement therapy for patients with rheumatic disease receiving long-term corticosteroid treatment who are undergoing surgery. Minor surgical procedures require the normal corticosteroid dose plus 25 mg of hydrocortisone on the day of the procedure. Moderate surgical procedures require the normal corticosteroid dose plus 50 to 75 mg of hydrocortisone on the day of the procedure with a rapid taper during 1 to 2 days. Major surgical procedures require the normal corticosteroid dose plus 100 to 150 mg of hydrocortisone on the day of surgery with a taper during 1 to 2 days. Patients receiving a daily dose of 5 mg or less of prednisone do not require supplemental therapy regardless of the surgical procedure.[11]

Crohn disease is an idiopathic chronic inflammatory disease of the gastrointestinal tract. Typical pathophysiology includes ulcerations all the way through the walls of the small or large intestines, but the disease may cause problems anywhere in the digestive track. Between 500,000 and 2 million people in the United

States are affected. Crohn disease follows a familial pattern and tends to be more prevalent in whites and African Americans than in Latinos and Asians.[6,8]

The immune system in patients with Crohn disease is activated without any known antigen. Continued activation causes inflammation and ulceration of the intestine with symptoms of diarrhea, abdominal pain, and weight loss. Once Crohn disease is diagnosed, a treatment regimen is instituted, typically including prescribed corticosteroids. These drugs act systemically to decrease the inflammation throughout the body. The corticosteroids of choice are prednisone and hydrocortisone. The goal is to taper to a single morning alternate-day dose as soon as symptoms are reduced.[6] Surgery is sometimes indicated but is reserved for incidences of obstruction, perirectal abscess, severe anal fistulae, and resection of internal fistulae because recurrence after bowel resection is high.[6,8] When surgery is indicated, disease experts recommend that 100 mg of hydrocortisone be administered intravenously every 8 hours for 48 hours. They also advocate that intravenous corticosteroids be replaced by oral prednisolone and that patients be weaned off the corticosteroid as soon as symptoms allow.[12]

"Asthma is a chronic inflammatory disease of the airways that causes airway hyperresponsiveness, mucosal edema, and mucus production."…"In 1998, asthma accounted for over 13.9 million outpatient visits to physician offices or hospital clinics and over 2.0 million emergency room visits."[9] It is the most frequent admitting diagnosis in children's hospitals.[6] Asthma most commonly occurs as a result of exposure to an allergen or irritant, which initiates actions of chemical mediators. When the tissues become inflamed, they produce a larger than normal amount of hyperviscous mucus, which forms plugs that clog smaller, more peripheral airways and progress to the larger mainstream airways.[8] In patients with asthma, inflammation does not completely subside, making it more likely that an asthma attack will recur. On a long-term basis, this may lead to thickening of the bronchial walls, referred to as *airway remodeling*.[13] When this occurs, bronchial tubes become permanently narrower and poorly responsive to medications. Chronic inflammation causes the patient to be in a hyperreactive state and easily susceptible to an allergen.[13]

The treatment for asthma includes the use of medications that relax bronchospasm and reduce inflammation. Bronchodilators, such as albuterol, and oral corticosteroids, such as prednisone, are used in the treatment of this disease.[9,14] Anti-inflammatory inhaled corticosteroids also may be used. A history of asthma and corticosteroid therapy should alert the anesthetist to the potential exacerbation of the disease or to the risk of circulatory collapse during the stress of surgery. Patients who have received oral corticosteroids for longer than 2 weeks during the 6 months before surgery should receive 100 mg of hydrocortisone every 8 hours intravenously during the surgical period. The dose of corticosteroids should be reduced rapidly within 24 hours following surgery,[15] so as to reduce the medication's interference with healing and resistance to infection.

Inflammation is a common denominator in rheumatoid arthritis, Crohn disease, and bronchial asthma. The common treatment for the inflammation in all of these disease states is a corticosteroid such as prednisone (Deltasone, Orasone, Prednicen-M) or methylprednisolone. Each of the corticosteroids suppresses the body's formation of cortisol. It is imperative that practicing anesthesia providers understand this phenomenon because cortisol has a synergistic action with epinephrine and norepinephrine in maintaining homeostasis and in preventing shock. A careful plan must be developed to replace corticosteroids during the course of anesthesia. It should be noted, however, that, for patients who receive coticosteroids only topically, HPA suppression is rare,[2,3] and replacement probably is unnecessary.

The HPA axis and patients receiving long-term corticosteroid therapy

The HPA axis is a physiologic mechanism. In healthy people, severe illness, trauma, and stress are accompanied by activation of the HPA axis.[4] When the body undergoes stress, the hypothalamus is stimulated to produce CRH. Corticotropin-releasing hormone stimulates the anterior pituitary to produce ACTH, which, in turn, stimulates the adrenal cortex to synthesize glucocorticoids. These hormones are required to sustain life. Patients who have HPA axis suppression require intraoperative replacement of corticosteroids.

Many studies[16-18] have been carried out to determine the extent of suppression of the HPA axis because of long-term use of corticosteroids. For example, in 1992, a study was designed to determine the degree of suppression of pituitary-adrenal function in patients treated for different periods with different doses of synthetic glucocorticoid.[16] To accomplish this, researchers measured the pituitary-adrenal response to the administration of exogenous human CRH. In the study, 279 subjects received 5 to 30 mg of prednisone per day for periods varying from 1 week to 15 years. Injections of CRH were administered 24 hours after the latest dose of corticosteroids. After administration of CRH, 43

patients had no increase in plasma concentrations of corticotropin and cortisol. The response was blunted in 133 patients and normal in 103 patients. The results showed poor correlation between the plasma cortisol response after the administration of CRH. Neither the dosage nor the duration of therapy influenced the response. The conclusion drawn was that pituitary-adrenal function in patients treated with synthetic glucocorticoids could not be estimated reliably from the dose of glucocorticoid, the duration of therapy, or the basal plasma cortisol concentration.[16]

Replacement of corticosteroids

In 1855, Sir Thomas Addison reported the destruction of the adrenal gland by tuberculosis. This caused a primary adrenal insufficiency.[18] Patients who have adrenal hypofunction due to conditions specifically involving the HPA organs belong in this category. Publication of the effects of cortisone for patients with rheumatoid arthritis began the era of glucocorticoid therapy for diseases other than primary adrenal insufficiency.[19] Reports supporting the state of adrenal insufficiency in patients who have been receiving corticosteroid therapy have been documented over the years. The patients are categorized as having secondary adrenal insufficiency.

The concept of secondary adrenal insufficiency was developed in 1952 when a case of surgery-related adrenal insufficiency as a consequence of preoperative withdrawal from glucocorticoid therapy was reported. The next year, another case was documented in which the patient died several hours after surgery.[18] The patient had rheumatoid arthritis and had been receiving cortisone daily for 5 months before the surgical procedure. The cortisone was discontinued the day

Table 1. Corticosteroid replacement doses recommended by Salem et al[18]

Degree of surgical stress	Recommended replacement dose
Minor (eg, inguinal hernia repair)	Usual corticosteroid dose + 25 mg of hydrocortisone at induction
Moderate (eg, nonlaparoscopic cholecystectomy, total joint replacement, abdominal hysterectomy)	Usual corticosteroid dose + 50-75 mg of hydrocortisone for 24-48 h
Major (eg, cardiac surgery, cardiopulmonary bypass, total proctocolectomy)	Usual corticosteroid dose + 100-150 mg of hydrocortisone intravenously every 8 h for 48-72 h

Table 2. Corticosteroid replacement doses recommended by Nicholson et al[5]

Medication Status	Prednisolone dosage, mg/d	HPA response*	Recommended replacement
Patients currently taking steroids	<10	Assume normal HPA response	No coverage
Patients currently taking steroids	>10	Minor surgery HPA response may be compromised	25 mg at induction of anesthesia
Patients currently taking steroids	>10	Moderate surgery HPA response may be compromised	Usual preoperative corticosteroids + 25 mg of hydrocortisone at induction of anesthesia + 100 mg/d for 24 h
Patients currently taking steroids	>10	Major surgery HPA response may be compromised	Usual preoperative corticosteroids + 25 mg of hydrocortisone at induction of anesthesia + 100 mg/d for 48-72 h
Patients who stopped taking steroids < 3 months	>10	HPA response may be compromised	Treat as if taking corticosteroids
Patients who stopped taking steroids > 3 months	>10	Assume normal HPA response	No coverage necessary

*** HPA indicates hypothalamic-pituitary-adrenal (axis).**

Table 3. Corticosteroid replacement doses recommended by Jabbour[3]

Degree of surgical stress	Recommended dose
Minor (eg, inguinal hernia repair)	Hydrocortisone, 100 mg, intravenously at induction of anesthesia + maintenance dose (approximately 20 mg/d)
Major (eg, chest or abdominal surgery)	Hydrocortisone, 100 mg, at induction of anesthesia + 100 mg of hydrocortisone every 8 h for 24 h

Table 4. Postoperative tapered doses of hydrocortisone recommended by Jabbour[3]

Postoperative day	Recommended dose
Day 1	Hydrocortisone, 100 mg, every 8 h starting with induction of anesthesia
Day 2	Hydrocortisone, lower dose to 50 mg every 8 h if patient is in stable condition and major postoperative stress is resolved
Day 3	Hydrocortisone, 25 mg every 8 h
Day 4	Hydrocortisone, 25 mg twice per day
Day 5	Hydrocortisone maintenance dose: 15-20 mg in the morning and 5-10 mg in the evening

before surgery. A postmortem examination revealed atrophic adrenal glands and hemorrhage into the glands. With this report came a recommendation for perioperative glucocorticoid treatment. The recommendation was that a 4-fold increase in the dose of corticosteroid be administered before surgery. Even though this far exceeded the natural amount of cortisol, the recommendation became the standard of therapy. There were detrimental side effects from this high replacement dose, such as reduced tissue repair rates, decreased glucose tolerance, and increased susceptibility to infection, but the possibility of death existed if replacement therapy was ignored.[18]

An example of a life-threatening event occurred when a 42-year old woman was admitted to a hospital for resection of a potentially malignant right ovarian cyst. The patient had no other medical problems but had been in a car accident 3 months before the planned admission. As part of her treatment, she had received the corticosteroid dexamethasone (Decadron), 16 mg/d, for 4 weeks. When she was evaluated for her resection, her vital signs were normal, as were the results of her chest radiograph, electrocardiogram, and other laboratory studies. The patient was cleared for surgery. After the surgery, the patient was taken to the recovery room, where her blood pressure fell to 80/42 mm Hg. Two liters of normal saline were infused with little result. Finally, intravenous hydrocortisone, 100 mg, was ordered by her surgeon, who had been aware of her previous corticosteroid treatment. Her blood pressure stabilized to her baseline pressure, and there were no other adverse occurrences.[2] This case shows that the anesthesia provider must be alert to health history, including medications prescribed within the past 3 months,[5] so as to avoid the effects of unknown corticosteroid therapy.

Opposing views remain regarding perioperative replacement and appropriate replacement dosages. In 1994, Salem et al[18] made the recommendations shown in Table 1. Table 2 shows the corticosteroid replacement doses recommended by Nicholson et al[5] in 1998. Aker and Biddle[20] followed in 1999 with recommendations similar to those published by Salem et al.[18] The most recent recommendations were put forth by Jabbour[3] in 2001 and are shown in Table 3 and Table 4.

Summary

Disease states that normally require long-term corticosteroid use include rheumatoid arthritis, Crohn disease, and bronchial asthma. Rheumatoid arthritis and Crohn disease often require surgical procedures to treat the disease itself. Asthma does not require surgery for relief, but patients with this disease often undergo surgical procedures. Patients receiving long-term corticosteroid treatment have suppression of the HPA axis, with the adrenal gland shown to become atrophic. When this is the case, the adrenal glands cannot function properly under the stress of surgery in which there is a need for more cortisol, especially if there is a sudden withdrawal from the medication.

Patients receiving long-term corticosteroid therapy require perioperative supplemental corticosteroids. Dosing regimens for corticosteroid replacement have remained controversial. To provide safe anesthesia, anesthesia providers must be aware of the functions of cortisol and choose the best perioperative replacement regimen available. This seems to be a protocol that includes not only replacement of corticosteroids at surgery but also tapering the corticosteroids after surgery. Only the latest article by Jabbour[3] concluded with a recommended method for tapering corticosteroid therapy after the surgical procedure. Even though some patients may respond normally after receiving corticosteroid therapy, because their pituitary-adrenal function cannot be estimated reliably from the dose or the duration of therapy, it seems wise to follow Jabbour's[3] recommendations. It is doubtful

that the extra corticosteroid for a period of 1 to 4 days will cause harm.[2]

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