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Dexamethasone Bridging Versus the Hydrocortisone Standard

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DEXAMETHASONE BRIDGING VERSUS THE HYDROCORTISONE STANDARD

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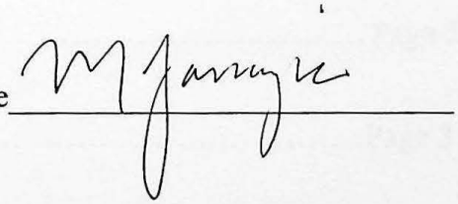
Signature 

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Abstract

A concern for anesthesia providers is the risk of perioperative shock due to secondary adrenal insufficiency in patients receiving long-term glucocorticoid therapy who do not receive supplemental stress steroid coverage for surgery. Dexamethasone is currently used by anesthesia providers as a perioperative anti-inflammatory agent and as an antiemetic adjunct. Hydrocortisone is currently the most commonly used drug for bridging patients who have previously received long term glucocorticoid therapy. The increased potency, duration of action, and antiemetic properties of dexamethasone may make it a desirable substitution for hydrocortisone.

The purpose of this independent project was to review the current literature investigating whether the substitution of dexamethasone for the hydrocortisone standard would reduce the need for re-dosing of glucocorticoids.

A comprehensive review of the literature was performed using PubMed and CINAHL databases. Current research findings on the topic of interest and related topics were reviewed. Relevant articles were reviewed along with their reference sections.

Even though dexamethasone has many desirable properties, further research is needed for practitioners to safely bridge patients with dexamethasone. Many pharmacologic properties of dexamethasone have been identified to date, and the current use of the drug is ever changing as new studies confirm increasing beneficial effects.

Anesthesia providers can take the pharmacologic properties of dexamethasone into consideration when formulating an anesthetic plan. Some properties may make it an attractive alternative to hydrocortisone and it may reduce the need for redosing of glucocorticoids.

Introduction

A common question asked in the pre-anesthetic exam is whether or not a patient has taken steroids for any reason in the past year. The risk of perioperative shock due to secondary adrenal insufficiency may exist in patients who have received long-term glucocorticoid therapy who do not receive supplemental stress steroid coverage for surgery. Due to patient variability, it is difficult to determine what dose of steroids or what duration of therapy will cause hypothalamic-pituitary-adrenal axis (HPA) suppression requiring intra-operative replacement (Barash, 2009). The anesthesia provider must take into account the duration and dose of steroids, and estimate the stress of surgery when determining if replacement will be necessary.

This project reviewed the current literature and investigated whether the substitution of dexamethasone for the hydrocortisone standard would reduce the need for re-dosing of glucocorticoids. The author hoped to answer the question of whether dexamethasone could safely be administered as a steroid bridge for patients on long-term exogenous steroid coverage who present for surgery. Case reports of patients experiencing adrenal crisis who were previously on long term exogenous steroids and did not receive adequate perioperative steroid supplementation have been identified. These case reports have acknowledged a need for steroid replacement during the perioperative and perhaps postoperative phases.

Many steroid preparations are available today. Steroids are primary treatments for diseases such as chronic obstructive pulmonary disease, rheumatoid arthritis, lupus, asthma, allergies, and many other conditions. The projection for 2020 indicates that chronic obstructive pulmonary disease will be the third leading cause of death worldwide (Global Initiative for Chronic Obstructive Lung Disease, 2007). Therefore, it can be anticipated that an increasing

number of patients may present on long term exogenous steroids, with the need for the best bridging therapy to be utilized.

Exogenously administered corticosteroids mimic the effects of natural hormones in the body such as cortisol. Cortisol is involved in the metabolism of carbohydrates, lipids, and proteins and has profound effects on immune and circulatory function (Becker, 2001). Lobato, Gravenstein, & Kirby (2008) state that normal adults secrete 20 mg of cortisol per day, increasing to 50 mg for minor surgery, 75-100 mg with major surgery, and as high as 200-500 mg under severe stress.

Glucocorticoid therapy over a prolonged period of time may decrease cortisol release during periods of stress. This is due to secondary adrenal insufficiency caused by the atrophy of pituitary corticotroph cells, which are responsible for secretion of adrenocorticotropic (ACTH) (Wiebke & Bruno, 2003). Corticotrophin hormone (CRH) from the hypothalamus and ACTH released from the anterior pituitary gland result in adrenal secretion of cortisol through a direct negative feedback loop (Jabbour, 2001). Thus, lower CRH and ACTH levels secreted from the pituitary gland may result in lowered levels of cortisol secreted from the adrenal gland.

Guidelines for perioperative steroid administration by Loh and Atherton (2003) indicate that patients on daily doses of more than 10 mg prednisolone or its equivalent within the last three months must have a specific perioperative treatment plan. Patients undergoing minor surgery should receive 25 mg hydrocortisone at induction, patients undergoing moderate surgery should receive 25 mg at induction and 100 mg over one day, and patients undergoing major surgery should receive 25 mg at induction and 100 mg/day for 2-3 days (Loh & Atherton, 2003). The potency and duration of biologic action of dexamethasone compared to cortisol and hydrocortisone were compared by Holte and Kehlet (2001). Their findings were as follows:

duration of action (doa) of cortisol is 8 hours compared to hydrocortisone doa of 36 hours and dexamethasone doa 72 hours; potency of cortisone is one compared to hydrocortisone, which is five times more potent than cortisol, and dexamethasone which is 25 times more potent than cortisol (see appendix A). Therefore, dexamethasone has a much longer duration of action and a greater potency than the hydrocortisone standard, making it a potentially attractive alternative to the hydrocortisone standard.

The hydrocortisone standard was initiated after case reports were published describing cardiovascular collapse and death in young patients presenting for surgery after withdrawal of longterm steroid therapy. These case reports were the initial clinical recognition of adrenal insufficiency resulting from exogenous glucocorticoid administration and were the beginnings of the rationale for perioperative steroid supplementation and the hydrocortisone standard. There is a wide variety of commercial steroid preparations that are currently used including solumedrol, solucortef, prednisone, and dexamethasone to name a few. There is a lack of consistency in practice regarding which drug and what dose is necessary for bridging patients, and this review will also discuss what the current best practice is regarding these.

Purpose

The purpose of this independent study was to investigate whether the addition of dexamethasone to a patient's anesthetic plan, versus the hydrocortisone standard used by many practitioners, will reduce the need for re-dosing. A review of the existing research performed on the two drugs provided a comparison of the drugs including advantages and disadvantages to the use of both. A review of the pathophysiology and history of steroid supplementation was provided as well.

The focus of this project was on comparing and contrasting the different glucocorticoids, discussing the pathophysiology of cortisol replacement, and identifying the current best practice for decreasing the risk of perioperative shock due to secondary adrenal insufficiency.

This information was presented at a clinical level to current anesthesia students and providers at the North Dakota Association of Nurse Anesthetists bi-annual meeting in Bismarck, North Dakota. With current evidence for practice presented, providers and students will be able to determine whether the substitution of dexamethasone would prove beneficial to the patient and decrease the need for re-dosing.

Significance

Long term exogenous glucocorticoid therapy has been found to cause secondary adrenal insufficiency due to negative feedback. The need for perioperative supplementation was first identified 59 years ago and much research has been done since then to determine the best practice for steroid supplementation for patients undergoing surgeries with varying stress responses.

Patients on long term glucocorticoids frequently present for surgery and have an increased risk of complications not only from adrenal suppression, but also from the disease or condition which required them to take the steroids. Therefore this patient population needs careful pre-anesthetic assessment of risks and potential complications of undergoing a surgical procedure. Developing an anesthetic plan for these patients includes estimating the degree of physiological stress associated with the surgery. Based on the amount of surgical stress anticipated, the anesthetist can determine how much cortisol replacement is necessary.

Failure to ensure adequate circulating cortisol levels are present in response to surgical stress may result in a circulatory collapse and hypotension similar to a hypoadrenal or

"Addisonian crisis." An acute adrenal crisis is a life-threatening condition that occurs when there is not enough circulating cortisol and may manifest as confusion or coma, dehydration, hypotension, tachycardia, tachypnea, and diaphoresis. The potential circulatory collapse may be refractory to catecholamines and only responsive to glucocorticoid replacement. Therefore, the need to supplement patients on long term glucocorticoids presenting for surgery with glucocorticoids may exist.

The choice of glucocorticoid replacement must consider the pharmacologic properties of the drug, the duration and dose necessary to obtain adequate coverage, and potential side effects. Dexamethasone is often discussed as an alternative for replacement, however literature comparing it to the current standard is not extensive. The 72 hour duration of action, 25 time increased potency to physiologic cortisol, and antiemetic properties of dexamethasone make it worth considering. This project reviewed the current literature to determine whether or not anesthesia practice and science could possibly benefit from the substitution of dexamethasone.

Theoretical Framework

A physiological framework was created examining the physiology of the hypothalamic-pituitary axis as well as pharmacokinetic and pharmacodynamic properties of dexamethasone in patients on long term exogenous steroid therapy for this project.

The two major classes of adrenal corticosteroids discussed are glucocorticoids and mineralocorticoids. The adrenal cortex also secretes sex steroids, however this project will focus on corticosteroids and their relation to the HPA axis. There have been more than 30 different corticosteroids isolated from the adrenal cortex, however only two are of major importance: cortisol, the principal glucocorticoid, and aldosterone, a mineralocorticoid (Stoelting & Hillier, 2006). Corticosteroids are life-sustaining cholesterol derivatives produced in the zona

fasciculate of the adrenal cortex under the negative feedback control of both the hypothalamus and pituitary gland (Coursin & Wood, 2002). Mineralocorticoids influence the plasma concentrations of sodium and potassium ions, whereas glucocorticoids influence carbohydrate, fat, and protein metabolism as well as exhibit anti-inflammatory effects.

The primary glucocorticoid activity is a result of the secretion of cortisol. Cortisol is one of the few hormones essential for life. The physiologic effects of cortisol are a) increased gluconeogenesis, b) protein catabolism, c) fatty acid mobilization, d) anti-inflammatory effects, and e) increased number or responsiveness of beta-adrenergic receptors resulting in improved cardiac function (Stoelting & Hillier, 2006). Cortisol exerts its mechanism of action through stimulation of mRNA in the nuclei of responsive cells, leading to the synthesis of appropriate enzymes (Holte & Kehlet, 2001). The most important stimulus for the secretion of cortisol is the release of ACTH from the anterior pituitary gland (Appendix B). Corticotropin-releasing hormone released from the hypothalamus is also partly responsible and circulating cortisol exerts a direct negative-feedback on the hypothalamus and anterior pituitary gland.

There are many surgery related variables which may stimulate the secretion or inhibit the secretion of cortisol. Surgical stress normally causes cortisol secretion to increase two to tenfold in order to mobilize cellular proteins, fat stores for energy, and other compounds. Anesthesia technique may also influence cortisol secretion. Large doses of opioids were found to attenuate the cortisol response to surgical stimulation (Bovill et al., 1983). The induction drug etomidate inhibits cortisol synthesis even in the absence of surgical stimulation due to its inhibition of the enzyme 11-beta-hydroxylase (Fragen, Shanks, Molteni, & Avram, 1984). Regional anesthesia has been found to limit the degree of surgical stress induced cortisol secretion due to neural mechanisms linking the operative site with the spinal cord, and increasing plasma cortisol levels

have been found to parallel the waning of regional anesthesia (Jabbour, 2001). Chronic administration of exogenous corticosteroids prevents the release of cortisol in response to stressful stimuli through a direct negative feedback loop, thus creating a need for peri-operative cortisol supplementation in patients on chronic therapy.

Aldosterone accounts for approximately 95% of the mineralocorticoid activity produced by corticosteroids. Cortisol has mineralocorticoid properties, but these are much less potent than the mineralocorticoid properties of aldosterone. Aldosterone causes absorption of sodium ions and simultaneous secretion of potassium ions in the lining of renal tubular epithelial cells of the distal renal tubules and collecting ducts. Water follows the sodium causing conservation of extracellular fluid. The mechanism of action of aldosterone involves the induction of messenger RNA in the interior of renal tubular epithelial cells, thus initiating the transport of sodium and potassium ions. The most important stimulus for aldosterone secretion is an increase in the plasma potassium concentration. The renin-angiotensin system is also an important determinant of secretion (Stoelting & Hillier, 2006).

Dexamethasone is among the most potent synthetic corticosteroids available, with a biologic half-life of 36-72 hours. Dexamethasone is a fluorinated derivative of prednisolone and an isomer of betamethasone which acts as an anti-inflammatory and immunosuppressant. The anti-inflammatory effect of 0.75 mg dexamethasone is equivalent to that of 20 mg of cortisol, and the mineralocorticoid effect is negligible. The bioavailability of dexamethasone is 80-90% with 70% being protein bound. Primary metabolism occurs in the liver with renal excretion of metabolites. Dexamethasone sodium phosphate is water soluble, rendering it appropriate for parenteral use (O'Sullivan et al., 1997).

Definitions

Steroids: for the purpose of this review only corticosteroids are discussed. Corticosteroids are a class of chemicals that are synthesized from cholesterol and naturally produced in the adrenal cortex. These steroid hormones are required for the maintenance of metabolic control, blood volume, and normal cardiovascular function. Analogues of these hormones are synthesized in laboratories. Two types of corticosteroids exist: glucocorticoids and mineralocorticoids. The primary natural glucocorticoid is cortisol and the primary natural mineralocorticoid is aldosterone. This review will focus primarily on glucocorticoids, however, mineralocorticoids will be discussed as well.

Steroid Treatment Regimen: for the purpose of this review is initiated when patients have received a regular daily dose of more than 10 mg of Prednisone or equivalent in the last three months or for longer than two weeks during the previous year (Nicholson, Burrin, Hall, 1998). The current, most common method of determining the appropriate amount of steroid replacement in patients on long term steroid equivalents is a subjective table titled *Suggested Steroid Treatment Regimen* (Appendix C).

Secondary Corticosteroid Insufficiency: for this review can be defined as the deficiency of adrenocorticotropic hormone (ACTH) and is characterized by atrophy of the adrenal cortex. The most common cause of secondary corticosteroid insufficiency is due to exogenous steroid use (Yong, Marik, Esposito, & Coulthard, 2009). Exogenous steroids cause adrenal atrophy and hypothalamic-pituitary-adrenal (HPA) axis suppression due to negative feedback of both hypothalamic and pituitary function (Arlt & Allolio, 2003). ACTH and CRH are under direct negative feedback from cortisol, Surgical stress in normal patients causes HPA axis activation leading to a surge in cortisol. ACTH secreted from the pituitary gland is necessary for normal

adrenal growth and function and in its absence the glands may become atrophic and unable to respond and secrete cortisol during periods of stress (Appendix B).

Cortisol: will be defined here as a natural steroid hormone produced in the zona fasciculata of the adrenal gland. It is released in response to stress and through negative feedback activation from low levels of blood glucocorticoid. The primary function of cortisol are to suppress the immune system, increase blood sugar concentrations through activating gluconeogenesis, and to aid in fat, protein, and carbohydrate metabolism (Stoelting & Hillier, 2006).

Re-dosing: for the purpose of this review will relate to how often a specific glucocorticoid must be administered to attain desired physiologic blood levels. The glucocorticoids administered to patients with anticipated secondary adrenal insufficiency have varying half lives, and thus may need to be re-dosed depending on the severity of the surgery. For example, hydrocortisone is deemed a short acting glucocorticoid with a half life of 8-12 hours, while dexamethasone is considered long acting with a half life of 36-54 hours (Appendix A). Chronic glucocorticoid therapy has been associated with hyperglycemia, fluid retention, and impaired wound healing; and re-dosing of glucocorticoids may put patients at risk for experiencing side effects from chronic administration.

Population: for this review the population includes patients on long term steroid equivalents for chronic disease who are receiving 10 mg Prednisone or more daily, or for longer than two weeks during the previous year. These patients, when presenting for surgery, may be at risk for perioperative shock due to secondary corticosteroid therapy and may require peri-operative steroid replacement.

Process

A comprehensive review of the literature was performed through the University of North Dakota Harley E. French Library through CINAHL, PubMed, Cochrane Collaboration, MEDLINE, and MeSH search engines using title, abstract, or keywords search. Search terms utilized included but were not limited to "dexamethasone," "perioperative inflammation," "corticosteroids," "C-reactive protein," "adrenal suppression," and "steroids." The date range of material found in the literature was between the years of 1952 and 2011. For historical purposes regarding the history of steroid supplementation, the date ranges were not limited. Results were limited to English language, randomized control trials, systematic reviews, and meta-analyses. Reference sections of applicable articles were reviewed for relevant articles.

A meeting with the University of North Dakota Harley E. French reference librarian added another tool to aide in obtaining literature relevant to the clinical question. ClinicalTrials.gov is a registry of federally and privately supported clinical trials. A search was performed through this website using keywords "dexamethasone AND cortisol." This search resulted a study not yet recruiting, titled *The effects of dexamethasone on cortisol levels in patients undergoing thyroid surgery.* Although this study has not been completed, the contact information was obtained from the website and the author was emailed questions relating to this clinical question.

The focus of the review of literature was two-fold: 1) To review the current guidelines for patients with chronic disease receiving long-term glucocorticoid coverage presenting for inpatient surgery requiring steroid bridging and re-dosing; and 2) To review the current literature on dexamethasone as a steroid bridge as well as its pharmacologic profile and uses. No current studies have exclusively reviewed dexamethasone versus hydrocortisone for steroid bridging.

Therefore the primary objective of this review will be to cover the currently available literature on dexamethasone, discussing its pharmacologic advantages and disadvantages, in order to form a hypothesis for the use of dexamethasone as an alternative to hydrocortisone.

The delivery of this information was provided to current nurse anesthesia students, CRNAs, and other anesthesia providers at the North Dakota Association of Nurse Anesthetists bi-annual meeting in Bismarck, North Dakota. Information was provided in the form of a power point lecture with the opportunity for discussion and questions after the material was presented.

The findings provided may be used to benefit anesthesia practice by decreasing the amount of redosing of glucocorticoids, as well as the unfavorable side effects associated with re-dosing glucocorticoids. A thorough review of the pathophysiology and history of steroid supplementation will also benefit anesthesia practice by providing the most current views on steroid supplementation.

Review of Literature

History

It has been 59 years since Fraser, Preuss, & Bigford (1952) first documented a patient who underwent a major operation who had received a prolonged course of cortisone therapy, and died of immediate postoperative shock unresponsive to therapy. This case, and others like it, began the research into secondary adrenal insufficiency resulting from long term exogenous glucocorticoid administration and developed a belief that patients on long term glucocorticoid therapy presenting for surgical procedures should receive perioperative supplementation. The current best practice for perioperative supplementation will be discussed as well as the use of dexamethasone as an alternative. There also has been recent controversy over the actual efficacy of steroid replacement in the literature, and this was reviewed as well.

No literature was found specifically addressing the substitution of dexamethasone for the hydrocortisone standard, however, a large amount of literature was found discussing the effects of dexamethasone on various organ systems in a wide variety of patients, warranting discussion of dexamethasone as a favorable substitution.

Dexamethasone

Dexamethasone is a synthetic adrenocortical steroid anti-inflammatory drug that can be administered by intravenous, intramuscular, intra-articular, intralesional, or inhalational routes (Barberio, 2011). The most common route for dexamethasone delivery is intravenous, and this route will be the primary route of administration in this review. Current literature provides numerous effects of systemic dexamethasone. These effects include, but are not limited to, a diminished inflammatory response, decreased postoperative pain and opioid consumption, decreased incidence of postoperative nausea and vomiting, and improved convalescence and recovery. Potential side effects of dexamethasone that have been discussed in the literature include delayed wound healing, increased infection rate, and hyperglycemia (Bisgaard, Klarskov, Kehlet, & Rosenberg, 2003). This review will discuss the effects of dexamethasone and discuss its place in an anesthetic plan.

Anti-inflammatory Effect

Diminished inflammatory responses are a beneficial side effect of dexamethasone and have been widely studied. Morariu et al., (2005) found decreased plasma levels of proinflammatory cytokines IL-6 and 8, increased anti-inflammatory cytokines IL-10, and decreased c-reactive protein (CRP) and tryptase levels after the administration of a single dexamethasone dose to patients undergoing on-pump coronary artery bypass grafting (CABG). This double-blind, placebo-controlled randomized trial concluded that dexamethasone inhibited

the systemic inflammatory response syndrome (SIRS) in patients undergoing on-pump CABG. Although this study was limited to on-pump CABG patients it is beneficial because this group of patients has one of the highest levels of inflammatory response.

A meta-analysis of randomized clinical trials by Holte and Kehlet (2002) concluded that proinflammatory mediators IL-6 and 8, *a*-TNF, CRP, and leukocyte receptors were reduced after the administration of both dexamethasone and hydrocortisone. The reduction in inflammatory mediators by the administration of dexamethasone and its parallel to hydrocortisone provide rationale that substituting dexamethasone for hydrocortisone will not decrease the anti-inflammatory and membrane stabilizing effects offered by hydrocortisone. This study further clarified that the use of dexamethasone reduces inflammatory mediators through a review of literature from 1966-2001 with a wide variety of surgeries reviewed.

Pain

Pain and opioid consumption are another area studied with the use of dexamethasone. The mechanisms are not fully understood, but dexamethasone may reduce pain and opioid requirements due to a decrease in local swelling and edema (Holte & Kehlet, 2002). A recent meta-analysis of randomized controlled trials was performed by Oliveira, Almeida, Benzon, & McCarthy (2011) reviewing the analgesic effects of dexamethasone. This article concluded that an intermediate dose (greater than 0.1 mg/kg) of dexamethasone is an effective addition in multimodal plans to reduce pain and opioid consumption after surgery, and also has been found to decrease time to hospital dischage (Oliveira et al., 2011). This study provides the most current evidence on dexamethasone regarding pain and opioid consumption. These studies present further evidence supporting the beneficial side effects of dexamethasone that can be used to recommend its substitution with hydrocortisone.

Nausea and Vomiting

Currently, the most common use of dexamethasone by anesthesia providers is as a postoperative nausea and vomiting (PONV) adjunct. Multiple studies have shown that dexamethasone decreases PONV rates, however the mechanism is not fully understood. It has been postulated that dexamethasone decreases PONV by producing a central antiemetic effect through its inhibition of prostaglandin synthesis, or by its inhibition of the release of inflammatory mediators which may stimulate the chemoreceptor trigger zone (Bisgaard, Klarskov, Kehlet, & Rosenberg, 2003). The long duration of action of dexamethasone makes it an attractive induction agent to decrease PONV throughout the perioperative period. A study comparing dexamethasone to methylprednisolone in the prevention of PONV found that both drugs were proven to be effective PONV agents, but that dexamethasone is effective in the prophylaxis of late PONV (Weren & Demeere, 2008). The substitution of dexamethasone for hydrocortisone as a steroid bridge may provide the added benefit of longer nausea and vomiting prophylaxis.

Convalescence

Improved convalescence, recovery, and hospital stay are other parameters that have been studied with the use of dexamethasone. These are important parameters to evaluate due to economic implications and overall patient satisfaction. Oliveira et al., (2011) found a reduction in time to hospital discharge in patients administered intermediate dose dexamethasone. Bisgaard et al., (2003) reports that recreational activities and work were resumed earlier in the dexamethasone group versus the placebo group. Holte and Kehlet (2002) established that mobilization was considerably improved with administration of dexamethasone. These findings are other beneficial side effect to the use of dexamethasone. The rationale of how

dexamethasone improves convalescence, recovery, and hospital stay is not fully understood. The aforementioned diminished inflammatory responses, decreased pain and opioid consumption, and decreased PONV rates are likely related to improved convalescence, recovery, and hospital stay.

Side Effects

The discussion of dexamethasone would not be complete without reviewing potential side effects of the use of dexamethasone that have been described in the literature. Delayed wound healing, increased infection rates, gastric ulcerations, catabolic effects on skin, muscle, bone and connective tissue, electrolyte disturbances, and hyperglycemia are often discussed as potential side effects of corticosteroids. A single dose of dexamethasone; regardless of whether low, intermediate, or high has not been found to increase infectious complications (Henzi, Walder, & Tramer, 2000). Bisgaard et al., (2003) found no evidence of impaired wound healing, postoperative infections, or other complications when a single dose of dexamethasone was administered to laparoscopic cholecystectomy patients.

Hyperglycemia has been reported in nondiabetic patients undergoing craniotomy who received dexamethasone. Lukins & Manninen (2005) recommend that blood glucose concentrations be monitored in diabetic patients for 12 hours after the administration of dexamethasone to avoid risk of hyperglycemia. Hyperglycemia is not a potential side effect of only dexamethasone. Weren and Demeere, (2008) describe hyperglycemia in nondiabetic patients administered methylprednisolone as well as dexamethasone in their study comparing the two drugs as PONV agents. There were no side effects of dexamethasone identified from the review of literature that differed greatly from the side effects of hydrocortisone or other corticosteroids, and the majority of side effects were found to occur after long term and multiple

administrations of these drugs. However, as anesthesia providers we must consider the benefits and the risks to every option we provide our patients.

Cortisol

An important point which must be compared between dexamethasone and hydrocortisone is their glucocorticoid and mineralocorticoid properties. Cortisol is the main naturally occurring glucocorticoid in the body which evolved to aid in survival. Cortisol causes fluid retention along with glucose, lipid and protein mobilization which may aid in the stress response. Nicholson, Burrin, and Hall (1998) describe natural cortisone as having both glucocorticoid and mineralocorticoid properties and normal production being between 25 and 30 mg a day with rapid increases in production to perhaps 100 mg in response to surgical stimulation lasting up to 48-72 hours following major surgery. Cortisol has many effects on different body systems. Cortisol activates intermediate metabolism of carbohydrate, fat and protein, stimulates gluconeogenesis in the liver, has anti-insulin effects, and decreases proinflammatory mediators such as leukotrienes and prostaglandins to name a few (Nicholson, Burrin, & Hall, 1998). Therefore, when choosing a drug to replace natural cortisol the anesthetist should consider its pharmacokinetic similarities to natural cortisol.

Pharmacokinetics/Pharmacodynamics

Dexamethasone and methylprednisone are two examples of commercial preparations of glucocorticoids which have differences in their pharmokinetic properties and glucocorticoid versus mineralocorticoid activity. As previously discussed, these drugs vary greatly in their duration of action and anti-inflammatory potency (appendix B). Dexamethasone differs from natural cortisol in its lack of mineralocorticoid properties, while hydrocortisone has similar mineralocorticoid activity to natural cortisol.

So what is the significance of mineralocorticoid activity? Mineralocorticoids received their name from early observations that they were involved in the retention of sodium and facilitate sodium and potassium homeostasis to aid in maintaining intravascular volume. Mineralocorticoid synthesis occurs in the adrenal zona glomerulosa and is stimulated by the renin-angiotensin-aldosterone system or hyperkalemia (Coursin & Wood, 2002). The primary endogenous mineralocorticoid is aldosterone which accounts for 95% of the mineralocorticoid activity produced by corticosteroids, and has a 3,000/1 effect on sodium retention when compared to cortisol (Stoelting and Hillier, 2006). Research suggesting that natural aldosterone has 3,000 times more mineralocorticoid activity in comparison to cortisol, and that aldosterone secretion is stimulated by the rennin-angiotensis-aldosterone system versus the HPA axis may suggest that a drug with mineralocorticoid properties similar to that of cortisol may not be necessary if the adrenal glands are able to respond with aldosterone secretion. However, the literature does not clearly delineate whether reported cases of surgical adrenal crises due to secondary adrenal insufficiency and inadequate exogenous steroid coverage were due to glucocorticoid deficiency or mineralocorticoid deficiency so further research is required on this topic.

Current Best Practice

After reviewing the literature on dexamethasone a review of the current best practice for steroid supplementation must be discussed. As previously discussed, the first case report of adrenal atrophy and irreversible shock associated with prolonged steroid therapy was published in 1952 in the Journal of the American Medical Association by Fraser, Preuss, and Bigford (1952). The first case involved a 34 year old man who died while undergoing routine orthopedic surgery after the withdrawal of chronic steroids. The second case involved a 20 year old woman

who had been taking cortisone daily for four months and died less than 6 hours after surgery without peri-operative steroid supplementation (Fraser et al., 1952). These authors discussed how both of these patients had autopsies which revealed gross bilateral adrenal hemorrhage and histological changes of complete adrenal cortical atrophy. Although it was stated that these cases were both complicated by other comorbidities it was speculated that the cause of death was due to acute adrenal insufficiency caused by the withdrawal of steroid therapy. This report and others like it began the initial clinical recognition of HPA axis suppression and adrenal atrophy from exogenous glucocorticoid administration, and the potential need for perioperative supplementation. The case report by Fraser and colleagues concluded with a list of recommendations for peri-operative glucocorticoid treatment which became the standard for therapy.

The primary problem with the necessity of stress steroid supplementation is due to the fact that the current best evidence for steroid supplementation stems from clinical case reports, and inferences drawn from these, rather than higher levels of evidence such as randomized controlled studies. This has sparked debate regarding the clinical necessity for stress steroids during surgery. Research by Friedman, Schiff, and Bromberg (1995) found that patients given only a baseline immunosuppressive dose of glucocorticoid, rather than stress doses exhibited no signs of adrenocortical insufficiency.

Another study reaffirming the cloudiness of the need for stress dose steroids was performed by Schlaghecke, Kornely, Santen, and Ridderskamp (1992) on 279 patients who were receiving daily prednisone therapy for chronic diseases for 1 week to 15 years. These authors did not follow patients peri-operatively, rather they used corticotropin releasing hormone (CRH) stimulating tests 24 hours after the most recent dose of glucocorticoids. CRH is released from

the hypothalamus and stimulates the anterior pituitary to secrete ACTH which stimulates the adrenal gland to release cortisol through the HPA axis (appendix C). What these authors found really sparked debate regarding the need for stress dose steroids. These authors found poor correlation between plasma cortisol response after the administration of CRH and concluded that pituitary-adrenal function in patients treated with synthetic glucocorticoids cannot be reliably estimated from the dose of glucocorticoid, the duration of therapy, or the basal plasma cortisol concentration (Schlaghecke et al., 1992). This prospective study evaluated equal distributions of men and women and used appropriate statistical analysis of the data.

Other studies have been performed using retrospective analysis. Salem, Tainsh, Bromberg, Loriaux, and Chernow (1994) reassessed the issue of peri-operative glucocorticoid therapy 42 years after the emergence of the first case reports. From their review of studies beginning with the first case reports of the physiologic actions of the adrenal glands in 1855 to the current practice they concluded that evidence supports the concept that the current amount of perioperative glucocorticoid coverage is excessive and has been based on anecdotal information (Salem et al., 1994). The review was very comprehensive and used appropriate statistics for the meta-analysis of data. The recommendations for coverage presented from this study formed the basis for what is the current standard of practice. Their recommendations are based on the magnitude of stress associated with the surgery and the known glucocorticoid production rate associated with it, and aimed to avoid the adverse clinical side effects of excessive glucocorticoid use. The suggested glucocorticoid target presented by these authors is presented in appendix C. There have been no recent studies corroborating their findings, thus a practice gap exists.

The evidence for these findings was evaluated using the levels set forth by the American Association of Critical Care Nurses (AACN) (Armola et al., 2009). This grading schema/hierarchy sorts evidence through six levels, A-E and M (appendix D). This evidence leveling system was chosen because of the wide variety of literature on dexamethasone. This system provided a way to sort through many articles on dexamethasone and steroid bridging to determine the highest level of evidence to support the research question. For example, manufacturer's recommendations regarding dexamethasone would fall at the bottom of this hierarchy (Level M), whereas meta-analysis of multiple controlled studies with results that consistently support a specific action, intervention, or treatment would be best (Level A) (Armola et al., 2009).

Meta-analysis (Level A) and well-designed controlled studies (Level B) were chosen as best evidence to support the research question, and many of the referenced articles reviewed are either meta-analysis or well-designed controlled studies. These studies consistently support a specific action, intervention, or treatment through multiple controlled studies or meta-analysis of studies (Armola et al., 2009).

Discussion

Interpretation

As the safety of anesthesia delivery and surgical techniques is enhanced through improved understanding of physiologic systems, increased use of evidence based practice, and enhanced pharmokinetic and pharmacodnamic profiles of anesthetic agents, the assessment of the quality of care has become an important primary endpoint in research. With a vast array of pharmacologic agents to choose from for any given patient, a sound understanding of pharmacology and physiology benefits anesthesia practice today. Anesthetists must formulate a

patient specific plan of care for each patient reflecting the current best practice and the patient's specific needs relating to the surgery performed.

When patients on long term exogenous glucocorticoid therapy present for surgery the anesthetist must consider whether the need exists to provide the patient with steroid bridging based on the degree of surgical stress. Consideration must also be given to why the patient was receiving the chronic steroid therapy and how that may affect the anesthetic plan of care.

This project reviewed the current literature investigating whether the substitution of dexamethasone for the hydrocortisone standard would reduce the need for re-dosing of glucocorticoids in patients on long term glucocorticoid therapy, and whether this would be feasible based on the pharmacologic profile of dexamethasone.

Even though there are large amounts of studies regarding peri-operative steroid supplementation, the evidence supporting the use of dexamethasone as a bridge is inconclusive. However, there is clear evidence to support the use of dexamethasone for prevention of pain and surgical site edema as well as for prophylaxis against postoperative nausea and vomiting. The long half-life of dexamethasone makes it an attractive treatment for the prevention of late postoperative nausea and vomiting. The table on the following page illustrates the half-life of dexamethasone in comparison to other steroid preparations:

CORTICOSTEROID CONVERSION TABLE				
Glucocorticoid	**Approximate equivalent dose (mg)**	**Half-life (hr)**	**Anti-inflammatory Potency**	**Mineralocorticoid Potency**
Short Acting				
Cortisone	25	8-12	0.8	2
Hydrocortisone	20	8-12	1	2
Intermediate-Acting				
Methylprednisolone	4	18-36	5	0
Prednisolone	5	18-36	4	1
Prednisone	5	18-36	4	1
Triamcinolone	42	18-36	5	0
Long-Acting				
Betamethasone	0.6-0.75	36-54	20-30	0
Dexamethasone	0.75	36-54	20-30	0

Holte & Kehlet (2001)

Outcome

While reviewing the literature regarding dexamethasone and secondary adrenal insufficiency, the need to discuss the current best practice for steroid replacement was evident. There is a degree of cloudiness in the literature regarding how much glucocorticoid a patient with presumed adrenal insufficiency from chronic exogenous steroid therapy should receive.

The original recommendation for the necessity of stress doses of steroids was based on case reports rather than well controlled prospective randomized studies, and current reports suggest that the glucocorticoid levels required for surgery are less than previously thought. The majority of studies to date recommend that patients with known adrenal insufficiency must receive at least their baseline therapy prior to any procedure or during an illness. The literature also recommends an individualized supplemental steroid replacement depending on the degree of surgical stress anticipated and makes recommendations regarding the use of corticotrophin stimulating tests to assess the degree of insufficiency prior to large surgical procedures.

Based on the best current practice, an anesthesia provider should adhere to the following table for steroid bridging:

Suggested Steroid Treatment Regime	
PATIENTS WHOSE HAVE RECEIVED A REGULAR DAILY DOSE OF MORE THAN 10MG PREDNISOLONE OR EQUIVALENT IN THE LAST THREE MONTHS	
Minor Surgery *i.e. hernias or distal extremities*	25mg Hydrocortisone at induction
Moderate Surgery *i.e. prostatectomy*	Usual pre-op steroids + 25mg Hydrocortisone at induction +100mg hydrocortisone/day
Major Surgery *i.e. major trauma, prolonged surgery, or surgery where there is delayed oral intake*	Usual pre-op steroids + 25mg Hydrocortisone at induction +100mg hydrocortisone/day for 2-3 days Resume normal oral therapy when gastrointestinal function has returned
ALL OTHER PATIENTS - no additional steroids required.	

Nicholson, Burrin, & Hall (1998)

Implications

Clinical Practice. The substitution of dexamethasone for the hydrocortisone standard in patients who have been deemed candidates for supplemental steroid supplementation was reviewed. Many pharmacologic properties of dexamethasone have been identified to date, and the current use of the drug is ever changing as new studies confirm increasing beneficial effects. There is a current lack of literature regarding dexamethasone bridging however. The current primary use of dexamethasone in anesthesia is as a PONV agent which provides coverage throughout the perioperative period. Other variables reviewed with the use of dexamethasone included its effects on the inflammatory response, postoperative pain and opioid consumption, convalescence and recovery, and fatigue.

Single dose dexamethasone had very favorable results reviewed in relation to these variables. A diminished inflammatory response was noted in a variety of patients undergoing a wide variety of surgical procedures, and the decreased production of prostaglandins and proinflammatory cytokines has been a postulated mechanism for its mechanism of action as a PONV agent. A statistically significant decrease in postoperative pain, opioid consumption, and fatigue as well as improved convalescence and recovery times were an interesting finding with the use of dexamethasone. In a surgical setting where pain and opioid consumption as well as recovery times are very closely monitored, a drug with a favorable pharmacologic profile for improving these measures is attractive.

Educational. The primary argument encountered for not substituting dexamethasone for hydrocortisone relates to its lack of mineralocorticoid properties. The framework of this review investigated the significance of this. The physiology of glucocorticoid and mineralocorticoid properties was evaluated. It is unclear whether the case reports of perioperative shock and

cardiovascular collapse were due to glucocorticoid deficiency, mineralocorticoid deficiency, a combination of both, or other comorbidities. An interesting finding was the mineralocorticoid activity of natural cortisol being 1 compared to aldosterone being 3,000. The stimulation of aldosterone secretion was reviewed as well. The most important stimulus for aldosterone secretion is an increase in plasma potassium concentration, followed by stimulation by the renin-angiotensin system; both systems independent of the hypothalamus and anterior pituitary glands. Mineralocorticoids are also secreted from different areas of the adrenal cortex, the zona glomerulosa, while glucocorticoids are secreted from the zona fasciculata.

In reviewing the literature the author found it unclear whether a drug with mineralocorticoid properties is even necessary in the presence of intact aldosterone secretion and stimulating mechanisms which are mostly independent of the HPA axis. The small degree of mineralocorticoid activity of natural cortisol raises question to its significance over glucocorticoid activity with an intact aldosterone response. Further research is needed regarding the substitution of these drugs, however a review of the literature found good logic for substitution of dexamethasone. A future study may review how important mineralocorticoid activity truly is for a steroid bridge.

Policy. Based on the evidence presented above, the author offers one practice recommendation. The strength of the practice recommendation was determined by the U.S. Preventive Services Task Force (USPSTF) scale. The USPSTF grades its recommendations according to one of five classifications (A, B, C, D, I) reflecting the strength of evidence and magnitude of net benefit (benefits minus harms) (appendix E).

The practice recommendation is a call for further research involving the substitution of dexamethasone for the hydrocortisone standard in patients on chronic glucocorticoid therapy

presenting for surgery (SOR C on USPSTF scale). A C strength of recommendation indicates that there is no current recommendation for or against routine substitution of dexamethasone. There has been good solid research done regarding the use of dexamethasone in a wide variety of patient populations and surgical settings, showing many aforementioned benefits to administering dexamethasone in the perioperative period. However, there has not been significant research to date regarding the comparison of dexamethasone to hydrocortisone as a steroid bridging therapy.

The level of support behind this recommendation stems from the fact that some practitioners are currently substituting dexamethasone for hydrocortisone in their practice with only fair quality of evidence supporting its use. Fair quality of evidence means that the evidence is sufficient to determine effects on health outcomes, but the strength of the evidence is limited by the number, quality, or consistency of the individual studies, generalizability to routine practice, or indirect nature of the evidence on health outcomes (USPSTF, 2000-2003). There currently is not strong enough evidence to support changing practice recommendations regarding corticosteroid supplementation.

Research. Implementing this recommendation may prove to be difficult, but not impossible. The author recommends that a large randomized control trial or meta-analysis be completed in which subjects would be divided into two groups and further grouped depending on the physiologic stress of their procedure; minor, major, or severe. The control group would include patients on chronic steroids receiving hydrocortisone bridging and the independent variable would be the substitution of dexamethasone. The use of a randomized controlled trial with dexamethasone versus a placebo may prove to be unethical as patients could be placed at risk for adrenal crisis if no corticosteroid is administered. Outcomes measured could include

inflammatory markers, postoperative convalescence and recovery scores, and postoperative hemodynamics. This study would likely require a timeline of two or three years, and would require a large number of subjects in order to find statistical significance. The budget of such a trial is difficult to assess at this point. In order for current practice to change statistical significance would have to be found regarding the use of dexamethasone for this purpose.

Summary

A review of the literature regarding dexamethasone found many favorable properties of the drug. These include diminished inflammatory response, decreased postoperative pain and opioid consumption, decreased incidence of postoperative nausea and vomiting, and improved convalescence and recovery. Reviewing the literature failed to find conclusive evidence to support the use of dexamethasone as a steroid bridge. Further studies are needed prior to practitioners safely substituting dexamethasone for the current standard.

After reviewing the current literature it is clear that additional research is required on this topic in order to recommend changing the current practice of steroid supplementation. Reviewing the physiology of steroid supplementation and the pharmacokinetics and pharmacodynamics of dexamethasone sheds insight onto the possibility that dexamethasone could be safely substituted, thus reducing the need for re-dosing. However, more research is required to form a practice recommendation, and patient specific consideration of the need for supplementation is at this point the best practice. The review of current literature also indicates that the current regimen of supplemental steroid administration may be excessive and the need may exist for modification.

There are many well-known and aforementioned pharmacologic properties of dexamethasone, including duration of action of up to 72 hours, a relatively long half-life, and

excellent bioavailability. These and other properties may make dexamethasone a nice addition to an anesthetic plan, however these properties do not make it a safe substitution for the current steroid standard at this time.

With the assessment of quality of recovery becoming such an important primary endpoint in outcomes research a drug with the potential to improve the aforementioned variables should receive careful consideration. Glucocorticoids are not without adverse effects, and these must be reviewed and rationalized as well.

It has now been over 60 years since a standard of care was established for perioperative glucocorticoid coverage based on case studies. Increasing experimental data and retrospective well controlled studies have supported the concept that new recommendations are needed. This review provides rationale and a framework for new recommendations regarding supplementation and advocates the importance of a patient specific plan of care. Hopefully the next 60 years will provide further clarity and shed more light on this important aspect of pharmacologic management.

References

Armola, R.R, Bourgault, A.M., Halm, M.A., Board, R.M., Bucher, L., Harrington, L., ...Medina, J. (2009). AACN levels of evidence: What's new? *Critical Care Nurse, 29 (4), 70-73.*

Arlt, W., Allolio, B. (2003). Adrenal Insufficiency. *The Lancet, volume 361, 1881-1893.*

Barash, P.G., Cullen, B.F., Stoelting, R.K., Cahalan, M. (2009). *Clinical Anesthesia* (6th ed.). Philadelphia, PA: Lippincott, Williams,& Wilkins.

Barberio, J.A. (2011). *Pocket drug guide 2011.* New York, NY: Mcgraw-Hill

Becker, K.L. (3rd Ed.). (2001). *Principles and practice of endocrinology and metabolism.* Philadelphia, PA: Lippincott Williams & Wilkins.

Bisgaard, T., Klarskov, B., Kehlet, H., Rosenberg, J. (2003). Preoperative dexamethasone improves surgical outcome after laparascopic cholecystectomy. *Annals of Surgery, 238(5), 651-660.*

Bovill, J.G., Sebel, P.S., Fiolet, J.W., Touber, J.L., Kok, K., & Philbin, D.M. (1983). The influence of sufentanil on endocrine and metabolic responses to cardiac surgery. *Anesthesia and Analgesia, volume 62 (4), 391-397.*

Coursin, D.B., Wood, K.E. (2002). Corticosteroid supplementation for adrenal insufficiency. *The Journal of the American Medical Association, volume 287 (2), 236-240.*

Fragen, R.J., Shanks, C.A., Molteni, A., & Avram, M.J. (1984). Effects of etomidate on hormonal responses to surgical stress. *Anesthesiology, 61 (6), 652-656.*

Fraser, C.G., Preuss, F.S., Bigford, W.D. (1952). Adrenal atrophy and irreversible shock associated with cortisone therapy. *JAMA, 149(17), 1542-1543.*

Friedman, R.J., Schiff, C.F., Bromberg, J.S. (1995). Use of supplemental steroids in patients having orthopaedic operations. *The Journal of Bone and Joint Surgery, volume 77 (12), 1801-1806.*

Henzi, I., Walder, B., Tramer, M.R. (2000). Dexamethasone for the prevention of postoperative nausea and vomiting: A quantitative systematic review. *Anesthesia & Analgesia, 90, 186-194.*

Holte, K., Kehlet, H. (2002). Perioperative single-dose glucocorticoid administration: Pathophysiologic effects and clinical implications. *Jounral of The American College of Surgeons, volume 195, 694-712.*

Jabbour, S.A. (2001). Steroids and the surgical patient. *Medical Clinics of North America, 85(5), 1-7.*

Lobato, E. B., Gravenstein, N., Kirby, R.R. (2008). *Complications in Anesthesiology.*Philadelphia, PA: Lippincott, Williams, & Wilkins.

Loh, N., Atherton, M. (2003). Guidelines for perioperative steroids. *World Anaesthesia, Volume 16(7), 1-1.*

Lukins, M.B., Manninen, P.H. (2005). Hyperglycemia in patients administered dexamethasone for craniotomy. *Anesthesia and Analgesia, 100 (4), 1129-1133.* doi: 10.1213/ 01.ANE.0000146943.45445.55

Morariu, A.M., Loef, B.G., Aarts, L.P., Rietman, G.W., Rakhorst, G., Oeveren, W.V., & Epema, A.H. (2005). Dexamethasone: Benefit and prejudice for patients undergoing on-pump coronary artery bypass grafting: A study on myocardial, pulmonary, renal, intestinal, and hepatic injury. *CHEST, 128(4), 2677-2687.*

Nicholson, G., Burrin, J.M., Hall, G.M. (2008). Peri-operative steroid supplementation. *Anaesthesia, volume 53 (11), 1091-1104.*

Oliveria, G.S., Almeida, M.D., Benzon, H.T., McCarthy, R.J. (2011). Perioperative single dose systemic dexamethasone for postoperative pain. *Anesthesiology, 115(3), 575-588.*

O'Sullivan, B.T., Cutler, D.J., Hunt, G. E., Walters, C., Johnson, G.F., & Caterson, I.D. (1997). Pharmacokinetics of dexamethasone and its relationship to dexamethasone suppression test outcome in depressed patients and healthy control subjects. *Biological Psychiatry, volume 41 (5), 574-584.*

Salem, M., Tainsh, R.E., Bromberg, J.,Loriaux, D.L., Chernow, B. (1994). Perioperative glucocorticoid coverage: A reassessment 42 years afteremergence of a problem. *Annals of Surgery, 219(4), 416-425.*

Sauerland, S., Nagelschmidt, M., Mallmann, P. Neugebauer, E. (2000). Risks and benefits of preoperative high dose methylprednisolone in surgical patients: A systematic review. *Drug Safety, volume 23 (5), 449-461.*

Schlaghecke, R., Kornely, E., Santen, R.T., Ridderskamp, P. (1992). The effect of long-term glucocorticoid therapy on pituitary-adrenal responses to exogenous corticotrophin-releasing hormone. *The New England Journal of Medicine, volume 326 (4), 226-230.*

Stoelting, R.K., Hillier, S.C. (2006). *Pharmacology & physiology in anesthetic practice (4th ed).* Philadelphia, PA: Lippincott Williams & Wilkins.

U.S. Preventive Services Task Force Ratings: Grade Definitions. (2000-2003). *Guide to Clinical Preventive Services. Retrieved from* http://www.uspreventiveservicestaskforce.org/3rduspstf/ratings.htm

Weren, M.W., Demeere, J.L. (2008). Methylprednisolone vs. dexamethasone in the prevention of postoperative nausea and vomiting: a prospective, randomized, double-blind, placebo-controlled trial. *Acta Anaesthesiologica Belgica, 59(1), 1-5.*

Wiebke, A., Bruno, A. (2003). Adrenal insufficiency. *The Lancet, volume 361 (9372), 1881-1893.*

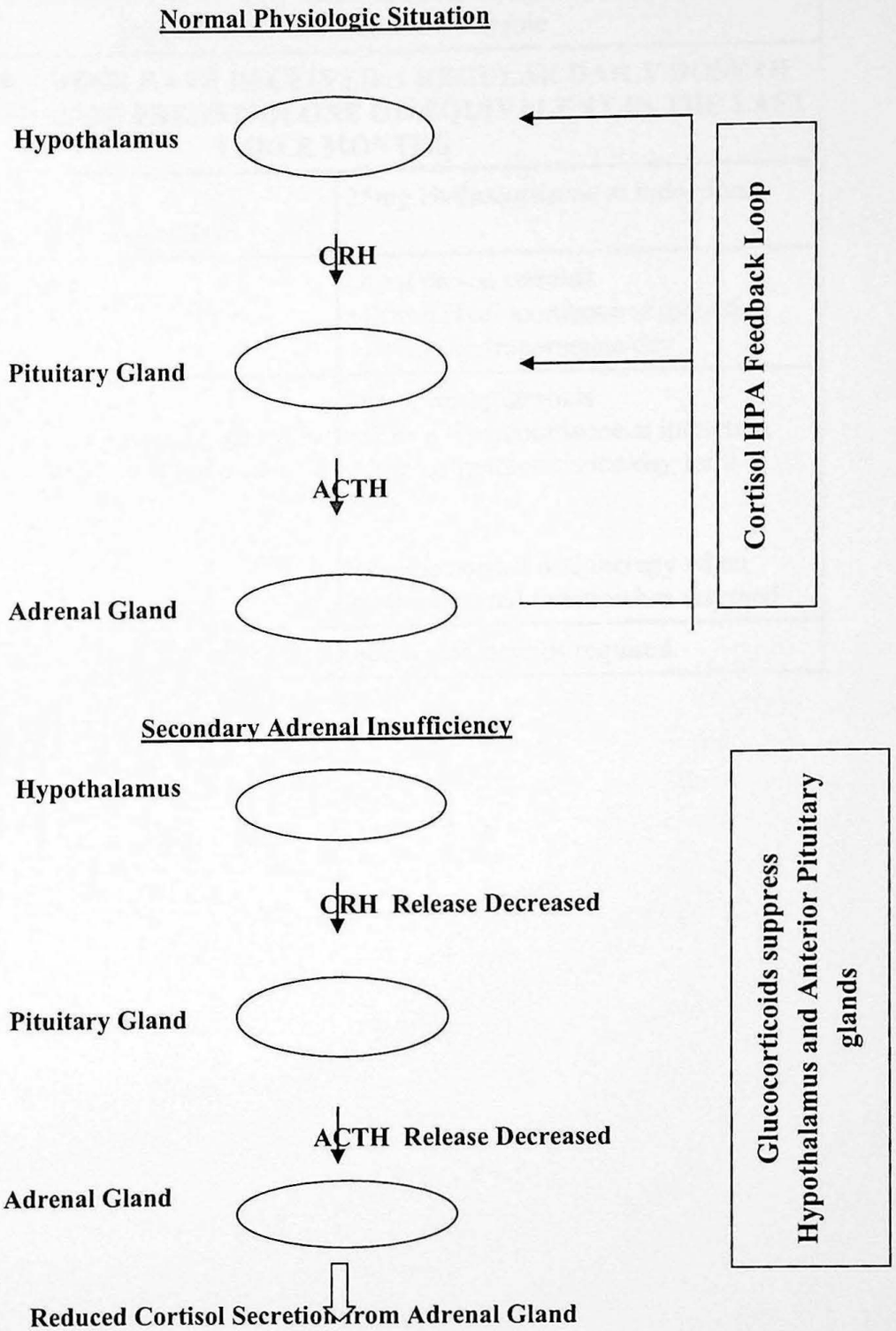
Yong, S.L., Marik, P., Esposito, M., Coulthard, P. (2009). Supplemental perioperative steroids for surgical patients with adrenal insufficiency. *Cochrane Database Systematic Reviews, 4.*doi: 10.1002/14651858.

Appendix A

CORTICOSTEROID CONVERSION TABLE				
Glucocorticoid	**Approximate equivalent dose (mg)**	**Half-life (hr)**	**Anti-inflammatory Potency**	**Mineralocorticoid Potency**
Short Acting				
Cortisone	25	8-12	0.8	2
Hydrocortisone	20	8-12	1	2
Intermediate-Acting				
Methylprednisolone	4	18-36	5	0
Prednisolone	5	18-36	4	1
Prednisone	5	18-36	4	1
Triamcinolone	42	18-36	5	0
Long-Acting				
Betamethasone	0.6-0.75	36-54	20-30	0
Dexamethasone	0.75	36-54	20-30	0

Data obtained from Holte & Kehlet (2001)

Appendix B



*CRH= Corticotropin releasing hormone, ACTH= Adrenocorticotropic hormone

Information for images obtained from Arlt & Allolio (2009)

Appendix C

Suggested Steroid Treatment Regime	
PATIENTS WHOSE HAVE RECEIVED A REGULAR DAILY DOSE OF MORE THAN 10MG PREDNISOLONE OR EQUIVALENT IN THE LAST THREE MONTHS	
Minor Surgery *i.e. hernias or distal extremities*	25mg Hydrocortisone at induction
Moderate Surgery *i.e. prostatectomy*	Usual pre-op steroids + 25mg Hydrocortisone at induction +100mg hydrocortisone/day
Major Surgery *i.e. major trauma, prolonged surgery, or surgery where there is delayed oral intake*	Usual pre-op steroids + 25mg Hydrocortisone at induction +100mg hydrocortisone/day for 2-3 days Resume normal oral therapy when gastrointestinal function has returned
ALL OTHER PATIENTS - no additional steroids required.	

Data for table obtained from Nicholson, Burrin, & Hall (1998)

Appendix D

AACN Evidence Labeling System	
Level A	Meta-analysis of multiple controlled studies or meta-synthesis of qualitative studies with results that consistently support a specific action, intervention or treatment
Level B	Well designed controlled studies, both randomized and nonrandomized, with results that consistently support a specific action, intervention, or treatment
Level C	Qualitative studies, descriptive or correlational studies, integrative reviews, systematic reviews, or randomized controlled trials with inconsistent results
Level D	Peer-reviewed professional organizational standards, with clinical studies to support recommendations
Level E	Theory-based evidence from expert opinion or multiple case reports
Level M	Manufacturers' recommendations only

(Armola et al., 2009)

Appendix E

The U.S. Preventive Services Task Force (USPSTF) grades its recommendations according to one of five classifications (A, B, C, D, I) reflecting the strength of evidence and magnitude of net benefit (benefits minus harms).

A.— The USPSTF strongly recommends that clinicians provide [the service] to eligible patients. *The USPSTF found good evidence that [the service] improves important health outcomes and concludes that benefits substantially outweigh harms.*

B.— The USPSTF recommends that clinicians provide [this service] to eligible patients. *The USPSTF found at least fair evidence that [the service] improves important health outcomes and concludes that benefits outweigh harms.*

C.— The USPSTF makes no recommendation for or against routine provision of [the service]. *The USPSTF found at least fair evidence that [the service] can improve health outcomes but concludes that the balance of benefits and harms is too close to justify a general recommendation.*

D.— The USPSTF recommends against routinely providing [the service] to asymptomatic patients. *The USPSTF found at least fair evidence that [the service] is ineffective or that harms outweigh benefits.*

I.— The USPSTF concludes that the evidence is insufficient to recommend for or against routinely providing [the service]. *Evidence that the [service] is effective is lacking, of poor quality, or conflicting and the balance of benefits and harms cannot be determined.*

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