Perioperative Glucocorticoid Therapy for Patients with Adrenal Insufficiency: Dosing Based on Pharmacokinetic Data

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Background: Perioperative glucocorticoid therapy for patients with adrenal insufficiency (AI) is currently based on anecdotal reports, without supporting pharmacokinetic data.

Methods: We determined the half-life, clearance, and volume of distribution of 2 consecutive intravenously (IV)-administered doses of hydrocortisone (15 or 25 mg every 6 hours) to 22 dexamethasone-suppressed healthy individuals and used the data to develop a novel protocol to treat 68 patients with AI who required surgical procedures. Patients received 20 mg of hydrocortisone orally 2 to 4 hours before intubation and were started on 25 mg of IV hydrocortisone every 6 hours for 24 hours and 15 mg every 6 hours during the second day. Nadir cortisol concentrations were repeatedly measured during that period.

Results: In healthy individuals, cortisol half-life was longer when the higher hydrocortisone dose was administered (2.02 ± 0.15 vs 1.81 ± 0.11 hours; $P < 0.01$), and in patients with AI, the half-life was longer than in healthy individuals given the same hydrocortisone dose. In both populations, the cortisol half-life increased further with the second hormone injection. Prolongation of cortisol half-life was due to decreased hydrocortisone clearance and an increase in its volume of distribution. Nadir cortisol levels determined throughout the 48 postoperative hours were within the range of values and often exceeded those observed perioperatively in patients without adrenal dysfunction.

Conclusions: Cortisol pharmacokinetics are altered in the postoperative period and indicate that lower doses of hydrocortisone can be safely administered to patients with AI undergoing major surgery. The findings of this investigation call into question the current practice of administering excessive glucocorticoid supplementation during stress. **(*J Clin Endocrinol Metab* 105: e753–e761, 2020)**

Key Words: HPA function, adrenal insufficiency, stress doses of glucocorticoids

Activation of the hypothalamic-pituitary-adrenal (HPA) function is one of several characteristic features of the physiologic response to psychological or physical stressors such as trauma, infections, and surgery. The intensity of the stress stimulus often dictates the degree and duration of HPA activation (1, 2). While the importance of having adequate glucocorticoid secretion during and after major surgery has been well recognized for decades, the magnitude of perioperative HPA activation required during that period has been debated for

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Abbreviations: AI, adrenal insufficiency; AUC, area under the curve; BMI, body mass index; HC, hydrocortisone; HPA, hypothalamic-pituitary-adrenal; IV, intravenous.

years (3, 4). Glucocorticoid administration to patients with adrenal insufficiency (AI) during major surgical procedures is empiric and is based on the anecdotal experience of 2 highly publicized case reports (5, 6) without supporting pharmacodynamic data. A study conducted in adrenalectomized monkeys demonstrated that animals receiving physiologic perioperative glucocorticoid supplementation during cholecystectomy had similar outcomes to others given supraphysiological doses of the hormone (7). Despite that evidence, the recommended perioperative glucocorticoid supplementation to patients with AI is empiric and is often excessive (8). Thus, the phrase "stress dosing" has variable meaning, with some recommendations exceeding 200 mg of hydrocortisone daily (8). Recent data showed that such doses could be associated with adverse events (9).

A common and serious limitation to most published data on this topic is that all patients are treated similarly without a critical assessment of the need, or lack thereof, for glucocorticoid supplementation. This limitation is manifested by the failure to consider the cause of possible HPA impairment, such that patients receiving chronic glucocorticoids for the treatment of inflammatory diseases are managed the same way as others who have central or primary AI. An earlier study suggested using the cosyntropin-stimulated response in those on chronic glucocorticoid therapy as a guide to offering additional perioperative supplementation (10). Recent data indicate that the perioperative period presents a potent stimulus for HPA activation that can be demonstrated even in patients with exogenous (11) or endogenous glucocorticoid excess (12, 13). Thus, HPA activation during the perioperative period may still occur in patients receiving suppressive doses of chronic glucocorticoids. However, perioperative glucocorticoid supplementation to patients with primary or central AI caused by hypothalamic/pituitary diseases is essential, since HPA activation would not be expected in these situations.

The optimal glucocorticoid dose necessary to maintain homeostasis and prevent cardiovascular collapse during the perioperative period in patients with primary or central AI is not known. We reasoned that it would be important first to examine the perioperative HPA alterations in individuals who have normal HPA function (11, 14) and use that data to develop a protocol to define therapeutic goals in patients with AI undergoing major surgery. Even though one might argue that patients with AI may not need to raise their ambient cortisol concentrations to those reported in individuals with normal HPA function, we reasoned that it would be best to err on the side of safety and provide patients with AI glucocorticoids doses that closely match what others with normal HPA function achieve during and after a major surgical procedure.

In light of the unique binding characteristics of cortisol to binding proteins (transcortin and albumin), one would also need to examine the pharmacokinetics of cortisol in the circulation after single and repeated administration of different doses of the hormone.

In the current investigation, we first examined the pharmacokinetics of cortisol in dexamethasone-suppressed healthy individuals given different and multiple doses of IV hydrocortisone. We then used the accumulated set of data to design a protocol to treat patients with central or primary AI during major surgical procedures.

Methods

The study examined the pharmacokinetics of hydrocortisone in 2 different settings as detailed below.

Hydrocortisone pharmacokinetics in dexamethasone-suppressed healthy individuals

Twenty-two healthy individuals (12 men and 10 women) with a mean age of 36.5 ± 5.2 years) were enrolled in this part of the investigation. None of the participants was receiving medications or supplements, including any form of hormonal contraceptives. The values for weight and body mass index (BMI) were 78.7 ± 3.1 kg and 27.3 ± 1.9 kg/m^2, respectively. Participants received 2 doses of dexamethasone, 1 mg each, given at 10 PM the night before and on the morning of the study day.

On arrival to the Research Center, participants confirmed having received the prescribed dose of dexamethasone the night before and were given the additional 1 mg of the latter glucocorticoid after a blood sample was drawn and an IV line was inserted. Participants were asked to stay relaxed and were allowed to walk around, sit, or lie in bed throughout the ensuing 12 hours. A light meal was offered approximately 3 to 4 hours after the first and second doses of hydrocortisone were administered (as will be described subsequently) and participants were allowed to drink water as needed.

One hour after arrival, volunteers were randomly assigned to receive 2 consecutive doses of either 15 or 25 mg of hydrocortisone administered IV over 10 to 20 seconds, 6 hours apart. Each injection was followed by the administration of 30 mL of saline through the indwelling catheter. Thus, 11 volunteers (6 men and 5 women) received 2 identical injections of either of the 2 assigned hydrocortisone doses at time 0 and at time 6 hours. Blood samples were drawn before each of the 2 IV injections and hourly for 6 hours thereafter. Four blood samples drawn from 4 participants throughout the 12 hours of sampling were not available. Participants were discharged after the completion of the 12-hour blood sample. Blood samples obtained from each participant were assayed the morning after the completion of the 12-hour sampling. None of participants experienced adverse events throughout the study period. In 8 participants, cortisol levels were measured every 10 minutes during the first hour of hydrocortisone injection to examine the early phase of cortisol pharmacokinetics. The goal of the latter part of the study was to determine the appropriate time points for blood sampling from patients during the perioperative period.

Perioperative cortisol pharmacokinetics in patients with AI

Over the past 40 years, our Center has been following a large number of patients with hypopituitarism and others with primary adrenal insufficiency. From this database, we recruited 68 consecutive patients (37 men and 31 women) who were known to have documented primary (n = 13) or central (n = 55) AI who required elective surgical procedures involving general anesthesia. Enrolled patients with AI were 39 to 77 years of age (56 ± 8) and had been on permanent and stable replacement therapeutic doses of hydrocortisone (plus fludrocortisone for those with primary disease) for over 18 months. We excluded patients receiving oral estrogen therapy and those with liver, kidney, or other diseases or conditions that can influence serum cortisol measurement, such as patients with hepatitis C and others with hypoproteinemia (15). All patients with central AI (32 men and 23 women) had prior surgical resection of sellar/parasellar masses, which were histologically demonstrated to be pituitary adenomas, Rathke cleft cyst, craniopharyngioma, meningioma, or autoimmune lymphocytic hypophysitis, while 12/55 received external irradiation as well. None of the 55 patients with central AI were receiving growth hormone supplementation, but 48 were on thyroxine replacement therapy. All participants were considered clinically and biochemically euthyroid. Transdermal testosterone therapy was given to 23 of the 32 men and transdermal estrogen was given to 6 of the 23 women with central AI. All patients with primary AI (5 men and 8 women) were clinically and biochemically euthyroid including 5/13 who were receiving thyroxine replacement therapy for primary autoimmune hypothyroidism. The mean weight and BMI for all patients with AI was 94.9 ± 8.9 kg and 29.3 ± 4.1 kg/m^2, respectively.

Study participants were scheduled to have elective major surgical procedures that required general anesthesia for more than 60 minutes. These included thoracic/vascular (n = 21), abdominal/pelvic (n = 20), and orthopedic (e.g., knee, hip, or back) (n = 27) procedures. We excluded patients undergoing cardiac bypass surgery to avoid the confounding effects of rapid volume changes on serum cortisol levels. Patients were asked to take 20 mg of hydrocortisone orally on the morning of their scheduled surgery, 2 hours before arrival to the preoperative area, and those with primary AI were also asked to take their daily dose of fludrocortisone at that time as well. This plan was based on an earlier study (unpublished observation) that demonstrated that the oral administration of 20 mg of hydrocortisone to patients with AI resulted in serum cortisol levels that were > 12 µg/dL (331 nmol/L) when measured 1 to 4 hours later. Patients were clinically evaluated shortly before intubation and all confirmed having taken the recommended hydrocortisone (plus fludrocortisone for those with primary disease) 2 to 4 hours earlier.

After going through routine preparation and IV insertion, a blood sample for cortisol level determination was obtained and IV hydrocortisone therapy was initiated just before intubation. At that time, patients were started on hydrocortisone 25 mg IV every 6 hours for 24 hours followed by 15 mg of hydrocortisone every 6 hours for an additional 24 hours. Thereafter, hydrocortisone doses were adjusted as clinically necessary. Nine patients inadvertently received additional glucocorticoids and were excluded from the study. Six additional patients were discharged shortly after the first 24-hour sample was drawn. Thus, within this group, 59 patients had data from the first 24 hours (while receiving 25 mg of hydrocortisone every 6 hours) and 53 had data from the second 24 postoperative hours (while receiving 15 mg of hydrocortisone every 6 hours).

Routine postoperative care was left up to the discretion of the primary management team, while patients were clinically evaluated by the endocrine service for clinical features of AI. Fludrocortisone was re-administered to patients with primary AI when their total daily hydrocortisone dose was less than 50 mg. Blood samples were drawn for determining serum cortisol concentration at the time of intubation, before IV hydrocortisone was administered, and subsequently at 2, 4, 6, 8, 10, 12, 18, 24, 36, and 48 hours. All blood draws at these specified times were obtained before the next dose of IV hydrocortisone was administered. Blood samples in all patients were obtained within 15 minutes of the specified scheduled time. Serum cortisol levels were measured consecutively on a daily basis to ensure adequate levels were achieved in all patients. The Institutional Review Board approved all studies in healthy individuals and patients and all participants gave written informed consent.

Pharmacokinetic data analysis

For each participant enrolled in all pharmacokinetics studies, we calculated clearance, volume of distribution, and cortisol half-life using established published methods (16–18). Since serum cortisol levels change rapidly after an IV injection of the hormone, a steady state is not achieved immediately, and we therefore elected to use the samples obtained at 1 hour as our first point in determining cortisol half-life. The latter determination was based on the pharmacokinetics data obtained during the first 60 minutes after the injection as will be discussed below. To illustrate the latter feature, we determined cortisol half-life during the first 40 minutes after an injection in a subgroup of healthy individuals (Fig. 1). The method used to calculate various pharmacokinetic data was identical to that used by several other investigators (16, 17). Serum cortisol concentrations were first plotted against time to calculate

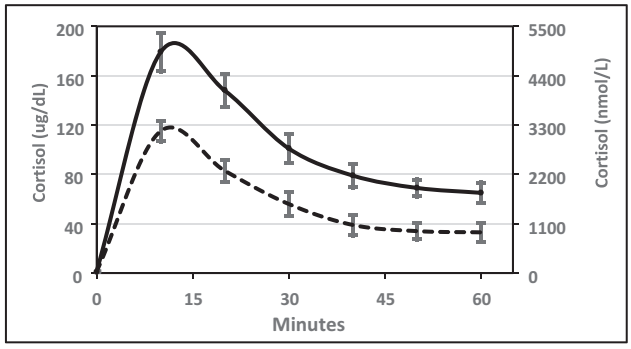

Figure 1. Serum cortisol levels measured in dexamethasone-suppressed healthy individuals during the first 60 minutes following the IV injection of either 15 mg (interrupted line) or 25 mg (straight line) of hydrocortisone. In each graph, the line represents the means of the values while the whiskers represent the 95% confidence limits for the mean (upper and lower) determined at each time point. The value between the tip of the upper whisker and the bottom of the lower whisker represents the 95% confidence interval at each point. Data are shown in µg/dL (primary Y-axis) and in nmol/L (secondary Y-axis).

the area under the curve (AUC) for each participant's data. Clearance was calculated by dividing the dose of hydrocortisone by the AUC. In addition, the natural log-transformed cortisol concentrations were also plotted against time for each participant's data. The slope of the regression line of the latter plot determined the elimination rate constant (k). In each of the latter plots, the correlation coefficients (r^2) between the natural logarithm of the cortisol concentration and time for all healthy individuals and patients were consistently over 0.90. The volume of distribution was calculated by dividing cortisol clearance by the elimination rate constant (k). The half-life was calculated by dividing $\log_e 2$ (0.693) by the elimination constant (k).

Laboratory analysis

Serum cortisol measurements were made using the direct chemiluminescent immunoassay method, using Advia Centaur XP instrument (Siemens, Malvern, PA). The lower limit of quantitation for the assay is 0.2 µg/dL. Intra-assay coefficients of variation for the lower, mid, and upper limits are 4.7, 3.9, and 2.3%, respectively. The inter-assay coefficients of variation for the lower, mid, and upper limits are 6.1, 5.2, and 4.4%, respectively. The same assay was used to determine cortisol concentrations in all samples analyzed in the study. Blood samples obtained from each healthy individuals were analyzed together the day after study completion, while those from the patients were determined consecutively on daily basis to ensure adequate cortisol levels are achieved during the perioperative period.

Statistical analysis

Data are presented as mean ± standard deviation (SD), unless stated otherwise. The data on serum cortisol levels, volume of distribution and plasma half-life among the groups were statistically analyzed utilizing the Kruskal-Wallis test, as a nonparametric alternative to the ANOVA test. Comparisons between groups were done using the Wilcoxon rank sum test for nonparametric measurements. Categorical data were compared using chi-square (χ^2) and Fisher exact tests. Differences were considered significant when the two-sided P values were less than 0.05. Bonferroni's correction factor for multiple comparisons was used as appropriate. Missing data were encountered only occasionally.

Results

Cortisol pharmacokinetics in healthy individuals

Serum cortisol levels measured the morning of testing were low (< 1.5 µg/dL; 41.4 ± nmol/L) with a mean value of 0.9 ± 0.1 µg/dL (24.8 ± 2.8 nmol/L), indicating adequate suppression of endogenous cortisol secretion.

The decline in serum cortisol levels between the 10th and 40th minute after hydrocortisone injection was rapid and followed a mono-exponential function model as shown in Fig. 1. Other investigators who examined the early phase of hydrocortisone pharmacokinetics (17) reported similar findings. The slope of the cortisol disappearance curve was less steep after the 50th minute of injection. Cortisol half-life during the 10th to the 40th minutes determined after 15 and 25 mg of hydrocortisone injections was 19.9 ± 4.1 and 24.4 ± 3.9 minutes, respectively. As will be discussed below, these half-life values are much shorter (P < 0.001) than those determined between the first and 6th hour. It is imperative to note that the rapid disappearance rate during the first hour of injection is primarily due to continued tissue distribution during that time.

The decline in cortisol levels after the first hour of injection followed a mono-exponential function model (Fig. 2). Nadir serum cortisol levels after the first 15 mg of hydrocortisone was administered ranged from 6.4 to 16.8 µg/dL (177-464 nmol/L) and were higher (15.0-23.2 µg/dL; 414-640 nmol/L; P < 0.01) after the second injection. A similar pattern of decline in serum cortisol was observed with the 25 mg dose (Fig. 2) where nadir level after the first injection ranged from 15.5 to 31 µg/dL (428-855 nmol/L) while the respective values after the second injection were higher (<0.01) ranging from 22 to 38 µg/dL (607-1048 nmol/L).

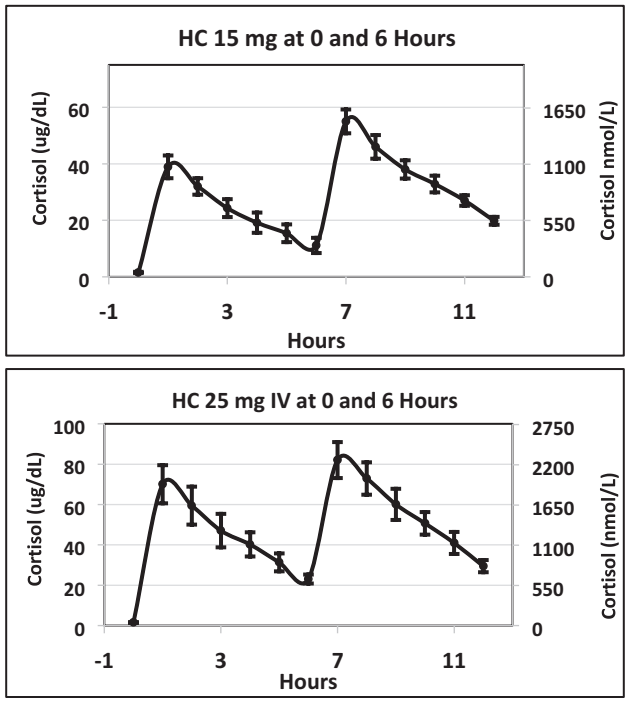

Figure 2. Serial measurements of serum cortisol levels obtained in dexamethasone-suppressed healthy individuals following the IV administration of 2 doses of hydrocortisone, 6 hours apart. The top panel depicts the data when 15 mg of hydrocortisone were injected IV every 6 hours while the lower panel shows serum cortisol levels when the administered dose was 25 mg every 6 hours. In each graph, the line represents the means of the values while the whiskers represent the 95% confidence limits for the mean (upper and lower) determined at each time point. The value between the tip of the upper whisker and the bottom of the lower whisker represents the 95%confidence interval at each point. Data are shown in µg/dL (primary Y-axis) and in nmol/L (secondary Y-axis).

Table 1. Cortisol Half-Life in the Circulation Under Different Conditions

Condition	Cortisol Half-Life (Hours)		
	Dexamethasone-Suppressed Healthy Individuals	Patients With Adrenal Insufficiency	*P* Values Healthy Individuals vs Patients
After first IV dose of hydrocortisone (15 mg)	1.81 ± 0.11 (1.75–1.87)[c]	N/A	
After second IV dose of hydrocortisone (15 mg)	2.13 ± 0.15[a] (2.04–2.22)[c]	N/A	
After first IV dose of hydrocortisone (25 mg)	2.02 ± 0.15[b] (1.92–2.21)[c]	3.11 ± 0.56 (2.84–3.34)[c]	$P < 0.001$
After second IV dose of hydrocortisone (25 mg)	2.42 ± 0.34[a] (2.22–2.63)[c]	3.61 ± 0.49[a] (3.33–3.89)[c]	$P < 0.001$

[a] $P < 0.01$ comparing the first and second dose data within the group.
[b] $P < 0.01$ as compared with that determined after the first 15 mg injection.
[c] 95% Confidence Interval.

Table 2. Calculated Volume of Distribution and Clearance of Hydrocortisone Determined in Dexamethasone-Suppressed Healthy Individuals and in Patients With Adrenal Insufficiency (AI)

	Healthy Individuals		Patients with AI
	15 mg Dose	25 mg Dose	25 mg Dose
First Dose			
Clearance (L/hour)	12.8 ± 1.5 (12.0–13.6)	11.6 ± 2.4[d] (10.9–12.5)	10.8 ± 1.7[c] (10.3–11.3)
Volume of distribution (L)	33.5 ± 4.9 (31.6–35.4)	34.9 ± 7.8 (31.7–38.1)	58.1 ± 10.8[c] (54.2–62.0)
Second Dose			
Clearance (L/hour)	11.6 ± 2.6[b] (10.4–12.8)	9.4 ± 1.3[b,d] (8.9–9.9)	8.4 ± 1.3[b,c] (7.8–9.0)
Volume of distribution (L)	38.8 ± 5.1[a] (35.8–41.8)	38.8 ± 3.2[a] (36.9–40.7)	68.6 ± 14.0[a,c] (62.7–73.9)

The data are presented as the mean ± SD while the values between brackets represent the 95% confidence intervals of the mean.
[a] $P < 0.05$ compared with first dose.
[b] $P < 0.001$ comparing first and second dose.
[c] $P < 0.001$ compared with similar data in healthy individuals.
[d] $P < 0.01$ compared with the lower dose of hydrocortisone.

Cortisol half-life obtained after the first 25 mg dose of hydrocortisone was longer than that observed after the 15 mg dose ($P < 0.01$) and both values increased further ($P < 0.01$) after the second injection (Table 1).

There was an increase ($P = 0.04$ for both doses) in the volume of distribution with the second injection of the hormone that was observed for both doses used. Cortisol clearance was lower ($P < 0.01$) with the 25 mg administration compared with that observed with the lower dose. Cortisol clearance decreased ($P < 0.001$) after the second administration of both the 15 and the 25 mg doses. The latter decrease in clearance and the slight increase in volume of distribution of the hormone accounted for the longer cortisol half-life demonstrated after the second injection (Table 2).

Cortisol levels and pharmacokinetics in patients with AI

Clinical observation. There were no adverse events observed during the perioperative period in any of the patients and all were discharged 1 to 7 days after surgery. None of the patients had symptoms or signs suggestive of AI during the perioperative period. Specifically, there were no episodes of hypotension (systolic blood pressure < 100 mm Hg) in any patient during the 48 postoperative period. While most patients had a slight decline in hemoglobin, none of the patients had any major alterations in their serum electrolyte (sodium, potassium) concentrations determined 24 to 48 hours after surgery.

Perioperative cortisol levels and pharmacokinetics in patients with AI. Patients reported taking the prescribed 20 mg oral dose of hydrocortisone 2 to 4 (3.2 ± 0.4) hours before intubation and consequently had baseline cortisol levels of > 12 µg/dL (>331 nmol/L). Baseline serum cortisol levels determined before the IV administration of hydrocortisone in patients with central AI (14.8 ± 3.9 µg/dL;

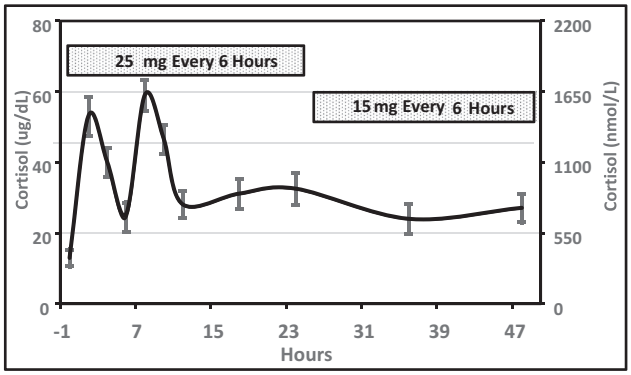

Figure 3. Serial measurements of serum cortisol levels in patients with adrenal insufficiency who had major surgical procedures and who were given a fixed regimen of glucocorticoids during the first 48 postoperative hours. Patients have received a 20 mg dose of hydrocortisone orally 2 to 4 hours before the first dose of IV hydrocortisone was administered at the time of intubation. The regimen included the administration of hydrocortisone 25 mg every 6 hours for 24 hours followed by 15 mg IV every 6 hours during the second 24 hours. In each graph, the line represents the means of the values while the whiskers represent the 95% confidence limits for the mean (upper and lower) determined at each time point. The value between the tip of the upper whisker and the bottom of the lower whisker represents the 95% confidence interval at each point. Data are shown in μg/dL (primary Y-axis) and in nmol/L (secondary Y-axis).

408 ± 108 nmol/L) were similar to the values determined in those with primary disease (15.4 ± 3.6 μg/dL; 423 ± 98.5 nmol/L). Nadir serum cortisol levels determined 6 hours after the first 25 mg dose of hydrocortisone ranged from 16 to 34 μg/dL (441-938 nmol/L) and were higher (>20 μg/dL; 552 nmol/L) with subsequent injections, reaching a mean of 32.5 ± 8.1 μg/dL(897.7 ± 223.5 nmol/L) at 24 hours (Fig. 3). Nadir serum cortisol levels during the second 24 hours were consistently over 22 μg/dL (607 nmol/L), with a mean nadir value of 25.1 ± 6.3 μg/dL (692.5 ± 173 nmol/L) at 48 hours (Fig. 3). When analyzed separately, nadir serum cortisol levels in patients with central AI were similar ($P > 0.08$) to the values observed in others with primary disease determined at all time points throughout the 48 postoperative hours.

Cortisol half-life values in patients with AI after the first injection were longer ($P < 0.001$) than those of healthy individuals given the same hydrocortisone doses. Furthermore, the cortisol half-life after the second dose was longer than that observed during the first injection (Table 1), a feature similarly noted in healthy participants. The volume of distribution in patients with AI was greatly increased compared with that of healthy individuals ($P < 0.001$). Cortisol clearance was lower in patients as compared with healthy individuals given comparable doses and decreased further with the second dose of the hormone (Table 1), a feature that was similarly observed in healthy individuals.

Discussion

Our goal in conducting the current investigation was to design a physiologically based regimen of hydrocortisone supplementation that can be used for patients with AI during major surgical procedures. To achieve that objective, we first determined the response to surgical stress in patients with normal HPA function (11, 14, 19) and used accumulated cortisol pharmacokinetic data derived from healthy individuals to design and test the current novel protocol. The findings in healthy individuals indicate that the administration of 25 mg of hydrocortisone would provide ambient cortisolemia that would match and even exceed that observed perioperatively in patients with normal HPA function. Nadir serum cortisol levels in dexamethasone-suppressed healthy individuals after the first 15 mg dose were lower than those observed shortly after surgery in patients with normal HPA function (11, 14, 19). These findings prompted the development of the current protocol detailed herein using 25 mg of hydrocortisone every 6 hours during the first postoperative day.

The perioperative protocol followed in the current investigation was safe and clinically effective. The oral administration of 20 mg of hydrocortisone 2 to 4 hours before intubation to patients with AI resulted in a baseline serum cortisol levels AI that is close to those observed in others with normal HPA function (11, 14, 19) and ensured that patients had adequate glucocorticoid milieu before surgery and are not at risk for having symptoms before arriving to the hospital.

This is the first study to examine cortisol pharmacokinetics in 2 different populations: healthy individuals and patients with AI. The data demonstrate that cortisol half-life increased when a larger dose was administered. This feature is consistent with a recent finding observed after resection of cortisol-secreting adenomas (13). In that study, we found that following resection of cortisol-secreting adenomas, cortisol half-lives were proportionate to the ambient serum cortisol levels at the time of resection (13). While the reason for the prolongation of cortisol half-life in those with higher serum levels is not known, it is possibly due to saturation of the transmembrane transport systems of intracellular nuclear receptors.

A unique and important feature of the study was the demonstration of prolongation of cortisol half-life with repeated injections of the hormone and the resulting progressive rise in nadir cortisol level, suggesting "stacking" over time. Although the concentration of free cortisol in our study was not determined, it is predicted to be quite high in light of the known binding characteristic of cortisol to transcortin, whereby the binding

sites of the latter globulin are fully saturated (1, 20) when the total serum cortisol concentrations reach 20 to 25 µg/dL (552-690 nmol/L)). The data showed that most measured values even at their nadir were higher than those observed when the latter binding protein is fully saturated.

The results of the current investigation suggest that the prolonged half-life of hydrocortisone is largely due to increased volume of distribution and a decrease in clearance. These 2 variables were more pronounced in patients with adrenal insufficiency. The mechanism(s) contributing to the latter alterations are unknown and need to be explored in future studies. There was a striking increase in the volume of distribution of cortisol in patients with AI during the perioperative period as compared with data from healthy individuals. Although the cause for the latter change is not clear, it is possible that the expansion of interstitial space resulting from the administration of IV fluids during that period could be an important contributing factor. Although perioperative fluid administration can vary greatly, the administered volume is often large and is commonly associated with increased subcutaneous fluid accumulation; at times it could lead to increased intravascular volume (21). The rationale commonly cited to explain administering large amounts of fluids perioperatively include efforts to minimize cardiovascular instability during general anesthesia, as the latter is associated with vasodilation, hypotension, and decreased sympathetic activity due to the anesthetic agents as well as narcotics (22, 23).

In investigating cortisol pharmacokinetics, some studies measured serum cortisol levels following the rapid IV administration of a single dose of the hormone (16, 17), while others used a constant infusion of radiolabeled hormone whereby a steady state can be achieved and the disappearance rate can be calculated (24). Although the former method might have some limitations, published data by different investigators showed that cortisol pharmacokinetic parameters (volume of distribution, clearance, and half-life) were quite similar when either of the 2 methods were used (16–18, 24–27). In our investigation, we opted to follow the former approach as we planned to extend the studies from healthy individuals to patients in the perioperative period whereby many practical considerations limit the use of constant infusion of a tracer dose of the hormone. It is important to note that the calculated half-life of cortisol using the approach followed in the current investigation is similar to that reported by other investigators using the constant infusion method (21). It is quite interesting to also note that the mean calculated half-life of cortisol determined in healthy individuals enrolled in the current investigation (1.81 ± 0.11 hours) was very similar to that (1.74 ± 0.34 hours) observed after resection of cortisol secreting adrenal adenomas (13) where cortisol had been in steady state for years before surgery.

The data on the first injection of hydrocortisone to healthy individuals in our study are similar to those reported earlier by others with respect to the volume of distribution, clearance, and the half-life of the hormone (16–18, 24–27). We are not aware of published data on cortisol pharmacokinetics obtained after repeated doses of the hormone. Only limited data are available on cortisol pharmacokinetics in the postoperative period (28). Kehlet and colleagues examined cortisol pharmacokinetics before and after surgery in only 4 patients and noted that the volume of distribution of ^{3}H- labelled cortisol increased in the postoperative period (28). In another study involving critically ill patients, Boonen and colleagues reported a higher volume of distribution and lower clearance of IV administered hydrocortisone (100 mg) when compared with similar measures determined in healthy individuals (29). However, in the latter study, the reported clearance and the volume of distribution of hydrocortisone in healthy individuals were both uncharacteristically much lower than those reported by several other investigators, including our own data (16–18, 24–27). Similarly, in the latter study, the volume of distribution of IV-administered hydrocortisone to critically ill patients was also much lower than expected. The reasons for the discordance between the latter study and many others, including our own data, remain unknown.

Although some reports suggest following a weight-based approach in providing hydrocortisone replacement therapy (30), we elected to use a simplified dosing schedule that can be generalized. Other studies that examined hydrocortisone pharmacokinetics suggested the presence of significant interindividual variations that cannot be explained by differences in weight, age, or gender (31). The lack of any episode of AI indicates that the doses are clinically effective and offer sufficient perioperative coverage. Similarly, nadir serum cortisol levels in all patients at all times were > 15 µg/dL (414 nmol/L) and were also within the range of values, and often higher than those observed in others with normal HPA function. The latter included some patients who were more than 130 kg in weight.

The stacking effect noted with repeated injection of the hormone suggest that the frequency of hydrocortisone administration can be decreased to every 8 hours instead of every 6 hours after the first 24 postoperative hours. Although the current investigation examined glucocorticoid replacement in patients with AI in a specific setting (perioperative period), we believe that the

dosing schedule proposed and used in our study will likely be as appropriate for other stressful events such as trauma and acute and chronic critical illnesses. The latter assertion is based on measurements of serum cortisol levels in a large population of patients with critical illness (1). Additional studies are needed to confirm the latter assessment.

In summary, this study provides data detailing the pharmacokinetics of hydrocortisone when different and multiple doses are administered to healthy individuals and others with AI. The data demonstrate that a longer cortisol half-life is observed when larger doses are administered and also when the same dose is repeatedly administered, indicating some stacking effect. The regimen detailed herein provides ambient serum cortisol concentrations that were similar and even higher than those achieved in patients with normal HPA function who had similar procedures. The results of the study call into question the practice of unnecessarily administering excessive doses of hydrocortisone to patients with AI during stressful events such as surgical procedures.

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