Letter to the Editor: "Our Response to Covid-19 as Endocrinologists and Diabetologists"

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In response to the editorial "Our Response to Covid-19 as Endocrinologists and Diabetologists," (1) I question the dosing recommendation of hydrocortisone 50 to 100 mg intravenously TID to critically ill patients suspected of having underlying secondary adrenal insufficiency. This recommendation has been acknowledged to be based on empiric practice, the lack of a proven lower dosing schedule, and the assumption that this dosing is prudent and not likely to be harmful (2). However, this traditional dosing plan in the critically ill neither takes into account the significant decrease in cortisol catabolic rate accompanied by only modest increases in daily cortisol production rates nor the major elevation of free biologically active cortisol that occurs in this state (3). The best estimate of cortisol replacement dosage in critically ill patients with the systemic inflammatory response syndrome is 60 mg/day and even less in those without systemic inflammatory response syndrome (3).

There is evidence that cortisol's clearance is reduced in severely ill patients by 50% in its conversion to cortisone via suppressed renal activity of 11 beta hydroxysteroid dehydrogenase-2 and a 77% lessening of hepatic A ring reductase activity (3). The increase of free cortisol is due to many factors, including declines in albumin and cortisol-binding globulin levels (3). A study of septic patients confirmed that free cortisol levels measured by equilibrium dialysis are 3 to 5 times greater than in controls (4). Furthermore, a sustained reduction in glucocorticoid hepatic receptor activity from pharmacologic hydrocortisone therapy of 150 to 300 mg/day is potentially deleterious in the septic patient (5). Higher dose IV cortisol may have a limited role in the early reversal of septic shock not responsive to fluids and inotropes and in delaying mechanical ventilation, but this is a pharmacologic and not a physiologic benefit (6).

Bolus hydrocortisone of 100 mg given to healthy individuals produces nonphysiologic peaks and valleys of serum cortisol levels (7). Cortisol-binding globulin saturates at a serum concentration of cortisol of 541 nmole/L (20 ug/dL), levels exceeded several fold by bolus hydrocortisone therapy (7). Furthermore, cortisol's half-life when given IV is prolonged from less than 2 h in normal patients to 12 h in the critically ill (3). A recent study showed that giving septic patients a continuous IV infusion of hydrocortisone at 200 mg/d after an initial bolus of 50 to 100 mg raised the total cortisol levels measured by liquid-chromatography-tandem mass spectrometry to levels about one-third greater than that seen in septic patients not receiving hydrocortisone and demonstrated greatly elevated free cortisol levels measured by liquid-chromatography-tandem mass spectrometry (8).

I applaud the authors' reminder that many patients receiving glucocorticoids, particularly from inhalers, may have underlying secondary adrenal insufficiency when stressed; however, treating critically ill Covid-19 patients with underlying secondary adrenal insufficiency with traditional hydrocortisone dosing should be tempered by an acknowledgment that this advice is empiric and does not match evidence of cortisol production and metabolism in the critically ill.

Additional Information

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