Commentary

Bolus or continuous hydrocortisone – that is the question

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See related research by Loisa *et al*., http://ccforum.com/content/11/1/R21

Abstract

Constantly evolving treatment guidelines based on a growing body of randomized controlled trials are helping us to improve outcomes in sepsis. However, it must be borne in mind that proven benefit from individual sepsis treatments does not guarantee synergistic beneficial effects when new treatments are added to sepsis management. Indeed, unexpected harmful interactions are also possible. A good example of this is the conflict between intensive insulin therapy and 'low dose' hydrocortisone in septic shock. The goal of tight glycaemic control is made more complicated by steroid-induced hyperglycaemia. In their recent study, Loisa and coworkers demonstrate a measure that reduces the risk for this interaction. They found continuous infusion of hydrocortisone to be associated with fewer hyperglycaemic episodes and reduced staff workload compared with bolus application.

In this issue of *Critical Care*, Loisa and coworkers [1] present the first randomized controlled trial on the influence of mode of hydrocortisone administration on glycaemic control in patients with septic shock.

During the past few years intensive insulin therapy has come to be recognized as a key component of treatment of critically ill patients, with significant impact on morbidity and mortality [2]. However, it has also been shown that these findings are not necessarily applicable to all the clinical situations encountered in critical care [3]. Moreover, there are certain clinical conditions in which achieving glycaemic control remains challenging. Clinicians are often faced with widely varying glucose levels in patients with severe sepsis or septic shock. Although stress-induced hyperglycaemia and reduced insulin sensitivity are the primary disorders of glucose metabolism in severe sepsis, iatrogenic hypoglycaemia - as a result of intensive insulin therapy - must now also be reckoned with [4]. It appears that not only high blood glucose levels but also high glucose variability (range of variation of greater than 30 to 40 mg/dl) is associated with increased morbidity and mortality [5]. In this situation 'low dose' hydrocortisone (200 to 300 mg/day), which is now recommended as an adjunctive therapy in septic shock, may further aggravate problems with glucose control. The Surviving Sepsis Campaign [6] favours neither bolus nor continuous administration of hydrocortisone in septic shock because of the lack of a comparative study. Moreover, a recent meta-analysis did not demonstrate significant differences in the risk for hyperglycaemia in septic shock patients treated with glucocorticoids [7]. However, it must be stressed that the definitions of hyperglycaemia in septic patients used in these studies are different from those in current use (<150 mg/dl) [8].

As their name implies, glucocorticoids affect blood glucose levels and insulin-dependent glucose uptake by skeletal muscle via the GLUT-4 glucose transporter. This physiological response in systemic inflammation is aggravated by the administration of exogenous glucocorticoids [9,10]. Hydrocortisone via continuous infusion results in plasma cortisol levels of 70 to 140 μg/dl [11], which are significantly higher that the levels of 40 to 50 μg/dl that are otherwise measured in patients with septic shock. Notably, peak plasma cortisol levels measured after intermittent boluses of 50 mg hydrocortisone (four times a day) considerably exceed these values (150 to 200 μg/dl) and fluctuate more widely, with nadir plasma cortisol levels of 40 to 50 μg/dl being reported [12]. This raises the question of whether bolus hydrocortisone therapy unnecessarily complicates glycaemic control in what is an already difficult situation.

In addressing this question, the study by Loisa and coworkers [1] is important and merits prominence. They conducted a prospective study in 48 septic shock patients, who were randomly assigned to receive either four times daily 50 mg hydrocortisone boluses or the same dosage as a continuous infusion. Blood glucose was recorded every 2 hours and insulin titrated to blood glucose levels of 4 to 7 mmol/l (72 to 126 mg/dl). The frequency of insulin adjustments was documented and used as a measure of staff workload. One

major finding was that significantly more episodes of hyperglycaemia (>126 mg/dl) occurred in the bolus group, although episodes of severe hyperglycaemia (>150 mg/dl) were rare and not significantly more frequent in either group.

So, why worry about the mode of application? Recent results of an observational study on the responses to these two modes of hydrocortisone application showed marked inter-individual variation and increases in blood glucose to levels above 150 mg/dl in the majority of patients when intermittent boluses were used [13]. Importantly, the baseline mean blood glucose values before hydrocortisone bolus application were considerably higher (about 130 mg/dl) in this study than in the one conducted by Loisa and coworkers [1]. Because tight glycaemic control (80 to 110 mg/dl) is not currently recommended in sepsis, we contend that the glucose levels encountered in our study [13] were closer to those one would expect to observe in current routine practice. We previously speculated that fluctuations in blood glucose would require more frequent insulin dose adjustments. This was now been prospectively demonstrated by Loisa and coworkers [1], who demonstrated a significant increase in staff workload during bolus hydrocortisone application.

Although the study did not demonstrate an impact on mortality, it is questionable whether a sufficiently powered study to address this question will ever be performed. As the range of therapies available to physicians treating sepsis widens, so too does the potential for adverse pharmacological events, and interactions in particular. Investigations such as this by Loisa and coworkers are vital if we are to ensure that the increasingly complex management of sepsis remains safe.

Competing interests

The authors declare that they have no competing interests.

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