Steroids in sepsis, etomidate and Pearl Harbor

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Steroids in sepsis, … etomidate, … Pearl Harbor, … what's the connection? Well, there is one, and it is relevant to the practice of emergency medicine.

Steroids have enjoyed mixed fortunes as part of the treatment for sepsis and multiple organ failure. When it was realised that an excessive inflammatory response was part of the pathogenesis of sepsis and multiple organ failure high-dose steroids seemed to have much to offer. Initial studies were encouraging.[1] But then larger studies failed to show benefit and steroids fell out of favour.[2 3] Things changed with increasing interest in the concept of adrenocortical failure or adrenocortical insufficiency in the critically ill.[4] Low-dose, or physiological doses of steroids then came under scrutiny as an adjunct to treatment for severe sepsis and septic shock. The publication of a large randomised controlled trial[5] and two meta-analyses, which suggested a survival benefit[6 7] resulted in steroids being incorporated into the Surviving Sepsis Campaign guidelines.[8]

Despite this evidence some controversy remained. In the study by Annane *et al*[5] fludrocortisone was given in addition to hydrocortisone for its mineralocorticoid activity. The use of fludrocortisone was not, however, included in the Surviving Sepsis Campaign guidelines.[8] Also the study by Annane *et al*[5] showed no benefit in those patients who had a normal or "adequate" cortisol response to a short corticotropin stimulation test.

The Corticosteroid Therapy of Septic Shock (CORTICUS) study, which was published earlier this year, aimed to resolve some of this controversy.[9] In this multicentre, randomised, double-blind, placebo-controlled study, 499 patients were randomly assigned to receive either low-dose hydrocortisone (50 mg intravenous bolus four times a day for 5 days and tapered over 6 more days) or placebo. The primary endpoint was the 28-day mortality of patients with septic shock, who did not respond to corticotropin. Once again patients were given a corticotropin stimulation test to assess their adrenocortical function.

An adequate response to corticotropin was defined as an increase in cortisol of more than 9 μg per decilitre (248 nmol per liter) and patients were divided into "responders" and "non-responders" accordingly.

Overall, there were 164 deaths at 28 days (32.8%): 86 in the hydrocortisone group (34.3%) and 78 in the placebo group (31.5%, $p = 0.51$). In contrast to the study by Annane *et al*,[5] hydrocortisone proved of no benefit in those patients (233) who did not respond to corticotropin. At 28 days there were 49 deaths in the 125 "non-responder" patients given hydrocortisone (39.2%) compared with 39 deaths in the 108 "responder" patients given placebo (36.1%, $p = 0.69$). There was no benefit in patients who did respond to corticotropin. Thirty-four of the 118 patients given hydrocortisone died (28.8%), as did 39 of the 136 patients who received placebo (28.7%, $p = 1.00$).

Part of the rationale for low-dose steroids in sepsis is that they improve the blood pressure response to catecholamines.[10] This usually manifests itself clinically as a reversal of shock. Disappointingly, in the CORTICUS study hydrocortisone did not increase the proportion of patients in whom shock was reversed. For the 77% of patients in whom shock was reversed, however, it happened more quickly in those given steroids.

Rather worryingly there was an increased incidence of superinfections in patients given hydrocortisone (odds ratio 1.37), which was one of the problems with the earlier high-dose steroid regimes.[2 3]

ETOMIDATE

One of the authors' many post-hoc analyses showed that there was an excess of deaths in those patients who received etomidate before entry into the trial (41 out of 96, 42.7%) compared with those who did not (123 out of 403, 30.5%, $p = 0.03$). Etomidate was first implicated in adrenocortical failure in the critically ill when it was used as an infusion to keep ventilated patients sedated.[11 12] Since then it has been shown that even a single dose of etomidate may impair the response to a corticotropin stimulation test.[13]

In the CORTICUS study, 96 of the 499 patients (19.2%) received etomidate before study entry. Of these 96, 58 did not respond to corticotropin (60.4%). Of the 403 who did not receive etomidate before entry into the study only 175 did not respond to corticotropin (43.4%, $p = 0.004$). So etomidate seems to be associated with an increased rate of corticotropin unresponsiveness and a higher mortality rate.

PEARL HARBOR

Sodium thiopentone, a barbiturate, introduced as an intravenous anaesthetic agent in the 1930s, gained notoriety in the aftermath of the Japanese attack on Pearl Harbor because of a rumoured high mortality rate.[14] This was attributed to a tendency to induce catastrophic respiratory failure in hypovolaemic casualties. As with many rumours it has been exaggerated over the years: "It may be apocryphal but it is claimed that iv anaesthesia was the cause of more fatalities among the servicemen at the base than were the enemy bombs."[15] Etomidate, on the other hand, has enjoyed a reputation, maybe undeservedly, as a much safer drug in the hypotensive patient. As a result it is often preferred for the induction of anaesthesia in patients with severe sepsis or septic shock.[13] Should this situation persist? A review of the Pearl Harbor story has suggested that probably only a handful of deaths were attributable to the use of intravenous thiopentone.[16]

CORTICUS IN CONTEXT

So where does the CORTICUS study leave us? We are better informed, but are we any the wiser? There was no survival benefit from low-dose hydrocortisone in this group of patients and there was an increased incidence of superinfection. However, the study failed to recruit the number of patients needed to reach its power calculation by some margin: 800 patients would have been needed. As Finfer[17] has already suggested, the study had a power of less than 35% to detect a 20% reduction in the relative risk of death. It is also apparent that the patients in the CORTICUS study[9] had lower simplified

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acute physiology scores (SAPS II) (49) than those in the study by Annane *et al*[5] (58.5) and a lower placebo group mortality (31.5% versus 61%, respectively). In addition, the CORTICUS study had a much longer recruitment window (72 h compared with 8 h in the earlier study). Also the hydrocortisone regimes were not the same (5 days plus a 6-day taper and no fludrocortisone in CORTICUS,[9] 7 days with fludrocortisone in Annane *et al*).[5] The trials are not directly comparable but the tide may be ebbing away from steroids once again. The CORTICUS authors suggested that part of their failure to recruit patients may have been a perceived lack of equipoise in the treatment arms. Maybe this trial, with its 499 patients, when added to the meta-analyses (only 465 patients), will re-establish that equipoise. It will then be necessary to re-address the question of steroids in sepsis in a much larger trial, maybe on the scale of the SAFE study[18] or even the CRASH trial.[19]

To paraphrase Benjamin Franklin "In the world of the critically ill nothing is certain but death and the fact that steroids will come in and out of fashion as autumn follows summer…." Steroids are now entering another autumn and their place in the Surviving Sepsis Campaign has been downgraded to 2C evidence, "stress-dose steroid therapy (should be) given only in septic shock after blood pressure is identified to be poorly responsive to fluid and vasopressor therapy".[20] For now, steroids should not be started in the emergency department unless these conditions have been met. In the meantime, we need to forget Pearl Harbor and think twice before using etomidate in the septic patient. In experienced hands there is no reason not to use thiopentone.

Competing interests: None.

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