Commentary

Etomidate, pharmacological adrenalectomy and the critically ill: a matter of vital importance

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Abstract

Etomidate is a potent suppressant of adrenal steroidogenesis, effectively inducing reversible pharmacological adrenalectomy. Recent evidence suggests that for every five patients with septic shock given etomidate without corticosteroid supplementation, one patient will die as a consequence. Other critically ill patients are also at possible risk, and this risk requires further exploration. Etomidate will also confound investigations into the effects of disease states on adrenal function, and should therefore be avoided. A moratorium on the use of etomidate in critically ill patients outside clinical trials may be prudent until its safety is established.

Etomidate is a hypnotic with a sixfold better therapeutic index than alternatives such as thiopental or propofol, making it an agent of choice for induction of anaesthesia in critically ill, haemodynamically unstable patients [1,2]. This together with its favourable pharmacokinetic profile also led to its use by infusion for sedation of ventilated patients in intensive care units (ICUs). This practice was largely abandoned more than 20 years ago as a result of etomidate's association with increased mortality, which was attributed to profound suppression of adrenal steroidogenesis primarily through its potent inhibition of the enzyme 11β-hydroxylase [3-5]. In contrast, single-bolus administration of etomidate has been considered safe by most commentators [6], but not all [7], and its niche use by many specialities has continued [2].

The risk–benefit profile of etomidate bolus administration has been brought into focus again by recent studies. In the present issue of *Critical Care* Mohammad and colleagues report results of a retrospective review of adrenal function in patients with septic shock, comparing patients who did receive and who did not receive etomidate [1]. The prevalence of a blunted response to cosyntropin was 50% greater in those patients who received etomidate, although the excess mortality was not statistically significant. The study size and design preclude inferences on mortality.

The results of Mohammad and colleagues add to a prospective observational study of critically ill, mechanically ventilated patients that found a single bolus of etomidate given 24 hours before a standard cosyntropin test to be the most important predictor of relative adrenal insufficiency – and overall nonresponders to cosyntropin had a significantly higher mortality [8]. Further evidence comes from an observational study of 60 children with meningococcal sepsis, none of whom received corticosteroid supplementation [9]. Adrenal dysfunction demonstrated by extremely high adrenocorticotrophin concentrations and low total cortisol concentrations were associated with increased IL-6 concentrations and use of etomidate. Seven of the eight patient deaths reported received etomidate.

While all of these studies confirm that etomidate is associated with adrenal insufficiency, they were not designed to answer whether this effect was detrimental. In this context, Annane has provided important data that strongly suggest that etomidate administration, if unsupplemented with corticosteroids, in patients with septic shock results in excess mortality [10]. In a reanalysis of a double-blind clinical trial of 299 patients with septic shock randomised to receive placebo or corticosteroids, 77 (26%) patients received etomidate [10,11]. Ninety-four per cent of these etomidate-treated patients were nonresponders to cosyntropin, and the blockade of steroidogenesis lasted around 72 hours. Fluid and vasopressor requirements were greater compared with those patients intubated with alternative methods. The key finding was the difference in mortality between those etomidate-treated patients randomised to placebo (76%) and those randomised to corticosteroids (55%). This statistically

ICU = intensive care unit; IL = interleukin.

significant absolute risk reduction (survival advantage) of 21% of those given corticosteroids translates into a number needed to treat of five patients. The early advantage of relative haemodynamic stability at intubation, which itself is not an important patient-centred outcome and can be managed in a critical care environment, seems trivial in this context.

Although it might be argued that steroid supplementation would obviate these important adverse consequences, there are problems with this approach in clinical practice. Firstly there is the problem of identifying which patients are at risk. Although the cumulative data for patients with septic shock are strong, not all of these patients are treated with corticosteroids [9]. Other critically ill patients without septic shock may also be at risk but the data are observational and weaker [8]. There can be a lag time between the onset of iatrogenic adrenal insufficiency, its recognition and corticosteroid supplementation, particularly if intubation occurs before ICU admission. Finally, the duration of need for steroid replacement may be variable and is as yet undefined.

It would therefore seem reasonable for ICU physicians to follow the advice of Annane and avoid the use of etomidate [12]. This 'solution' is only partial, as many critically ill patients are intubated by other practitioners [13]. This poses two problems. The first is that clinical and intensive care physicians need to be aware that other colleagues may have employed etomidate prior to care in the ICU. These patients must be actively identified and given appropriate corticosteroid supplementation [10,13]. The second problem is educational, in that we need to inform anaesthetic and Emergency Department colleagues regarding current evidence in the critical care literature.

There are also implications for clinical researchers. Firstly, the risks of etomidate in patient groups other than those with septic shock need to be more clearly defined. Are patients with severe sepsis or sepsis also at risk from pharmacological adrenalectomy? And what of critically ill patients with nonseptic conditions such as cardiogenic shock? Secondly, some studies of adrenal function have either not highlighted etomidate as an issue or have been insufficiently rigorous in dealing with etomidate as a confounding factor [2,5,13,14]. This in part might explain the wide variation of incidence of adrenal insufficiency (0–95%) quoted for high-risk critically ill patients [15].

In summary, pharmacological adrenalectomy does not seem intuitively beneficial to critically ill patients. Current evidence strongly suggests that this has a detrimental impact on survival for patients with septic shock. Although the evidence is less strong for other critically ill patient groups, perhaps it is time to call a moratorium on etomidate's use outside of clinical research in these at-risk groups until its utility and safety is assured. For investigations into adrenal function in various disease states, etomidate should be avoided because of its confounding effects. To do otherwise constitutes inadequate research design, contributing to poor clinical science and to continued uncertainty as regards best clinical practice.

Competing interests

The authors declare that they have no competing interests.

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