

Correspondence

Etomidate – misused or misunderstood?

In response to the recent editorial by Morris and McAllister [1] concerning the use of etomidate, which follows other publications questioning its continued use both in anaesthesia and critical care [2, 3], we agree that the use of a single dose of etomidate is associated with suppression of the adreno-cortical axis. However, we dispute the assertion that there has been a proven link between a single dose of etomidate and excess mortality. One previous study published in *Anaesthesia*, quoted by the authors, showed no significant differences in mortality between critically ill patients given single dose etomidate compared with thiopental. Moreover, the authors commented that the clinical implications of the ACTH suppression were unclear in this group [4].

The Helicopter Emergency Medical Service based at the Royal London Hospital uses etomidate as the standard induction agent in the prehospital environment due to its wide therapeutic index and safe cardiovascular profile. In a small study of 22 such polytrauma patients admitted to the ICU at the Royal London, all had ACTH stimulation tests with baseline and 60 min cortisol levels within 36 h of admission. Impaired adrenal function was seen in 36% of these patients, but the presence of adrenal suppression did not predict

mortality [5]. Obviously, this is a small number of patients and a larger study would be required to make categorical conclusions. Another study of 62 patients published this year [6] suggested that a single dose of etomidate for intubation in intensive care may be detrimental on the basis of response to ACTH stimulation; the evidence was by no means absolute. The conclusion was that a larger randomised controlled study is required. We agree and plan to undertake a phase II clinical study which will, hopefully, inform an adequately powered, phase III clinical study with mortality as the primary outcome. To undertake such a multicentre clinical trial will require a critical care clinical trials network, which within the UK and Ireland have been slow to develop compared to other international groups [7].

A rush to judgement in the absence of such evidence would seem premature. Similar advice was given previously about the use of albumin in intensive care, which was later withdrawn following the SAFE study, which performed a randomised, controlled trial comparing albumin with normal saline [7].

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In the recent editorial written by Morris and McAllister [1] it is stated that 'etomidate...has been withdrawn in the

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United States, Australia, Canada and the Republic of Ireland...’ However, to our knowledge, this drug has never been withdrawn from use in the United States. Upon further investigation by perusing multiple drug information references, accessing the website for the Food and Drug Administration and contacting the manufacturer Hospira Pharmaceuticals, there is no evidence of the drug being withdrawn. This issue is of great importance to us as we know that this medication is commonly used throughout the US, particularly in the Emergency Room and Operating Room settings.

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Reference

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A reply

We thank Drs Shirley and McAuley and Drs Jackson and Ramos for their interest in our recent editorial. We are delighted to see that debate has been stimulated – a very healthy situation for the specialty.

Firstly, we agree with Drs Shirley and McAuley that etomidate is a stable induction agent around the time of administration. This would be perfect in the prehospital setting; after all, an agent which is painful, emetogenic, induces myoclonus and dyskinesia and adrenal suppression needs some redeeming features. As we have stated, ketamine shares the stability properties and we would reach for it every time. Our point throughout is that etomidate produces adrenocortical suppression which the data provided seem strongly to support; 36% of their own patients demonstrate adrenal suppression. The work by the Annane group [1] suggested that mortality was 82% amongst non-responders compared with 26% in responders during septic shock. This would certainly be enough to put us off using this agent in the critically ill.

We admire their determination to perform a multicentre, phase III study using mortality as an outcome measure. However, we suggest the realities of performing such a study would make it prohibitive. To be powered to detect an excess mortality of 5–10%, for example, hundreds of patients will require randomisation. To adequately match such groups of critically ill patients is notoriously difficult and undermines recruitment; for example, sepsis and trauma are not comparable. Having identified a homogeneous ‘category’ of critical illness one must then control for a myriad of confounding factors such as lead-time bias, pre-ICU care, adequacy of resuscitation and whether patients are managed in ‘dry’ or ‘wet’ units. There is currently no accepted standard for adrenal insufficiency and the short Synacthen test is far from ideal. Should this test constitute an end point? The effect etomidate will exert on mortality will *probably* be moderate and this may easily be missed; for example, how will we know whether adrenal insufficiency and mortality is related to etomidate or the sepsis itself? How will one resolve the ethical issues of withholding hydrocortisone replacement from patients with a documented abnormality on Synacthen testing following etomidate? If patients are to receive ‘rescue’ hydrocortisone, a second adequately powered study is required to determine the efficacy of combined etomidate and hydrocortisone. We do not believe such a study will ever be performed in a useful or meaningful way. A recent editorial has highlighted the practical obstacles to pharmaceutical research in the United Kingdom at present [2] and makes depressing reading.

Clinicians require ethical equipoise to allow their patients to participate in a trial, namely a reasonable uncertainty that the study agent offers benefit or harm to patients. While we recognise Dr Shirley and McAuley’s equipoise and would be delighted to ‘eat our words’ should etomidate ever be proven to be benign and without consequence, we would have to decline the offer to randomise patients since we have no such confidence in etomidate for all

the reasons we outlined originally. To suggest this is a ‘rush to judgement’ on a drug which has been used for over 30 years is not accurate. Furthermore, while the SAFE study [3] is indeed a testament to perseverance and multicentre recruitment, we would suggest it exemplifies the problems of large critical care trials, namely it has resolved little. It suggests that critically ill patients may behave differently (trauma vs. sepsis) and that albumin is a pretty ineffective colloid in a pressure-guided management protocol. The interest comes from subgroup analyses which are hypothesis generating; this rather undermines a multicentre trial and will probably always undermine critical care studies. This brings us full circle – we don’t believe the study, as proposed by Shirley and McAuley, will ever be completed and so clinicians will have to decide using the available evidence as to whether they wish to use a drug with a number of safety concerns or any of a number of alternatives.

Finally, information on countries where etomidate is licensed was provided to us by Janssen-Cilag UK, Ltd. We are grateful for the correction from Drs Jackson and Ramos regarding etomidate’s status in the United States.

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