Etomidate in the management of hypercortisolaemia in Cushing’s syndrome: a review

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Abstract
This review addresses the practical usage of intravenous etomidate as a medical therapy in Cushing’s syndrome. We reviewed the relevant literature, using search terms ‘etomidate’, ‘Cushing’s syndrome’, ‘adrenocortical hyperfunction’, ‘drug therapy’ and ‘hypercortisolaemia’ in a series of public databases. There is a paucity of large randomised controlled trials, and data on its use rely only on small series, case study reports and international consensus guideline recommendations. Based on these, etomidate is an effective parenteral medication for the management of endogenous hypercortisolaemia, particularly in cases with significant biochemical disturbance, sepsis and other serious complications such as severe psychosis, as well as in preoperative instability. We suggest treatment protocols for the safe and effective use of etomidate in Cushing’s syndrome.

Introduction
Endogenous Cushing’s syndrome results from excessive glucocorticoid production with a failure of the normal negative feedback effect on the hypothalamo-pituitary–adrenal axis. It is traditionally divided into ACTH-dependent and ACTH-independent Cushing’s syndrome. In the majority of cases, it is caused by an adenoma in the pituitary gland secreting ACTH hormone (Cushing’s disease), more rarely due to ACTH secretion by an ectopic source; of the adrenal causes, these are usually adrenal adenomas or carcinomas, with a small group due to bilateral adrenal hyperplasia (1). Detailed biochemical and imaging paradigms have been designed to diagnose the presence of Cushing’s syndrome and to differentially identify ACTH dependence or independence and the precise pathology. If untreated, there is significant morbidity and potential mortality related to life-threatening infections, diabetes mellitus, hypertension and an increased risk associated with surgery.

For Cushing’s disease, surgical removal of the pituitary tumour is the usual first-line therapy, with radiotherapy reserved for surgical failure, or occasionally bilateral adrenalectomy. Laparoscopic adrenalectomy is highly effective in the ectopic ACTH syndrome (2) and occasionally in Cushing’s disease, but its use may cause unnecessary or inappropriate delay. Patients should be referred in a timely fashion to a facility where appropriate laparoscopic surgical expertise exists. Earlier planned surgical intervention may be a means of resolving hypercortisolaemia, although even with modern techniques preoperative lowering of the hypercortisolaemia may be important. However, there is still a widespread requirement for medical therapy. In the first instance, severe biochemical disturbance (e.g. hypokalaemia), immunosuppression and/or mental instability may need immediate and life-saving cortisol-lowering therapy, while following radiotherapy, medical therapy may be necessary whilst waiting for the treatment to become effective. In some cases, surgical cure is impossible and management with drugs able to lower cortisol may be needed in the short term or even in the long term (1, 3).

The medical therapy of hypercortisolaemia in Cushing’s syndrome is predominantly based on the inhibition of adrenal steroidogenesis at one or more enzymatic sites, or alternatively by antagonism of the glucocorticoid receptor or the suppression of ACTH. Oral therapy with ketoconazole and metyrapone are the most frequent steroidogenic enzyme inhibitors currently in use, but these agents are not always well tolerated. Ketoconazole is associated with disturbances of hepatic function, while metyrapone may cause nausea independent of its cortisol-lowering activity and thus large doses cannot be taken, and accumulation of androgenic precursors may be problematic (4). Occasional patients may need to be treated with the
Etomidate

Etomidate and ketoconazole are members of the imidazole family. Etomidate is a carboxylated imidazole synthesised in 1964 and introduced into use in 1972. It was developed as an intravenous hypnotic non-barbiturate induction anaesthetic agent (7) and has a plasma half-life of 3–5 h. The anaesthetic effects of etomidate in the CNS are thought to be via activation of γ-aminobutyric acid type A receptors (8). Etomidate was popular for its reputation in cardiovascular stability, with little change in blood pressure and heart rate, as well as lack of histamine release, but was noted to result in increased mortality in critically unwell patients (9): this was later shown to be associated with low serum cortisol levels resulting in hypoadrenalism (10). However, a recent meta-analysis was unable to conclude that there was an increase in mortality in patients who were given etomidate as a single dose in rapid sequence induction anaesthesia (11): the debate on the usage of etomidate in the anaesthetic literature continues. Etomidate inhibits the mitochondrial cytochrome P450-dependent adrenal enzyme 11β-hydroxylase that catalyses the production of cortisol from deoxycortisol and is 95% homologous to the aldolase enzyme in the pathway to aldosterone synthesis, lowering serum cortisol levels within 12 h (12, 13, 14, 15). On this basis, it was suggested that etomidate could be a useful therapy for severe hypercortisolaemia in patients intolerant of or unable to take oral medication. At higher doses, etomidate blocks side chain cleavage enzyme. More recent work has not only shown etomidate to potently block 11β-hydroxylase and side chain cleavage enzyme but also aldosterone synthase and may have anti-proliferative effects on adrenal cortical cells (16, 17). Therefore, etomidate also has therapeutic relevance for aldosterone blockade and anti-tumorigenesis for metastatic adrenocortical tumours. Post-translational work is underway to manufacture synthetic similar compounds to etomidate with high potency inhibition of the steroid pathway and weak interactions with γ-aminobutyric acid type A receptors in order to harness its therapeutic benefits in treating hypercortisolism and to minimise its anaesthetic properties (8).

Methodology

Publications were identified by means of a systematic literature search in the period of January 1946 to April 2012 using the Medline, EMBASE, Cochrane and Scopus databases, limited to English language publications. Other studies were identified from the bibliography of short-listed articles. The search criteria used in the Medical Subject Headings (MeSH) are as follows: ‘etomidate, Cushing’s syndrome, hypercortisolaemia, adrenocortical hyperfunction and drug therapy’. Supplementary references for guidelines were identified via Google Scholar. An initial review of all titles and abstracts was performed for relevance. If deemed appropriate for further review, access to the full article was obtained. Eighteen key clinical references, most of which were case reports for the primary therapeutic use of etomidate in hypercortisolism, were identified.

Clinical experience

Gärtner et al. (18) used the therapeutic effect of sedative doses of 15–30 mg/h etomidate in a 53-year-old patient with an ectopic ACTH-producing tumour and untreatable psychosis. They were the first to demonstrate the beneficial effect of etomidate on hypercortisolism for clinical benefit over a 14-day infusion with improvement in the patient’s hypertension and hypokalaemia associated with a fall in cortisol levels. Engelhardt et al. (19) demonstrated the cortisol-lowering effect of non-sedating etomidate in three normal volunteers in 1986. Alloio et al. (20) in 1988 were the first to demonstrate that a 32-h infusion of low-dose 2.5 mg/h ethyl alcohol etomidate could inhibit cortisol secretion in patients with hypercortisolaemia within 11–24 h. They were able to demonstrate that low plasma doses achieved adrenocortical blockade distinct from the sedative potential used in anaesthesia, which was typically at a dose of an initial induction anaesthetic bolus of 0.03 mg/kg followed by a continuous infusion of 0.3 mg/kg per h to maintain sedation. (For the average 70 kg subject, this equates to a bolus dose of 2.1 mg followed by 21 mg/h etomidate infusion.) At the dose of 2.5 mg/h, there was suppression of excess cortisol within the reference range; however, the cortisol response to exogenous ACTH of 250 μg was reduced but not completely blocked, in contrast to the
Table 1  Summary of etomidate use in Cushing’s syndrome in the literature.

<table>
<thead>
<tr>
<th>Ref.</th>
<th>Diagnosis</th>
<th>Gender (M/F), age</th>
<th>No. pat.</th>
<th>Indication</th>
<th>Dose regime</th>
<th>Duration</th>
<th>Cortisol levels</th>
</tr>
</thead>
<tbody>
<tr>
<td>(18)</td>
<td>Ectopic ACTH-secreting tumour</td>
<td>53 M</td>
<td>1</td>
<td>Sedation hypokalaemia; alkalosis; hypertension and psychosis</td>
<td>15–30 mg/h</td>
<td>14 d</td>
<td>Normalised</td>
</tr>
<tr>
<td>(20)</td>
<td>Ectopic ACTH from pancreatic islet cell tumour</td>
<td>6</td>
<td>1</td>
<td>Study of low-dose etomidate and correction of hypercortisolemia</td>
<td>2.5 mg/h (n=5) 0.05 mg/kg per h</td>
<td>32 h</td>
<td>Normalised</td>
</tr>
<tr>
<td>(21)</td>
<td>Ectopic ACTH from pancreatic islet cell tumour</td>
<td>35 M</td>
<td>1</td>
<td>Variable 40–200 mg/d dose titrated to cortisol levels</td>
<td>5.5 mo</td>
<td></td>
<td>Normalised</td>
</tr>
<tr>
<td>(23)</td>
<td>Cushing’s disease</td>
<td>6 M</td>
<td>1</td>
<td>Acutely unwell, severe vomiting with metabolic disturbance, respiratory failure; requiring parenteral therapy and sedation</td>
<td>1.0 mg/h up-titrated to 3 mg/h 0.03-0.08 mg/kg per h</td>
<td>12 d</td>
<td>Normalised</td>
</tr>
<tr>
<td>(36)</td>
<td>Cushing’s disease</td>
<td>70 F</td>
<td>1</td>
<td>Acutely unwell, pneumonia, septicaemia, upper gastrointestinal bleeding; parenteral therapy required</td>
<td>12 mg/h</td>
<td></td>
<td>Normalised</td>
</tr>
<tr>
<td>(37)</td>
<td>Cushing’s disease</td>
<td>59 F</td>
<td>1</td>
<td>Acutely unwell, pneumonia, hypercortisolaemia, upper gastrointestinal bleeding; parenteral therapy required</td>
<td>0.06 mg/kg per h (4 mg/h)</td>
<td>9 d</td>
<td>Normalised</td>
</tr>
<tr>
<td>(38)</td>
<td>Ectopic ACTH (prostate cancer)</td>
<td>73 M</td>
<td>1</td>
<td>Metabolic alkalosis, hypertension, neutropenic sepsis post-chemotherapy, respiratory failure; parenteral therapy required</td>
<td>0.2 mg/kg per d with mifepristone 8 mg/kg per d</td>
<td>4 d (mifepristone continued 800 mg/d)</td>
<td>Normalised</td>
</tr>
<tr>
<td>(39)</td>
<td>Ectopic ACTH small cell lung cancer</td>
<td>46 F</td>
<td>1</td>
<td>Metabolic alkalosis, hypokalaemia, psychosis; requiring parenteral therapy</td>
<td>5 mg/h</td>
<td></td>
<td>Not specified</td>
</tr>
<tr>
<td>(40)</td>
<td>Cushing’s disease</td>
<td>57 F</td>
<td>1</td>
<td>Florid psychosis requiring sedation and parenteral therapy for cortisol excess</td>
<td>10 mg bolus then 2.5 mg/h</td>
<td>1 d</td>
<td>Normalised</td>
</tr>
<tr>
<td>(41)</td>
<td>Ectopic ACTH</td>
<td>17 F</td>
<td>1</td>
<td>Metabolic alkalosis, hypokalaemia, psychosis; requiring parenteral therapy</td>
<td>7 mg/h</td>
<td></td>
<td>Normalised</td>
</tr>
</tbody>
</table>
significantly higher anaesthetic dosages showing complete blockade.

Given the wide dosing range between adrenostatic and anaesthetic effects, further work by Schulte et al. in 1990 reported the differential effects. They published the effect of etomidate on cortisol levels after an initial bolus of 0.03 mg/kg for all patients (n = 21) followed by an infusion in 15 normal volunteers for 5 h and six patients with Cushing’s syndrome over 24 h of varying doses in the normal group of 0.03, 0.1 and 0.3 mg/kg per h, and 0.3 mg/kg per h in the Cushing’s group, elegantly separating the dose-related adrenostatic and anaesthetic effects (12). They concluded that etomidate at a dose of 0.1 mg/kg per h or lower was effective for the control of severe hypercortisolaemia. Further case reports have demonstrated the long-term (months) use of both ethyl alcohol etomidate and propylene glycol etomidate (6, 21). Multiple case reports have used parenteral etomidate for shorter durations in the setting of required parenteral therapy in both adults and children. This has been for Cushing’s-induced psychosis, severe metabolic disturbances that need concurrent mechanical ventilation, normalisation of hypercortisolaemia before bilateral adrenalectomy, patients failing usual per oral medical therapy, subjects with increased surgical risk and in those not appropriate for surgery due to intra-abdominal sepsis (Table 1).

In anaesthesia, induction bolus doses of etomidate are typically 0.2 mg/kg–0.4 mg/kg per h with resultant apnoea and hypnosis within 10–15 s of the onset of the infusion (22). In the original study by Allolio et al. (20) using etomidate for cortisol suppression, tiredness was reported in some patients at doses of 0.3 mg/kg per h. Doses of 0.04–0.05 mg/kg per h were found to adequately inhibit, but not sedate, and this was further clarified in dose–response studies by Schulte et al. (12) demonstrating inhibition of adrenal steroidogenesis at 0.01–0.1 mg/kg per h (20). Several publications that followed report sub-hypnotic i.v. 2.5–3.5 mg/h doses of etomidate completely inhibiting endogenous cortisol production (21, 23, 24). In the case reports where patients were rendered hypoadrenal, this was demonstrated by serum cortisol levels < 100 nmol/l and glucocorticoid replacement therapy was provided by a continuous i.v. hydrocortisone infusion, using a dose that guaranteed serum cortisol level of around 500 nmol/l. This was considered to be appropriate as a ‘physiological stress’ in an intensive care setting (21, 25).

Dosages of etomidate need to be individualised to the clinical scenario. A recent case presentation of a severely ill 57-year-old female patient with ACTH-dependent Cushing’s syndrome from a pituitary microadenoma, complicated by bowel perforation, who was not controlled by the initial etomidate dose of 2.5 mg/h or the up-titrated dose of 5 mg/h, may have required a further up-titration of dose. This requires measurement of the cortisol levels and also the cortisol response to exogenous ACTH to demonstrate complete or partial

<table>
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<th>Table 1 Continued</th>
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<tr>
<td>Ref.</td>
</tr>
<tr>
<td>(43)</td>
</tr>
<tr>
<td>(44)</td>
</tr>
<tr>
<td>(27)</td>
</tr>
</tbody>
</table>

M, male; F, female; y, year; d, day; mo, month; wk, week; Ref, references; No. pat., number of patients.

*aDuplicate case report by Metherau & Bradley on the same patient in 2009 (45).*
blockade. In order to demonstrate ‘escape’, an increase in endogenous ACTH and cortisol secretion must occur with exogenous ACTH (20, 26). There is no true resistance to etomidate with this escape phenomenon. In the clinical situation of increased ACTH secretion, in Cushing’s disease, this most likely increases the availability of steroidogenic enzymes, shifting the balance to free enzyme available for steroid synthesis: an increase in etomidate should therefore block the higher concentration of steroidogenic enzymes. However, at these higher doses, sedation is induced. In the alternative scenario of patients with adrenal Cushing’s syndrome, or most patients with the ectopic ACTH syndrome, where there is no compensatory ACTH increase, they may be particularly sensitive to the blocking effect of etomidate resulting in adrenal insufficiency. It is a common feature of all enzyme inhibitors that there is a higher sensitivity of ACTH-independent Cushing’s syndrome to adrenal enzyme blockade. Thus, we stress the importance of a monitored environment such as a high dependency ward, with medical staff equipped with the capacity to support the airway if sedation does occur, and to monitor patients and their cortisol levels closely to rapidly respond to hypoadrenalinism. Dosages of etomidate therefore require individualisation, and lack of dose titration is a more likely explanation for failed adequate therapy in the literature with etomidate for Cushing’s disease (27).

Etomidate is highly plasma bound and is metabolised to inactive metabolites by hepatic and plasma esterases. The metabolites are inactive and excreted in the urine and to a lesser degree in bile. Elderly or ill patients require reduced doses as there is decreased protein binding and reduced renal clearance (8). Etomidate is unstable in water at physiological pH, and to increase solubility, it is most commonly available in the UK as a clear colourless liquid formulated as 0.2% in 35% propylene glycol. It is also available as a lipid emulsion, and formulations in cyclodextrins, starch-derived molecules that can form reversible inclusion complexes with lipophilic drugs, have also been developed (28). Propylene glycol is a solvent used in many topical, oral and injectable medications. A side effect of the most commonly available propylene glycol preparation vehicle is thrombophlebitis and pain on injection in 25% of patients (29), which is considerably reduced with the lipid preparation (30). Haemolysis has been recorded due to the high osmolality of the preparation of etomidate in propylene glycol compared with the lipid formulation (31). Propylene glycol is associated with nephrotoxicity due to proximal renal tubular injury and lactic acidosis at high doses (32). Krakoff et al. reported the prolonged use of etomidate for over 5 months without haemolysis, worsening nephrotoxicity or metabolic acidosis, and many of the case reports for the treatment of hypercortisolaemia do not comment on this being a significant issue. The World Health Organization recommends a daily maximal dose of 25 mg/kg of propylene glycol to decrease the possibility of toxicity (6). Care with dosing to ensure appropriate margins of safety is therefore important. Ideally, the lipid formulation would be the preferred formulation as it avoids the propylene glycol vehicle side effects. Finally, other potential adverse effects from the etomidate include myoclonus, nausea, vomiting and dystonic reactions in up to one-third of patients at anaesthetic dosages (33).

Clinical recommendations
A consensus statement on the treatment of ACTH-dependent Cushing’s syndrome comprising leading endocrinologists, other clinicians and neurosurgeons with expertise in the management of ACTH-dependent Cushing’s syndrome was published in 2008 (1). This included a recommendation for the use of etomidate where rapid control of cortisol levels is required and oral therapy is problematic. In practice, etomidate is a safe and effective drug for the control of hypercortisolaemia in a patient requiring parenteral therapy. A highly co-ordinated multidisciplinary approach is, however, necessary for the management of unwell hypercortisolaemic patients, as this group has complex problems beyond the daily ward scope of medical and nursing staff. The clinical setting of an intensive care or high dependency unit is therefore recommended for close monitoring of the patient’s response to therapy, supported by a highly co-ordinated multidisciplinary team.

Table 2: Treatment of hypercortisolism with etomidate recommendations.

<table>
<thead>
<tr>
<th>Etomidate infusion rate options</th>
<th>Blockade</th>
<th>Target cortisol level</th>
<th>Biochemical monitoring</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.04–0.05 m/kg per h = 2.5–3.0 mg/h</td>
<td>Partial</td>
<td>Titrated to serum cortisol 500–800 nmol/l in physiologically stressed patient, 150–300 nmol/l in non-physiologically stressed patient</td>
<td>Potassium level</td>
<td>Sedation scoring initially every 2 h then every 12 h after first 24 h</td>
</tr>
<tr>
<td>0.5–1.0 mg/h</td>
<td>Complete (will need steroid replacement)</td>
<td>&lt;150 nmol/l</td>
<td>Cortisol level</td>
<td>Sedation scoring initially every 2 h then every 12 h</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Potassium level</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Cortisol level</td>
<td></td>
</tr>
</tbody>
</table>
patient and biochemical testing monitoring, particularly for serum cortisol and potassium levels and the documentation of the level of sedation.

Intravenous low-dose etomidate infusion rates for the treatment of hypercortisolism are 0.04–0.05 mg/kg per h, thus equating to ~2.5–3 mg/h with dose titration according to serum cortisol. Based on etomidate’s pharmacokinetics, cortisol levels fall within 12–24 h. Frequent monitoring is necessary for serum cortisol levels to achieve either complete or partial blockade and to prevent hypoadrenalism. Intravenous hydrocortisone at 0.5–1 mg/h is required if complete rather than partial blockade is desired (‘block and replace’) and is often more convenient than frequently altering the etomidate infusion rate to achieve only partial blockade. Nevertheless, both approaches may be considered as valid. The target serum cortisol based on mean 24-h cortisol levels in patients in an intensive care setting is 500–800 nmol/l (25). This is higher than the non-physiologically stressed individual in a non-acute setting in which the accepted range for serum cortisol is 150–300 nmol/l (34). Clearly, the level aimed for depends on the clinical context and will need to be carefully considered in special situations, such as severe sepsis. Our own approach is always to take into account the serum cortisol level that would be expected in a given clinical context in the absence of Cushing’s syndrome (Table 2).

Other considerations when using etomidate include access and minimisation of thrombophlebitis with the transport vehicle. Given the monitored clinical setting, particularly where patients are generally unwell and they are likely to require multiple i.v. therapies, central venous access is most appropriate when using the propylene glycol preparation. Although etomidate is degraded into inactive metabolites by hepatic enzymes and plasma esterases, it rarely causes issues with significant hepatotoxicity. Etomidate has a plasma half-life of 3–5 h. Dose adjustment in renal failure should be made, as most etomidate is usually protein bound, and in the context of renal failure, there is therefore an increase in the free etomidate (6). Etomidate is a safe drug, with a 30-fold difference between the lethal and effective dose at the higher perceived as prejudicing the impartiality of the review reported.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the review reported.

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