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Continuous Etomidate Infusion for the Management of Severe Cushing Syndrome: Validation of a Standard Protocol

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Objective: Demonstrate the safety and efficacy of a standardized intravenous etomidate infusion protocol in normalizing cortisol levels in patients with severe and life-threatening hypercortisolism.

Methods: A retrospective case series of seven patients representing nine episodes of severe hypercortisolism at two large academic medical centers was conducted. Patients were included in this series if they received an etomidate infusion for the treatment of severe and life-threatening hypercortisolism. The etomidate infusion was administered via a newly developed protocol designed to safely reduce cortisol levels until more long-term medical or definitive surgical therapy could be instituted.

Results: Seven patients representing nine episodes received etomidate treatment. In eight of nine episodes of therapy, rapid control of hypercortisolemia was achieved, generally defined as a serum cortisol level of 10 to 20 μg/dL. Patients with a median baseline cortisol of 105 μg/dL (range, 32 to 245 μg/dL) achieved a median nadir serum cortisol of 15.8 μg/dL (range, 6.9 to 27 μg/dL) after a median of 38 hours (range, 26 to 134 hours).

Conclusions: A standardized continuous intravenous etomidate infusion protocol is a safe and effective means of achieving a serum cortisol level of 10 to 20 μg/dL in patients with severe hypercortisolemia.

Endogenous hypercortisolism (Cushing syndrome) is a well-known endocrinopathy whose clinical manifestations include many metabolic disorders (obesity, hypertension, diabetes, and osteoporosis) as well as neurocognitive and neuropsychiatric consequences [1]. Endogenous Cushing syndrome may be the result of an ACTH-secreting pituitary (Cushing disease), nonpituitary (ectopic) tumor, or autonomous cortisol production from adrenal glands [2]. Most patients with Cushing syndrome present with an indolent course over several years before the clinical and biochemical diagnosis is considered and established [3].

Abbreviation: RASS, Richmond Agitation-Sedation Scale.

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It is less appreciated that Cushing syndrome may present as an endocrine emergency because of the prodigious and often rapid onset of hypercortisolism, with very serious and life-threatening metabolic, infectious, and neuropsychiatric sequela. Most of these patients have an ectopic ACTH-secreting tumor; the rapid control of severe cortisol excess is mandatory and may be life-saving [4].

Medical therapy for severe hypercortisolemia is challenging and options are limited. Inhibition of adrenal steroidogenesis and direct antagonism of glucocorticoid receptors have been used in patients with Cushing syndrome. The most widely used adrenostatic agents, ketoconazole and metyrapone, normalize cortisol secretion in only 50% of patients with Cushing disease [5]. In addition, "serious hepatotoxicity, including cases with a fatal outcome or requiring liver transplantation has occurred with the use of oral ketoconazole" [6], thus limiting its use in many severely ill patients, whereas metyrapone is difficult to acquire in the United States. Although mifepristone, a glucocorticoid receptor antagonist, ameliorates the signs and symptoms of cortisol excess, particularly hyperglycemia, it has not been extensively studied in critically ill patients with severe hypercortisolemia [7].

Etomidate, an imidazole derivative similar to ketoconazole, is an intravenous hypnotic nonbarbiturate induction agent often used for intubation. After its introduction in the 1970s, etomidate was shown to substantially and rapidly decrease cortisol secretion [8, 9]. Subsequently, it was discovered that etomidate decreases steroidogenesis by inhibiting not only side chain cleavage enzyme but also 11β-hydroxylase, an enzyme that catalyzes the production of cortisol from its immediate precursor, 11-deoxycortisol [10]. Accordingly, reports of the successful use of etomidate to rapidly control severe hypercortisolemia emerged in the late 1980s [11]. Since then, most reports have been isolated case studies, with <20 total patients reported in the literature [12].

Here we report a standardized intravenous etomidate protocol from our institutions for the control of severe hypercortisolemia that was used in nine separate episodes (seven patients with severe Cushing syndrome, of whom two had two separate episodes of etomidate infusion). This protocol should help clinicians manage patients with severe metabolic and neuropsychiatric consequences of prodigious hypercortisolemia and serve as a bridge to more long-term medical or definitive surgical therapy.

1. Materials and Methods

This is a descriptive retrospective analysis of patients who were admitted to Froedtert Hospital in Milwaukee, Wisconsin, or NorthShore University Health System, Evanston, Illinois, and were initiated on a standardized intravenous etomidate protocol for the control of severe hypercortisolemia. The protocol was developed by the surgical intensive care clinical pharmacists in collaboration with endocrinologists and surgeons. Its development was based on the interpretation of published case reports and their understanding of pharmacokinetic and pharmacodynamic principles. At the time of therapy, this protocol was not approved by the institutions' Pharmacy, Nutrition, and Therapeutic Committees, but it existed as a newly developed departmental protocol (Fig. 1). Patients were included if they received the etomidate infusion for treatment of hypercortisolism between January 1, 2012, and December 31, 2015. Patients were to be excluded if they were <18 years of age or pregnant, although no patients were ultimately excluded for either of these reasons. This retrospective review was approved by the institutional review boards of Froedtert Hospital and the Medical College of Wisconsin and of NorthShore University Health System.

In preparation for etomidate infusion, all patients were admitted to the intensive care unit, where close metabolic, hemodynamic, respiratory, and neurologic monitoring was initiated. Before treatment with etomidate, the following laboratory parameters were obtained: serum basic chemistry (sodium, potassium, chloride, urea nitrogen, creatinine, bicarbonate, calcium), cortisol, and ACTH. In addition, baseline blood pressure, heart rate, respiratory rate, and level of sedation were ascertained. Level of sedation was assessed by using the Richmond Agitation-Sedation Scale (RASS) score, with a target RASS score of 0, which correlates with a patient who is alert and calm [13, 14].

Etomidate Infusion for Cushing's Syndrome Medication Guideline

Purpose: To provide guidance for administration of etomidate by intravenous infusion for the management of endogenous hypercortisolism.

Introduction: Endogenous Cushing's syndrome is caused by failure of the normal negative feedback pathway of the hypothalamo-pituitary-adrenal axis in response to excessive glucocorticoid production. Etomidate inhibits 11 β-hydroxylase, a cytochrome P450-dependent adrenal enzyme involved in steroidogenesis, thereby lowering serum cortisol levels.

Restrictions: Endocrinology

Froedtert Indication(s): Endogenous hypercortisolemia in patients who are intolerant to, refractory to, or have a contraindication to conventional oral therapy

General Considerations

- Etomidate has a plasma half-life of 3-5 hours[1]
- Etomidate is highly plasma bound and is metabolized to inactive metabolites by hepatic and plasma esterases[1]
- Control of severe hypercortisolism has been achieved with etomidate infusion rates of 0.1 mg/kg/hr or lower, which is less than infusion rates utilized for sedation[2]
- Serum cortisol levels fall within 12-24 hours based on etomidate's pharmacokinetics[1]
- Administer the etomidate infusion in an intensive care unit with the ability for close monitoring and capacity to support the patient's airway if sedation occurs
- Etomidate for sedation has been typically at an initial induction anesthetic bolus of 0.03 mg/kg followed by a continuous infusion of 0.3 mg/kg/hr to maintain sedation[1]

Cortisol Goal

- The desired cortisol level depends on the clinical situation and should take into consideration the serum cortisol level that would be expected in the given clinical scenario in the absences of Cushing's syndrome
  - Normal physiologic cortisol levels are considered to be 5-25 mcg/dL at 8:00 AM and 5-15 mcg/dL from noon to 8:00 PM[3]
  - Cortisol levels of 15-30 mcg/dL have been associated with the stress of critical illness[4-5]
  - A consensus has not been established for cortisol goal (while on cortisol- suppression drug therapy) for Cushing's syndrome[6,7]
- The goal cortisol level is generally 10-20 mcg/dL, but may be specified by endocrinology or managing physician

Dosing

- Give etomidate 5 mg IV bolus once over 30 to 60 seconds
- Start etomidate infusion rate at 0.02 mg/kg/hr
- Measure serum cortisol every 6 hours
- Maintain infusion rate if cortisol is trending in the desired direction
- Increase or decrease infusion rate in increments of 0.01 to 0.02 mg/kg/hr to achieve desired cortisol level
- Do not titrate infusion rate more frequently than every 6 hours
- Maximum infusion rate is 0.3 mg/kg/hr[7]

Figure 1. Etomidate infusion protocol.

The etomidate infusion was formulated to a concentration of 1 mg/mL (etomidate 40 mg per 40 mL dextrose 5% in water). At the time of our first treatment, no intravenous solution compatibility or stability data were available for etomidate. Because of the low starting dose and resultant infusion flow rate that would be needed, it was necessary to dilute the

Etomidate Infusion for Cushing's Syndrome

Dose Adjustments

- Elderly or critically ill patients
  - May require reduced doses due to decreased protein binding and reduced renal clearance[8]
- Renal impairment
  - No dosage adjustment provided in manufacturer's labeling
  - May require reduced dose due to decreased protein binding and therefore an increased free concentration of etomidate[9]
- Hepatic impairment
  - No dosage adjustment provided in manufacturer's labeling - use with caution

Adverse Effects

- Sedation
  - Higher infusion rates (0.3 mg/kg/hr) are associated with sedation[10]
  - If mild sedation occurs (RASS of -1 to -2), decrease infusion rate in increments of 0.02 mg/kg/hr until patient becomes alert
  - If moderate to deep sedation occurs (RASS of -3 to -5), discontinue the etomidate infusion and consider alternative therapies or re-initiating the etomidate infusion at a lower dose
- Propylene Glycol
  - Etomidate solutions are available as 2 mg/mL in 35% v/v propylene glycol
  - Side effects commonly associated with propylene glycol preparations are thrombophlebitis and pain upon injection (25%); consider infusion via central line[11]
  - High doses of propylene glycol can cause toxicity and result in acute renal failure and anion gap metabolic acidosis[12]
  - To decrease the possibility of toxicity the World Health Organization recommends a daily maximal dose of 25 mg/kg of propylene glycol[9]
  - Immediately discontinue the etomidate infusion if any signs of propylene glycol toxicity occurs
- Other potential adverse effects
  - Sedative doses have caused nausea (>10%), vomiting (>10%), myoclonus (33%) and dystonic reactions
  - Hemodynamic changes (hypertension, hypotension, tachycardia, bradycardia) is a rare (<1%) but potentially serious adverse effect of etomidate
  - Data are lacking on clinically significant drug interactions

Monitoring

- Serum cortisol every 6 hours
- Richmond Agitation Sedation Scale (RASS) at least every 2 hours for the first 24 hours then every 8 hours
- Serum basic metabolic panel (BMP) daily
- Blood pressure and heart rate every 8 hours
- Monitor for signs of propylene glycol toxicity such as acute renal failure, lactic acidosis, and osmol gap

Other Considerations:
The acquisition of oral therapeutic alternatives may take a few days; plan accordingly and notify the pharmacist as soon as possible.

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Figure 1. (Continued)

etomidate. Given the concerns of diluting this relatively insoluble lipophilic medication, we chose to dilute the 2-mg/mL product in a 1:1 ratio with dextrose 5% in water, in EXCEL® IV Containers (B. Braun Medical Inc., Bethlehem, PA). This chosen method was based on our well-documented preparation of a pharmaceutically similar agent, lorazepam for infusion. Lorazepam injection is a water-insoluble drug that is similarly solubilized with propylene glycol. To further safeguard against risk for possible precipitation, similar to lorazepam

Etomidate Infusion for Cushing's Syndrome

References:

1. Preda VA, Sen J, Karavitaki N, Grossman AB. Etomidate in the management of hypercortisolaemia in Cushing's syndrome: a review. *Eur J Endocrinol*. 2012;167(2):137-143.
2. Schulte HM, Benker G, Reinwein D, Sippell WG & Allolio B. Infusion of low dose etomidate: correction of hypercortisolemia in patients with Cushing's syndrome and dose–response relationship in normal subjects. *J Clin Endocrinol Metab*. 1990;70:1426–1430.
3. Molina P. Endocrine Physiology. 3rd. The McGraw-Hill Companies Inc; 2010.
4. Drucker D, Shandling M. Variable adrenocortical function in acute medical illness. *Crit Care Med*. 1985;13:477–479.
5. Reincke M, Allolio B, Wurth G, Winkelmann W. The hypothalamic-pituitary-adrenal axis in critical illness: response to dexamethasone and corticotropin-releasing hormone. *J Clin Endocrinol Metab*. 1993;77:151–156.
6. Trainer PJ, Eastment C, Grossman AB, Wheeler MJ, Perry L, Besser GM. The relationship between cortisol production rate and serial serum cortisol estimation in patients on medical therapy for Cushing's syndrome. *Clin Endocrinol (Oxf)*. 1993;39(4):441-443.
7. Biller BM, Grossman AB, Stewart PM, et al. Treatment of adrenocorticotropin-dependent Cushing's syndrome: a consensus statement. *J Clin Endocrinol Metab*. 2008;93(7):2454-2462.
8. Forman SA. Clinical and molecular pharmacology of etomidate. *Anesthesiology*. 2011;114:695–707.
9. Krakoff J, Koch CA, Calis KA, Alexander RH, Nieman LK. Use of a parenteral propylene glycol-containing etomidate preparation for the long-term management of ectopic Cushing's syndrome. *J Clin Endocrinol Metab*. 2001;86:4104–4108.
10. Allolio B, Schulte HM, Kaulen D, Reincke M, Jaursch-Hancke C, Winkelmann W. Nonhypnotic low-dose etomidate for rapid correction of hypercortisolaemia in Cushing's syndrome. *Klin Wochenschr*. 1988;66:361–364.
11. Zacharias M, Clarke RS, Dundee JW, Johnston SB. Venous sequelae following etomidate. *Br J Anaesth*. 1979;51:779–783.
12. Yorgin PD, Theodorou AA, Al-Uzri A, Davenport K, Boyer-Hassen LV, Johnson MI. Propylene glycol-induced proximal renal tubular cell injury. *Am J Kidney Dis*. 1997;30:134–139.

Figure 1. (Continued)

infusion administration, the etomidate infusion was given through a 0.2-micron inline filter. Given the lack of evidence for long-term stability of this solution, we assigned the prepared solution a 24-hour expiration. Following the baseline patient assessments, an optional 5-mg IV bolus of etomidate was administered over 2 to 3 minutes and a continuous infusion of etomidate was initiated at a rate of 0.02 to 0.04 mg/kg/h. During the etomidate infusion, with an abundance of caution, serum cortisol was measured at least every 6 hours, along with basic chemistry. All measurements of cortisol were performed with the Roche Elecsys® Cortisol I assay (Roche Diagnostics, Risch-Rotkreuz, Switzerland). This assay has a 4.1% cross-reactivity with 11-deoxycortisol, which increases with etomidate use. ACTH was measured by using an electrochemiluminescence immunoassay manufactured by Roche Diagnostics, Inc. (Indianapolis, IN) performed in the Cobas e or Modular system. The detectable range for this assay is 1.0 to 2000 pg/mL.

Vital signs were taken hourly, and sedation assessments were conducted every 4 hours per standard of care for patients receiving a continuous infusion sedative. On the basis of the absolute values and the rate of change in serum cortisol, the etomidate infusion was titrated in increments of 0.01 to 0.02 mg/kg/h to target a default cortisol concentration of 10 to 20 μg/dL. A goal cortisol of 10 to 20 μg/dL was chosen because it is slightly above the "normal" cortisol level and in the range expected for patients with substantial physiological stress. The goal cortisol also allows for a small increase in cortisol that can be attributed to cross-reactivity of other steroid metabolites (such as 11-deoxycortisol) that increase with etomidate use. The goal, as determined by the attending endocrinologist in collaboration with the surgeon in surgical cases, was to achieve the target cortisol concentration during a 24- to 48-hour period. Once the target cortisol concentration was achieved, the etomidate infusion was titrated to maintain serum cortisol in the desired range until long-term medical or definitive surgical treatment could be initiated.

Rate of change of the serum cortisol concentration, time to achieve serum cortisol goal, and continuous infusion rate required to achieve and maintain cortisol in the target range were of particular interest.

2. Results

A. Clinical features

Seven patients representing nine distinct episodes of standardized intravenous etomidate infusion for the medical treatment of severe hypercortisolemia are described. Patient clinical

Table 1. Summary of Patient Demographic Characteristics

Episode	Diagnosis	Age/ Sex	Admission Diagnosis	Reason to Start Etomidate Therapy
1	Ectopic ACTH-producing tumor	73/F	Symptomatic Cushing syndrome, hypokalemia, hyperglycemia	Preoperative bilateral adrenalectomy
2	ACTH-secreting pituitary tumor with prior failed pituitary surgery	40/F	Hypercortisol-induced psychosis	Preoperative bilateral adrenalectomy; inoperable tumor with extensive cavernous sinus invasion
3	Ectopic ACTH-producing tumor	67/F	Metastatic cancer with perforated diverticulitis	Preoperative bilateral adrenalectomy
4	Ectopic ACTH-producing tumor	67/F	Metastatic cancer with perforated diverticulitis	Preoperative bilateral adrenalectomy
5	Ectopic ACTH-producing tumor	50/M	Symptomatic Cushing syndrome, hypokalemia, hypoxia	Await metyrapone
6	Ectopic ACTH-producing tumor	19/M	Thymic carcinoid resection	Preoperative thymic carcinoid resection
7	ACTH-secreting pituitary tumor	38/F	Petrosal sinus sampling	No enteral access due to ileus, holding long-term ketoconazole
8	Metastatic adrenal carcinoma	49/M	Shortness of breath	No enteral access during intubation, holding long-term metyrapone, mitotane; ketoconazole
9	Metastatic adrenal carcinoma	49/M	Shortness of breath	No enteral access during intubation, holding long-term metyrapone, mitotane; ketoconazole, pasireotide

(*Continued*)

features are reported in Table 1. The diagnosis of neoplastic hypercortisolism was confirmed by elevations of serum, urine, late-night salivary cortisol, and/or ACTH measurements. Etomidate was administered to reduce preoperative cortisol before surgery in five episodes. In three of these episodes, the patient ultimately underwent surgery, and in the other two episodes, both in the same patient, therapy was discontinued in pursuit of medical management as an alternative to surgery. Etomidate was eventually discontinued in this patient as hospice care was ultimately pursued. In three episodes, patients had previously received long-term oral therapy but acutely became unable to tolerate oral therapy; therefore, etomidate was used as temporary bridge therapy. Another patient received etomidate while awaiting a special order of metyrapone to arrive to pursue long-term medical management. Baseline cortisol was elevated in all patients (Table 1).

B. Dosing

All episodes were dosed per protocol, including initial dose and subsequent dose adjustments. Treatment began with an optional 5-mg intravenous bolus of etomidate. The bolus was at the discretion of the treating endocrinologist and based on desired rapidity of cortisol reduction. Starting dose was consistently 0.02 mg/kg/h, with the exception of one patient who had previously tolerated a higher infusion rate, in whom etomidate was reinitiated at 0.04 mg/kg/h. Serum cortisol levels were then measured every 6 hours. The infusion rate was maintained if the cortisol level was trending toward goal. If the cortisol level was not trending to goal, then the infusion rate was adjusted in increments of 0.01 to 0.02 mg/kg/h to achieve desired cortisol levels. The infusion rate was not up titrated more frequently than every 6 hours. A maximum allowed infusion rate was set at 0.3 mg/kg/h. This maximum infusion rate was not reached in any of the nine episodes. The maximum achieved etomidate infusion rate was identical to the infusion rate when goal cortisol levels were achieved in all episodes with a median of 0.081 mg/kg/h (range, 0.033 to 0.150 mg/kg/h). The infusion was continued for a median duration of 63.6 hours (range, 36.3 to 168.8 hours).

Table 1. Summary of Patient Demographic Characteristics (Continued)

Reason to Stop Etomidate Therapy	Baseline ACTH (pg/mL)	Baseline Cortisol (μg/dL)	Lowest Cortisol (μg/dL)	Cortisol Goal (μg/dL)	Time to Goal Cortisol (h)	Cortisol Reduction Rate (μg/dL /h)	Survival to Discontinuation of Infusion
Postoperative	134.0	101	15.1	10–20	94	0.92	Yes
Postoperative	93.5	32	10.6	10–20	26	0.82	Yes
Surgery aborted, ketoconazole and chemotherapy started	364.0	245	13.3	10–20	134	1.73	Yes
Surgery aborted in pursuit of hospice care	1002.0	192	53.6	10–20	33 (deceased)	4.20	No
Metyrapone started	362.0	197	18.2	10–20	36	4.97	No
Postoperative	559.4	59	16.5	10–20	29	0.81	Yes
Ileus resolved, resume long-term ketoconazole	27.7	32	6.9	10–20	33	0.78	Yes
Enteral access achieved following extubation, resume long-term metyrapone, mitotane; ketoconazole, start pasireotide	6.3	159	17.0	10–20	131	1.09	Yes
Palliative care due to high tumor burden	6.3	108	27.0	30–40	40	2.04	No

Abbreviations: F, female; M, male.

C. Efficacy

In eight of the nine episodes, the target cortisol concentration was <20 μg/dL (one episode targeted <40 μg/dL) and was achieved in all episodes except for one where the patient entered hospice care before achieving goal. Detailed results of cortisol dynamics on therapy are shown in Table 1. In the episodes where etomidate therapy reached completion, median baseline cortisol was 105 μg/dL (range, 32 to 245 μg/dL). It took a median of 38 hours (range, 26 to 134 hours) to achieve a median nadir serum cortisol of 15.8 μg/dL (range, 6.9 to 27 μg/dL). The median cortisol reduction rate was 1.09 μg/dL/h (range, 0.78 to 4.97 μg/dL/h), resulting in a median reduction in cortisol of 86.8 μg/dL (range, 19.8 to 179.6 μg/dL), or a median 80% reduction (range, 67% to 95%) (Fig. 2). The one patient who did not complete etomidate therapy was on a trajectory to do so before dying, representing one of the fastest rate reductions observed in this case series.

D. Safety

All patients tolerated their etomidate infusion well. In all but one episode, mentation was measured via the RASS. At baseline, seven patients had a RASS score of 0, which remained largely unchanged throughout the infusion. One episode who was admitted with hypercortisolemia-induced psychosis had a RASS score of −1 during the infusion and

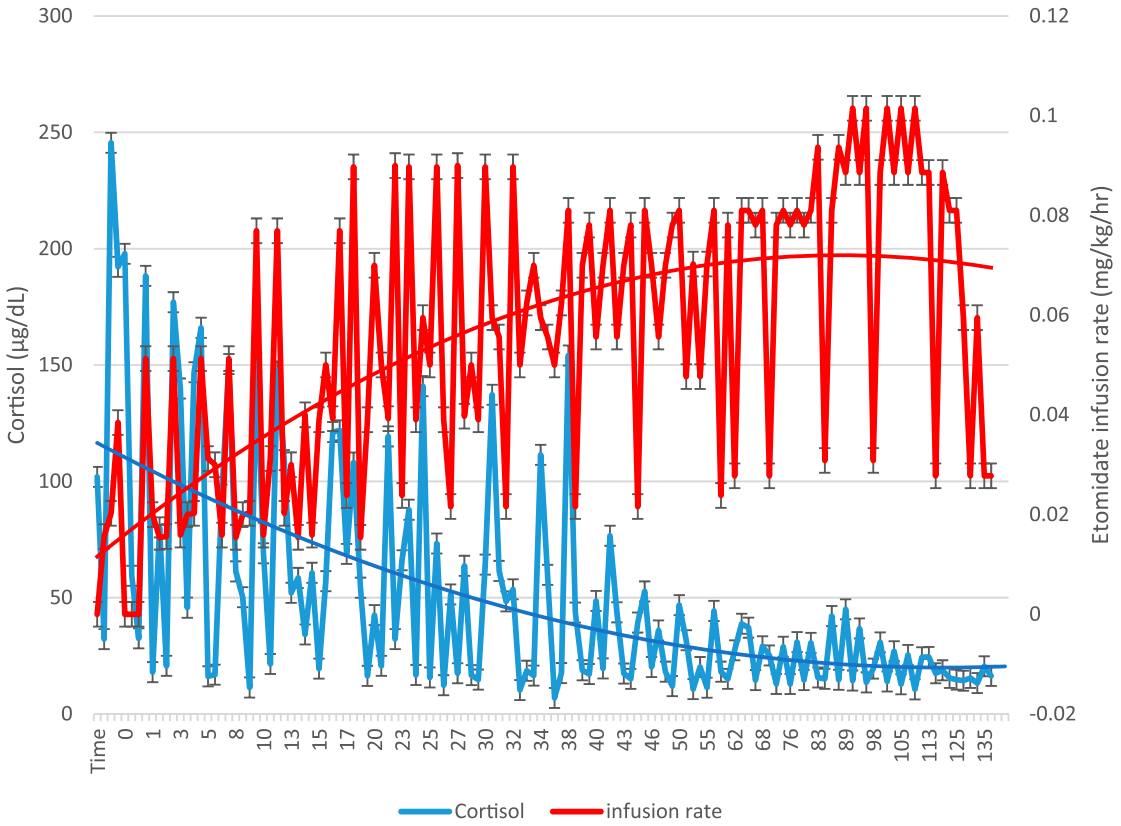

Figure 2. Plot of serum cortisol vs rate of etomidate infusion in seven of the nine episodes with available data.

improved to 0 upon termination of etomidate therapy. The one episode without documented RASS score revealed no mentation changes per physician and nursing progress notes. At no time throughout the etomidate infusion did any RASS score go < -1 or > 0, nor did a change in RASS score necessitate discontinuation of etomidate.

Patients did not experience any electrolyte abnormalities or substantial changes in renal function during the etomidate infusion, nor did they experience metabolic acidosis. Glucose control improved slightly overall from the beginning of therapy compared with discontinuation of therapy.

All episodes except one realized a gradual reduction in blood pressure, whereas the heart rate remained almost unchanged for all patients and did not correlate with changes in blood pressure. No patient experienced hypotension while receiving the infusion protocol.

Two episodes experienced nausea and vomiting toward the end of etomidate infusion (35 hours into a 38-hour infusion and 33 hours into a 36-hour infusion, respectively) and may be attributed to rapid reduction of cortisol levels, given a relative reduction of cortisol of 68% and 72%, respectively (cortisol of 10.3 µg/dL down from baseline level of 32.5 µg/dL and 53.6 µg/dL down from baseline level of 192.2 µg/dL). No patients required a dose adjustment as a result of adverse effects.

Cumulative median propylene glycol exposure was 90.3 g (range, 32 to 187 g) or 818 mg/kg (range, 284 to 1762 mg/kg) or 232 mg/kg/d (range, 112 to 328 mg/kg/d). No propylene glycol–related adverse effects, such as acidosis, intravascular hemolysis, altered mentation, seizure, hypoglycemia, or renal failure, were noted, although they were prospectively monitored for during the entire etomidate infusion.

3. Discussion

This report describes the implementation of a standardized continuous etomidate infusion protocol for the rapid and safe normalization of cortisol levels in patients with prodigious

hypercortisolism complicated by severe life-threatening metabolic and/or neuropsychiatric manifestations. A standardized protocol for etomidate infusion was used in nine separate episodes among seven patients with severe hypercortisolemia. For all eight episodes in which therapy was completed, the protocol-driven etomidate infusion achieved a target cortisol level < 20 μg/dL (goal < 40 μg/dL in one episode) within a median of 36 hours (Table 1). Patients with ACTH-producing neoplasms (pituitary or ectopic) and non–ACTH-dependent (metastatic adrenal cortical carcinoma) hypercortisolism benefited from therapy with a median reduction in cortisol of 91.5 μg/dL throughout the duration treatment. The etomidate infusion served as a bridge to bilateral adrenalectomy in three patients and removal of a thymic neuroendocrine carcinoma in another patient. None of the patients developed any evidence of sedation or mental status changes during infusion. In addition, safety monitoring showed no substantial changes in renal function or anion gap during the etomidate infusions (Table 2).

Failure to promptly decrease severe hypercortisolemia may result in life-threatening cortisol–related metabolic, infectious, and neuropsychiatric complications. Etomidate is widely available and can be easily used in an intensive care unit setting. It is also the only parenterally available agent that can achieve prompt control of severe cortisol excess. Unfortunately, few oral medications can provide such rapid control of severe hypercortisolemia. Corcuff *et al.* [15] reported the use of a combination of metyrapone and ketoconazole for correction of severe hypercortisolism in patients with ectopic ACTH or adrenocortical carcinoma. They demonstrated a substantial improvement in clinically relevant endpoints such as blood pressure, hypokalemia, and hyperglycemia within 1 week and 1 month after starting the steroidogenic inhibitors. Ketoconazole may be associated with substantial hepatotoxicity, and its use may be precluded in some patients with severe multisystem failure associated with severe cortisol excess. Metyrapone therapy is difficult to secure in the United States without preauthorization and may take several days to become available to pharmacists and clinicians. Mifepristone, a glucocorticoid receptor antagonist, is the only US Food and Drug Administration–approved oral medication for the treatment of hyperglycemia in patients with Cushing syndrome [7]. Although mifepristone may be effective in the management of patients with all forms of endogenous hypercortisolism, mifepristone has not been widely used in seriously ill patients with severe hypercortisolemia. The need for preauthorization prevents quick attainment of this therapy for acutely ill patients. Sides effects also complicate its use; many patients presenting with severe hypercortisolism have substantial hypokalemia, which may be worsened by the well-appreciated potassium-lowering effects of mifepristone. In addition, glucocorticoid receptor antagonism does not reduce serum cortisol, which makes the monitoring of its effectiveness nearly impossible in the short term in patients with severe hypercortisolemia. Given these factors, mifepristone is likely not an ideal agent in the setting of acute, severe Cushing syndrome.

Although doses of etomidate need to be individualized in each clinical situation, this protocol provides clinicians with a practical algorithm to control patients with severe hypercortisolism in an intensive care unit setting with minimal morbidity. In most patients, an intravenous bolus of 5 mg of etomidate may be a good starting point, followed by a starting infusion rate of 0.02 mg/kg/h with dose titration based on frequent cortisol determinations. Our protocol recommends the measurement of cortisol at 6-hour intervals. On the basis of our safety results, combined with other reports, it is reasonable to measure serum cortisol less frequently in some patients. Two of our patients experienced some nausea and vomiting toward the end of the etomidate infusion, possibly resulting from substantial and abrupt reduction in cortisol levels. One patient had a cortisol level as low as 10.3 μg/dL. It should be recognized that total cortisol measurements by means of immunoassay may overestimate the actual cortisol level [16]. Because etomidate inhibits 11β-hydroxylase, marked increases in the precursor of cortisol synthesis, 11-deoxycortisol, are expected. Many polyclonal antibody–derived cortisol immunoassays will have substantial cross-reactivity with 11-deoxycortisol, resulting in an overestimation of the actual cortisol level. The use of more specific cortisol assays, such as a monoclonal antibody cortisol immunoassay or tandem mass

Table 2. Safety Monitoring

Variable	Serum Sodium (mmol/L)	Serum Potassium (mmol/L)	Serum Chloride (mmol/L)	Serum HCO_3 (mmol/L)	Serum BUN (mg/dL)	Serum Cr (mg/dL)	Serum Glucose (mg/dL)
Initiation of etomidate	143 (134–146)	3.4 (2.9–4.0)	103 (98–108)	29 (22–36)	19 (10–54)	0.86 (0.59–1.89)	168 (95–239)
End of etomidate	143 (137–147)	3.6 (3.3–4.6)	105 (97–109)	27 (24–30)	12 (5–65)	0.87 (0.74–2.21)	122 (73–178)

(*Continued*)

spectrometry, will provide more accurate and reliable measurements of cortisol with use of an etomidate infusion.

Etomidate is highly plasma-bound and metabolized to inactive metabolites in the liver, which are then excreted in the kidneys. Consequently, elderly patients, patients with low plasma proteins, and patients with impaired liver or renal function may require reduced doses. Etomidate is a clear colorless liquid formulated in propylene glycol. Propylene glycol is used as a solubilizing agent in many topical, oral, and injectable medications [17]. Propylene glycol has been associated with thrombophlebitis and pain on injection [18]. Etomidate with propylene glycol has also been reported to cause hemolysis [19]. Nephrotoxicity due to proximal renal tubular injury and lactic acidosis may occur at high doses of propylene glycol [20]. None of our patients experienced any observed propylene glycol–related adverse effects.

Some investigators have suggested high doses of etomidate infusion (0.1 to 1.0 mg/kg/h) for complete blockade of adrenal steroid biosynthesis (target cortisol < 5 μg/dL) and provide supplemental exogenous hydrocortisone—a "block and replace" strategy—as another alternative treatment strategy [12]. The use of a block and replace method is an option in severely ill patients but has the potential for increased side effects from higher doses of etomidate (and propylene glycol).

Several reports have been published on longer-term use of etomidate, up to 5.5 months of therapy [20, 21]. Nonetheless, it is not clear whether prolonged etomidate infusion is safe in most patients beyond 1 to 2 weeks. As such, on the basis of limited data, we currently recommend its use for no more than 7 to 10 days.

Our study has several limitations, including the small number of study participants and the lack of patients with hypercortisolism as a result of benign adrenal disease, making the generalizability of these data to that patient population unclear.

The failure of a consistent etomidate loading dose in all patients, and the wide variation in cortisol levels in the patients reported (although this wide variation in cortisol levels is certainly expected in patients with severe hypercortisolism) are also limitations. Although we could not clearly identify any advantage in achieving target cortisol levels more rapidly with a loading dose bolus injection of etomidate, we still recommend this therapy because it was well tolerated, was easily obtainable in the acute setting, and has been endorsed by others [12]. We strive to make dosing patient-specific by using weight-based dosing, which yielded successful outcomes in our cohort, but we acknowledge that doing so may add an opportunity for a calculation error. For institutions without a mechanism to mitigate calculation errors (*e.g.*, those without smart pump technology), it may be reasonable to avoid weight-based dosing because this approach has also demonstrated efficacy in other publications.

Additionally, none of our patients were treated with lipid a formulation of etomidate. Such a lipid formulation of etomidate (Etomidate-®Lipuro, B Braun, Melsungen, Germany) may be a therapeutic alternative to the conventional formulation of etomidate in some countries. Although it is believed to exert the same effects on cortisol metabolism, the lipid formulation may offer better tolerability with lower rates of thrombophlebitis and other propylene glycol–related toxicities because of its reduced concentration of propylene glycol. However, published reports of its use to treat hypercortisolemia are lacking, as are stability data for use as a continuous infusion.

Table 2. Safety Monitoring (Continued)

Serum Calcium (mg/dL)	Serum Magnesium (mg/dL)	Serum Phosphorus (mg/dL)	BP (mm Hg)	HR (beats/min)	Anion Gap (mmol/L)	RASS
8.9 (7.4–9.4)	2.0 (1.9–2.3)	3.3 (2.3–4.0)	156/99 (130/60–188/97)	87 (48–112)	11 (6–16)	0 (−1 to 0)
8.7 (6.9–9.5)	1.7 (1.3–2.1)	3.1 (1.9–5.2)	116/86 (96/54–163/77)	89 (82–132)	11 (8–14)	0 (−1 to 0)

Values are expressed as the median (range).
Abbreviations: BP, blood pressure; BUN, blood urea nitrogen; CR, creatinine; HR, heart rate.

Despite these limitations, the rarity of prodigious, life-threatening hypercortisolism, as well as the small reported number of patients with Cushing syndrome treated with etomidate, make this report and the creation of a standardized, validated protocol, with the cooperation of pharmacists and endocrinologists a valuable contribution to the management of these challenging patients.

4. Conclusion

In conclusion, our protocol-driven continuous etomidate infusion demonstrated rapid control of severe hypercortisolism secondary to neoplastic Cushing syndrome without any observed adverse side effects. This protocol should help guide clinical endocrinologists and pharmacists in the management of seriously ill patients with severe hypercortisolism as a bridge to long-term medical therapy or definitive surgical intervention.

Acknowledgments

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References and Notes

1. Findling JW, Raff H. Screening and diagnosis of Cushing's syndrome. *Endocrinol Metab Clin North Am*. 2005;**34**(2):385–402, ix–x.
2. Javorsky BR, Carroll TB, Findling JW. Differential diagnosis of Cushing's syndrome. In: Swearingen B, Biller BMK, eds. *Cushing's Disease*. New York: Springer; 2011:85–106.
3. Raff H, Findling JW. A physiologic approach to diagnosis of the Cushing syndrome. *Ann Intern Med*. 2003;**138**(12):980–991.
4. Nieman LK, Biller BMK, Findling JW, Murad MH, Newell-Price J, Savage MO, Tabarin A; Endocrine Society. Treatment of Cushing's syndrome: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab*. 2015;**100**(8):2807–2831.
5. Feelders RA, Hofland LJ, de Herder WW. Medical treatment of Cushing's syndrome: adrenal-blocking drugs and ketaconazole. *Neuroendocrinology*. 2010;**92**(Suppl 1):111–115.
6. Ketoconazole [package insert]. Titusville, NJ: Janssen Pharmaceuticals, Inc.; 2013.
7. Fleseriu M, Biller BMK, Findling JW, Molitch ME, Schteingart DE, Gross C; SEISMIC Study Investigators. Mifepristone, a glucocorticoid receptor antagonist, produces clinical and metabolic benefits in patients with Cushing's syndrome. *J Clin Endocrinol Metab*. 2012;**97**(6):2039–2049.
8. Gooding JM, Corssen G. Etomidate: an ultrashort-acting nonbarbiturate agent for anesthesia induction. *Anesth Analg*. 1976;**55**(2):286–289.
9. Wagner RL, White PF, Kan PB, Rosenthal MH, Feldman D. Inhibition of adrenal steroidogenesis by the anesthetic etomidate. *N Engl J Med*. 1984;**310**(22):1415–1421.
10. Duthie DJR, Fraser R, Nimmo WS. Effect of induction of anaesthesia with etomidate on corticosteroid synthesis in man. *Br J Anaesth*. 1985;**57**(2):156–159.
11. Schulte HM, Benker G, Reinwein D, Sippell WG, Allolio B. Infusion of low dose etomidate: correction of hypercortisolemia in patients with Cushing's syndrome and dose-response relationship in normal subjects. *J Clin Endocrinol Metab*. 1990;**70**(5):1426–1430.

12. Preda VA, Sen J, Karavitaki N, Grossman AB. Etomidate in the management of hypercortisolaemia in Cushing's syndrome: a review. *Eur J Endocrinol*. 2012;**167**(2):137–143.
13. Sessler CN, Gosnell MS, Grap MJ, Brophy GM, O'Neal PV, Keane KA, Tesoro EP, Elswick RK. The Richmond Agitation-Sedation Scale: validity and reliability in adult intensive care unit patients. *Am J Respir Crit Care Med*. 2002;**166**(10):1338–1344.
14. Ely EW, Truman B, Shintani A, Thomason JW, Wheeler AP, Gordon S, Francis J, Speroff T, Gautam S, Margolin R, Sessler CN, Dittus RS, Bernard GR. Monitoring sedation status over time in ICU patients: reliability and validity of the Richmond Agitation-Sedation Scale (RASS). *JAMA*. 2003;**289**(22): 2983–2991.
15. Corcuff JB, Young J, Masquefa-Giraud P, Chanson P, Baudin E, Tabarin A. Rapid control of severe neoplastic hypercortisolism with metyrapone and ketoconazole. *Eur J Endocrinol*. 2015;**172**(4): 473–481.
16. Daniel E, Newell-Price JDC. Therapy of endocrine disease: steroidogenesis enzyme inhibitors in Cushing's syndrome. *Eur J Endocrinol*. 2015;**172**(6):R263–R280.
17. Zacharias M, Clarke RS, Dundee JW, Johnston SB. Venous sequelae following etomidate. *Br J Anaesth*. 1979;**51**(8):779–783.
18. Doenicke A, Roizen MF, Hoernecke R, Mayer M, Ostwald P, Foss J. Haemolysis after etomidate: comparison of propylene glycol and lipid formulations. *Br J Anaesth*. 1997;**79**(3):386–388.
19. Yorgin PD, Theodorou AA, Al-Uzri A, Davenport K, Boyer-Hassen LV, Johnson MI. Propylene glycol-induced proximal renal tubular cell injury. *Am J Kidney Dis*. 1997;**30**(1):134–139.
20. Krakoff J, Koch CA, Calis KA, Alexander RH, Nieman LK. Use of a parenteral propylene glycol-containing etomidate preparation for the long-term management of ectopic Cushing's syndrome. *J Clin Endocrinol Metab*. 2001;**86**(9):4104–4108.
21. Drake WM, Perry LA, Hinds CJ, Lowe DG, Reznek RH, Besser GM. Emergency and prolonged use of intravenous etomidate to control hypercortisolemia in a patient with Cushing's syndrome and peritonitis. *J Clin Endocrinol Metab*. 1998;**83**(10):3542–3544.