0021-972X/98/$03.00/0
Journal of Clinical Endocrinology and Metabolism

Vol. 83, No. 10
Printed in U.S.A.

Emergency and Prolonged Use of Intravenous Etomidate to Control Hypercortisolemia in a Patient with Cushing's Syndrome and Peritonitis

W. M. DRAKE, L. A. PERRY, C. J. HINDS, D. G. LOWE, R. H. REZNEK, AND G. M. BESSER

Departments of Endocrinology, Clinical Biochemistry (L.A.P.), Intensive Care (C.J.H.), Pathology (D.G.L.), and Diagnostic Imaging (R.H.R.), St. Bartholomew's Hospital, London, United Kingdom EC1A 7BE

ABSTRACT

We report the emergency and prolonged use of etomidate to control circulating cortisol levels in a patient with Cushing's syndrome secondary to ectopic ACTH production from a pancreatic islet cell tumor. Duodenal perforation and peritonitis complicated an episode of salmonella septicemia, precluding the use of conventional oral medical adrenolytic therapy. Endogenous cortisol secretion was abolished by parenteral etomidate, allowing serum cortisol levels to be controlled with an iv infusion of hydrocortisone over an 8-week period in intensive care before definitive pancreatic surgery. (*J Clin Endocrinol Metab* **83:** 3542–3544, 1998)

THE USE OF oral metyrapone (1) and ketoconazole (2) is well established in the medical management of hypercortisolemia due to Cushing's syndrome. Neither drug is available in parenteral form, presenting a particular problem when Cushing's syndrome coexists with an emergency situation that precludes oral adrenolytic therapy. We report the successful use of iv etomidate to control hypercortisolemia over an 8-week period in a patient with severe Cushing's syndrome secondary to ectopic production of ACTH from a pancreatic islet cell tumor who developed life-threatening peritonitis after a perforated duodenum.

Case Report

A 35-yr-old man presented to another hospital with a 4-month history of abdominal pain, diarrhea, and weight loss on a background of consumption of 50–60 U/week of alcohol. Ultrasound revealed an atrophic pancreas. He was prescribed opiate analgesia and pancreatic enzyme supplements with omeprazole for presumed alcohol-induced chronic pancreatitis and gastritis. Some clinical improvement followed.

A year later he developed severe abdominal pain sufficient to require hospitalization, at which time he was noted be Cushingoid. He was transferred to this hospital. On examination he was obviously Cushingoid, with thin skin, moon facies, and marked proximal myopathy. The spleen was palpable 4 cm below the costal margin, but there was no hepatomegaly or lymphadenopathy.

Investigations revealed a serum potassium level of 3.1 mmol/L and a bicarbonate level of 18 mmol/L, but electrolytes and liver function tests were otherwise normal. Cushing's syndrome was proved by loss of circadian variation of serum cortisol, a detectable sleeping midnight serum cortisol level, and lack of suppression of serum cortisol after dexamethasone administration (0.5 or 2 mg, every 6 h for 48 h). The mean serum cortisol level (calculated from the average of five samples taken through the day) was 1442 nmol/L (52.2 μg/dL). There was no rise in either serum cortisol or ACTH after iv injection of 100 μg human CRH or 10 μg desmopressin (3). A diagnosis of ectopic ACTH syndrome was made.

Computed tomography and magnetic resonance imaging scanning showed a 7 × 6-cm enhancing mass lesion in the tail of the pancreas, encasing the splenic artery and obliterating the splenic vein. Gastric rugal thickening, bilateral smooth adrenal hyperplasia, and a large perirenal pancreatic pseudocyst were noted.

Oral ketoconazole (200 mg, every 8 h) and later, in addition, metyrapone 250 mg, every 8 h) were started to control circulating cortisol levels before pancreatic surgery. During weekend leave the patient ate a restaurant meal and 2 days later, became unwell with fever and tachycardia. *Salmonella enteritidis* was grown from blood cultures. Parenteral antibiotics were started, but he developed peritonitis. At laparotomy a ruptured infected pancreatic pseudocyst and perforation of the third part of the duodenum were noted and repaired. He was transferred to the intensive care unit, where he spent 58 days. All oral medication, including ketoconazole and metyrapone, had to be stopped. Recurrent intraabdominal abscesses were drained under ultrasound guidance and treated with antibiotics according to laboratory sensitivity studies. Upper gastrointestinal hemorrhage necessitated repeated transfusions of blood and fresh frozen plasma. High dose omeprazole (80 mg daily) was given iv. Octreotide (600 μg daily) was administered by continuous sc infusion to inhibit pancreatic exocrine and endocrine secretion. GH (24 U daily) was given for its anabolic effects. Mean serum cortisol levels at this time were around 1200 nmol/L.

Endogenous cortisol secretion, which had been uninfluenced by octreotide, was completely inhibited with a low dose iv etomidate infusion (2.5 mg/h). Steroid replacement was given, initially with im dexamethasone (to allow endogenous cortisol levels to be monitored) and subsequently with a continuous iv hydrocortisone infusion (1–3 mg/h; Fig. 1). After 6 days the dose of etomidate was reduced to 1.2 mg/h, with no increase in serum cortisol levels. This regimen and response were continued for the 8 weeks that he spent on artificial ventilation. Subsequently, etomidate was discontinued, and enteral nutrition and oral medication recommenced, as before.

Seven weeks later he underwent laparotomy and resection of a 7.5 × 6 × 6-cm mass in the mid/distal body and tail of the pancreas together with three adjacent lymph nodes. Histology showed an islet cell tumor staining positively for gastrin and ACTH. Tumor was evident in one of the three resected lymph nodes and had invaded the splenic vein. Postoperatively, after the withdrawal of perioperative steroid cover, two

Received February 11, 1998. Revision received June 12, 1998. Accepted June 22, 1998.

Address all correspondence and requests for reprints to: Dr. W. M. Drake, Department of Endocrinology, St. Bartholomew's Hospital, West Smithfield, London, United Kingdom EC1A 7BE. E-mail: w.m.drake@mds.qmw.ac.uk.

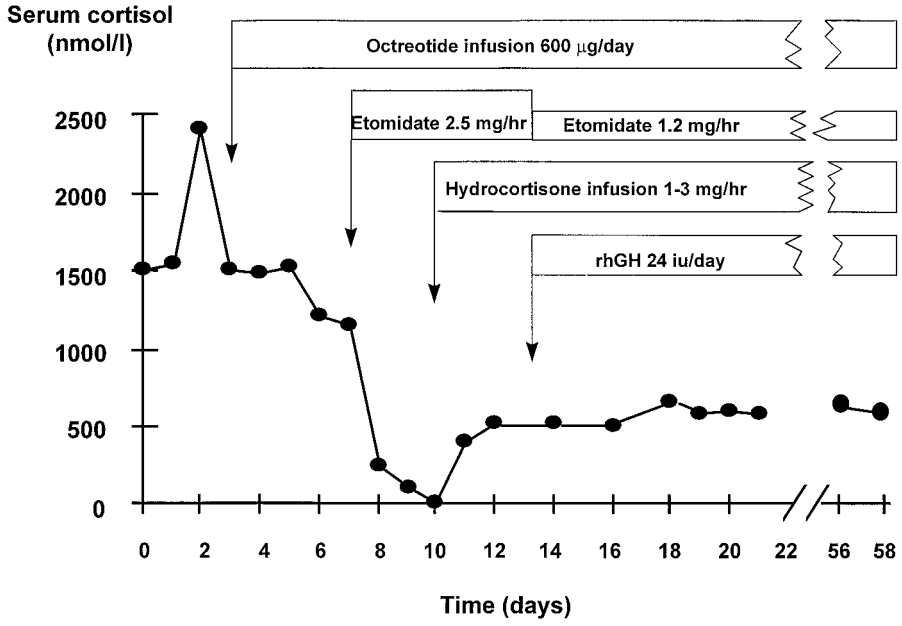

FIG. 1. Serum cortisol at 0900 h on successive days before and for 8 weeks after the commencement of iv etomidate with, subsequently, the addition of hydrocortisone. Dexamethasone (0.5 mg, every 6 h) was given between days 9–11. 27.6 nmol/L serum cortisol = 1 μg/dL.

consecutive 0900 h serum cortisol measurements were below 50 nmol/L, suggesting effective removal of the ectopic source of ACTH.

Materials and Methods

Serum cortisol was assayed using the Bayer Immuno-1 autoanalyzer (Bayer Corp., Newbury, Berkshire, UK). Serum 11-deoxycortisol and 17α-hydroxyprogesterone levels were measured using in-house RIAs (the latter requiring an initial ether extraction step) (4, 5). Plasma ACTH was quantitated using an in-house RIA after an initial extraction process (6). Serum dehydroepiandrosterone sulfate (DHEAS) levels were measured using a RIA kit purchased from Hammersmith Hospital (London, UK). Plasma gastrin samples were assayed at the supraregional service laboratory at Hammersmith Hospital.

Discussion

The use of metyrapone (1) and ketoconazole (2) for the correction of hypercortisolemia in Cushing's syndrome is well established. They are often used preoperatively, once the precise etiology is established, to prepare patients for surgery and promote improved tissue healing. Neither drug, however, is available in parenteral form, presenting a significant management problem when Cushing's syndrome coexists with an emergency situation that precludes the use of oral therapy. Bilateral adrenalectomy remains an option if serum cortisol levels cannot be controlled medically, but in such circumstances, this and other surgical procedures carry a high peri- and postoperative mortality. In our patient, serum cortisol levels had just started to fall during treatment with ketoconazole and metyrapone, but oral therapy had to be stopped because of peritonitis. After the original report of Allolio *et al.* (7), we used low, subhypnotic iv doses of the anesthetic agent etomidate to inhibit completely endogenous cortisol production, such that serum cortisol was less than 50 nmol/L by 48 h. Glucocorticoid replacement therapy was provided with im dexamethasone until complete inhibition was demonstrated, and then a continuous iv hydrocortisone infusion was used at a dose that guaranteed a serum cortisol level of around 500 nmol/L (18.1 μg/dL) appropriate to the postoperative and intensive care setting (8, 9). Neither the acute severe illness, necessitating admission to intensive care, nor subsequent treatment with octreotide and recombinant human GH influenced the circulating corticosteroid levels.

Etomidate and ketoconazole are members of the imidazole family of drugs. The observation that patients in intensive care receiving long term sedation with etomidate had increased mortality compared to other anesthetic agents (10) was later shown to be associated with low serum cortisol levels (11). Subsequent reports documented blunting of the cortisol response to ACTH *in vivo* (7, 12) and inhibition of ACTH-stimulated cortisol secretion from dispersed adrenal cells *in vitro* (13) by etomidate, suggesting a direct effect on the adrenal cortex rather than an inhibition of ACTH secretion. Studies using dispersed guinea pig adrenal cells (14) suggested that etomidate inhibits four cytochrome P450-dependent enzymes involved in corticosteroidogenesis, although the relative importance of each of these steps *in vivo* is not clear. Previous reports have documented a rise, compared with control values, in 11-deoxycortisol and 11-deoxycorticosterone after the administration of etomidate for the induction of anesthesia, suggesting inhibition of 11β-hydroxylation of both glucocorticoid and mineralocorticoid precursors (15). Levels of progesterone and 17-hydroxyprogesterone were unchanged from control values. Similar results are seen in dogs given etomidate when dramatic rises in ACTH and renin are provoked by acute hemorrhage (16). In our patient, by 3 days after the commencement of etomidate, levels of 11-deoxycortisol had fallen (Table 1), but were still above normal. However, by this time levels of 17-hydroxyprogesterone and DHEAS had fallen to subnormal levels, but cortisol had become undetectable. These data would suggest that the major immediate site of action of etomidate in our patient was earlier than previously reported, proximal to 17α-hydroxylase. An additional, partial, delayed, inhibitory action of etomidate on 11β-hydroxylase is also indicated, as 11-deoxycortisol levels continued to fall slowly over

TABLE 1 Serum levels of cortisol, 11-deoxycortisol, 17-hydroxyprogesterone (17-OHP), and DHEAS before and after the commencement of low dose etomidate by continuous iv infusion

Etomidate infusion (dose rate)	Cortisol (nmol/L)	11-Deoxycortisol (nmol/L)	17-OHP (nmol/L)	DHEAS (μmol/L)
Before etomidate	1170	235	13	8.2
3 days (2.5 mg/h)	<50	120	1	2.1
5 days (2.5 mg/h)	<50	95	<1	1.2
8 days (1.3 mg/h)	<50	62	<1	<0.5
Normal range, unstressed at 0900 h	300–700	26–46	1–10	2–10
Conversion factor	1 μg/dL = 27.6 nmol/L	1 μg/dL = 28.8 nmol/L	1 μg/L = 3.3 nmol/L	1 ng/mL = 0.0027 μmol/L

Continuous sc octreotide (600 μg daily) had been started 4 days before commencing etomidate and rhGH (24 U daily, im) 6 days after.

the next 5 days. It is possible that the onset of inhibition of 11β-hydroxylase is faster than that of other cytochrome P450-dependent enzymes, leading to a rapid fall in cortisol and consistent with the rise in 11-deoxycortisol levels reported when anesthesia is induced with etomidate in normal subjects. With more prolonged use, inhibition of enzymatic steps more proximal in the corticosteroidogenic pathway appears to become more important, leading to a progressive fall in 11-deoxycortisol, 17-hydroxyprogesterone and DHEAS levels.

Despite the description of the value of short term etomidate administration in critical situations in 1983 (7), there have been few reports of the use of etomidate to control hypercortisolemia in Cushing's syndrome and none of its use for a prolonged period in an emergency. Schulte *et al.* (17) reported the effect of infusion of etomidate on cortisol levels in normal volunteers and six patients with Cushing's syndrome over 24 h, and Gartner *et al.* (18) successfully used etomidate for 14 days in a single patient with the ectopic ACTH syndrome and steroid-induced psychosis. Sedation was seen in this latter patient and in some of the volunteers studied by Schulte *et al.*, but in our patient, sedation was not observed, and no adverse clinical or metabolic side-effects were noted during the 8 weeks of etomidate infusion.

Since this case we have used iv etomidate as an emergency drug to control hypercortisolemia in two other patients, both with pituitary-dependent disease (Cushing's disease). Serum cortisol levels were lowered usefully by etomidate, but, unlike the present case, in neither patient was endogenous corticosteroidogenesis completely abolished. It may be that etomidate is most effective either when the ACTH drive is fixed (as in the ectopic ACTH syndrome) or in ACTH-independent disease, so that the ability of the pituitary to reset its feedback loop makes etomidate less effective in controlling hypercortisolemia secondary to Cushing's disease.

In summary, this patient with severe Cushing's syndrome due to a pancreatic islet cell tumor secreting ACTH and gastrin survived peritonitis secondary to intestinal perforation and rupture of a pancreatic pseudocyst. We believe this to be due to the ability to inhibit completely excessive endogenous cortisol production with subhypnotic doses of etomidate. A serum cortisol level appropriate to the intensive care unit setting was achieved with a continuous hydrocortisone infusion. We wish to alert clinicians to the value of etomidate in circumstances where the coexistence of Cushing's syndrome and serious abdominal pathology precludes the use of oral adrenolytic therapy.

Acknowledgments

We thank Dr. B. Allolio, University of Cologne (Cologne, Germany), for his advice on the use of etomidate, and Mr. Maclean and Mr. Carpenter, who carried out the surgery.

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