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CONTENTS

# ETOMIDATE AND ADRENAL SUPPRESSION

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1. Introduction.....	3
2. The end of etomidate as a sedative infusion in ICU.....	3
3. Mechanism of adrenal suppression.....	4
4. Adrenal suppression with single dose Etomidate .....	6
5. The Physiological Role of Cortisol .....	12
6. The Cardiovascular stability of Etomidate.....	16
7. Options are good... ..	18
8. Is there a place for Etomidate in Anaesthetics today?.....	20
References.....	21



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## ETOMIDATE AND ADRENAL SUPPRESSION

### 1. Introduction

Etomidate was introduced into clinical practice in 1972. For a decade thereafter it held its place as an anaesthetic induction agent providing cardiovascular stability for haemodynamically unstable patients. (1) These properties naturally lead to its use as a sedative infusion in intensive care units.

In 1983, Ledingham and Watt published data relating to a sudden increase in mortality in their ICU. The evidence against Etomidate was damning – adrenal suppression caused by the drug was found to be the cause. Its use as a continuous infusion was no longer considered good practice but it continued to be used as an anaesthetic induction agent. (2)

In 2002, while investigating the effect of steroids in septic shock, Annane et al highlighted the lack of cortisol response to exogenous ACTH that was found in patients who had received a single dose of etomidate. (3) This reopened the debate.

The following commentary is an investigation into the demise of etomidate in anaesthetic practice.

### 2. The end of etomidate as a sedative infusion in ICU

#### **Mortality amongst multiple trauma patients admitted to an intensive therapy unit**

I. Watt and I. McA. Ledingham  
Anaesthesia 1984; 39: 973 – 981

Ledingham and Watt conducted a retrospective audit in their ICU to identify the reason for a sudden increase in mortality. From 1969 to 1981, their highest mortality rate had been 29%, but between 1981 – 1982, it had increased to 47%. This mortality was seen in a subset of patients who had survived more than 5 days from the time of injury, were mechanically ventilated and had died from multiple organ failure associated with severe sepsis.

Etomidate was introduced into their ICU in 1981 as a hypnotic infusion. By 1982, all patients needing mechanical ventilation were receiving morphine and Etomidate infusions. Toward the end of 1981, an Addisonian crisis in a patient prompted them to measure cortisol in all their patients – some of these patients received hydrocortisone replacement.

The authors compared patients in the period 1979 - 1980 to patients in the period 1981-1982. The groups were similar in terms of: age, Injury Severity

Score, pattern of referral and proportion of patients receiving mechanical ventilation. Significant differences were found when the 2 groups were compared in terms of sedative regimen used:

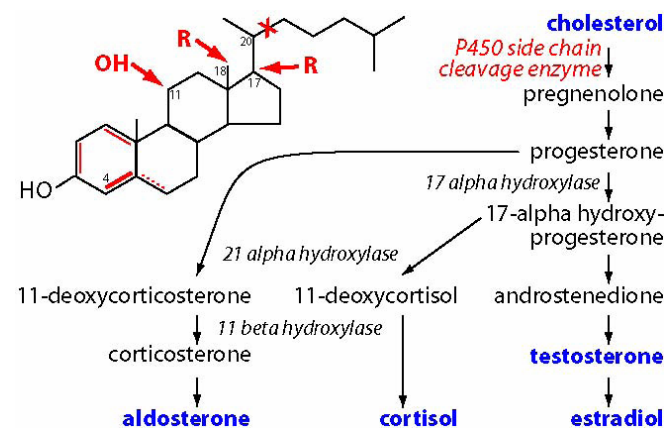
- 28% mortality in the group given opiates with or without benzodiazepines
- 77% mortality in the group given opiates and etomidate – there was a higher mortality in this group for all severities of injury.

Other significant findings in this study:

- 17 / 27 patients who received etomidate, had had their cortisol measured – all were below normal
- 8 of these patients received hydrocortisone and 4 of this group died
- Regarding the use of inotrope infusions:
  - 10 / 50 patients receiving morphine and/or benzodiazepine infusions received inotropes, commenced on average 9.5 days after admission.
  - 22 / 27 patients receiving morphine / etomidate infusions received inotrope infusions, commenced 3.4 days after admission.

The findings of Ledingham and Watt, substantiated by other studies confirming the impact of Etomidate infusions, lead to the removal of Etomidate as an hypnotic infusion in intensive care units.

### 3. Mechanism of adrenal suppression



### STEROID HORMONE SYNTHESIS IN THE ADRENAL CORTEX.

The effect of etomidate is limited to the adrenal cortex – it has no suppressive effect on the adrenal medulla. The block occurs at the initial rate-limiting step, the conversion of cholesterol to 20-22 dihydrocholesterol (not shown in the above diagram) (4). It causes a dose – dependant, reversible inhibition of 11 beta hydroxylase, with also a minor effect on 17 alpha hydroxylase (1). This block:

- i. prevents the increase in cortisol ( and aldosterone ) secretion in response to ACTH ,and
- ii. results in accumulation of 11 deoxycortisol, 17 hydroxy progesterone and Adrenocorticotropic hormone (ACTH)

The free imidazole radical of the drug binds directly to cytochrome p450. The result is blockade of ascorbic acid resynthesis which is required for steroid synthesis in humans(4). Both cortisol and aldosterone are affected (although there seems to be no effect on glucose and electrolytes). Catecholamines, synthesized in the adrenal medulla via a completely different pathway, are not directly affected by the adrenal suppression caused by etomidate (1).

**Most studies have indicated a duration of effect of 24 to 48 hours but it may extend as long as up to 72 hours.(6)**

When testing the function of the adrenal gland, generally, glucocorticoid (cortisol) measurement is more important than mineralocorticoid (aldosterone) measurement.

One may measure:

- a. random serum cortisol.
- b. or serum cortisol after the administration of exogenous ACTH

The nature of the chemical disturbance induced by etomidate, has been described as “relative adrenal insufficiency”. This means that cortisol levels are appropriately normal but the cortisol response to ACTH (endogenous or exogenous), is reduced. The implication is that cortisol secretion cannot increase in response to further stress. In fact, in patients who have received Etomidate, ACTH levels may be as high as 100x normal – an indication of a physiological attempt to overcome the block at the level of the adrenal cortex.

Surgical stimulation gives rise to an endocrinological response. This “stress response” involves the secretion of a number of hormones including

catecholamines, renin-angiotensin-aldosterone, ACTH and cortisol. Although physiological, an excessive stress response can be detrimental. Inhibition of the stress response to surgery (including cortisol) is in fact desirable. Many induction agents suppress cortisol secretion as a result of their central nervous system depressant effects – ACTH secretion is reduced and therefore cortisol secretion is reduced.

This is different to the effect of etomidate in that, with etomidate:

1. the relationship between ACTH levels and serum cortisol levels is not preserved, and
2. a subsequent stress that increases ACTH will not lead to an increase in serum cortisol levels

#### **4. Adrenal suppression with single dose Etomidate**

##### **Effect of Treatment With Low Doses of Hydrocortisone and Fludrocortisone on Mortality in Patients With Septic Shock**

Annane et al,  
JAMA. 2002;288:862-871.

The studies of Professor Annane and colleagues have focused on the use of steroids for septic shock. In 2002 they published a study concerning the role of steroids in patients with septic shock and adrenal insufficiency. They looked at 28 day survival and the timing of vasopressor withdrawal in these patients – comparing a group who received placebo to a group who received steroids.

18 months into the study, they decided that patients who had received etomidate within 6 hours of randomization, would be excluded from the study because 94% of 77 patients with septic shock who had received etomidate, failed to respond to corticotropin ie cortisol secretion did not increase in response to exogenous ACTH.

There were 2 other important findings regarding etomidate in this study:

- a. patients who had received etomidate required larger amounts of fluid and vasopressors.
- b. within this group (ie patients who received etomidate), the administration of steroids significantly reduced 28-day mortality (76% vs 55%).

It is important to pause a while to interpret the findings of this study carefully and it is also important to recognize that Etomidate was not the subject or main focus of the study at all.

Firstly ,the mortality figures refer to :

- 76 % mortality for patients with septic shock + adrenal suppression who had received etomidate and were given placebo.
- 55 % mortality for patients with septic shock +adrenal suppression who had received etomidate and were given steroids.

Secondly, probably because Etomidate was not the focus of the study , there is no comparison between the patients who received Etomidate and those who did not , in terms of severity of illness .The high incidence of adrenal insufficiency in critical illness and the possibility that the patients who received Etomidate may have been more ill to start with ,will confound the high incidence of adrenal insufficiency found in the patients who received Etomidate .

There is no large prospective trial that shows increased mortality as a result of the use of single dose etomidate. Many smaller trials have also failed to show an increase in mortality:

### 1. Does Etomidate confound the diagnosis of adrenal insufficiency in the trauma patient?

Turk et al

Critical care medicine ,December 2005 ,Vol 33 (12)

This study looked at 103 patients admitted to the ICU of a Level 1 trauma unit.90 patients were intubated , 70 with etomidate and 20 with a different drug.

There was no difference between the Etomidate and the non – Etomidate group in terms of : mortality , severity of illness , initial cortisol , incidence of adrenal insufficiency (27% vs 18 %) , vasopressor requirements , or hospital length of stay .But they did find higher ICU length of stay ( 10 vs 5 days)and ventilator days ( 8 vs 4.6 days)in the etomidate group.

### 2.ICU physicians should not abandon the use of Etomidate!

Dmello et al

Critical Care Medicine. December 2006; Volume 34(12)

A retrospective study that looked at intubated , mechanically ventilated patients with severe sepsis or septic shock .

113 patients received Etomidate , 111 did not .The patients had the same APACHE II scores .

They found no increase in mortality and no difference in vasopressor use; but they did find increased steroid use in the Etomidate group.

### 3. Effect of induction agent on vasopressor and steroid use, and outcome in patients with septic shock

David Charles Ray and Dermot William McKeown

Critical care 2007 ,11 R56

This study looked at patients with septic shock .The authors investigated the association between induction agent used and :

- use of vasopressors
- use of steroids
- outcome (hospital mortality )

Of the 159 patients in the study :

74 patients received etomidate

25 patients received propofol

26 patients received thiopentone

18 patients received either ketamine , midazolam or other

16 patients did not receive an induction agent

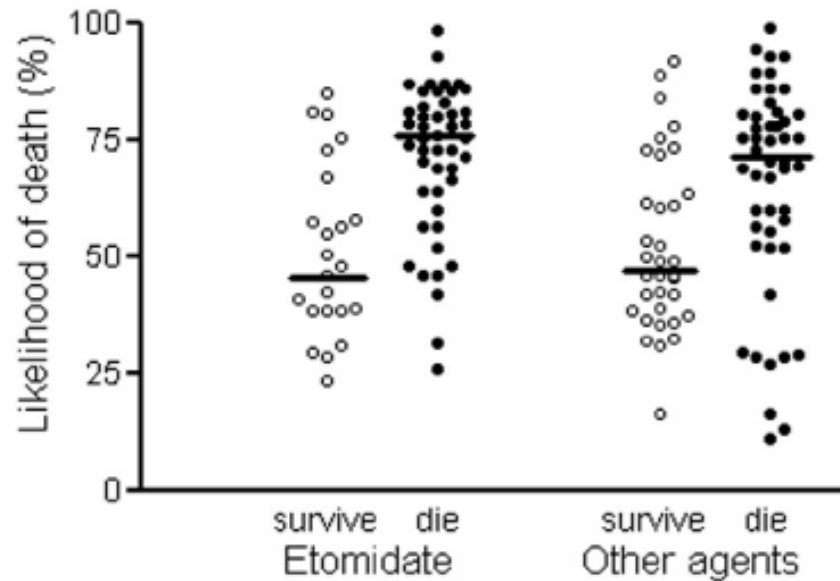
Details of severity of illness and outcome for each induction agent

	Etomidate (n = 74)	Propofol (n = 25)	Thiopental (n = 26)	Other (n = 18)	Nil (n = 16)	P value
Mean age in years	65	63	66	66	66	0.35
APACHE II score	28	24	24	29	30	0.70
Predicted mortality	69%	57%	52%	71%	75%	0.49
Hospital mortality	69%	56%	46%	67%	81%	0.23
SOFA score	10	10	8	11	10	0.40
Crude SMR	1.0	0.98	0.88	0.94	1.08	

Except for age, data shown are median values. APACHE II, Acute Physiology and Chronic Health Evaluation II; SMR, standardised mortality ratio; SOFA, Sequential Organ Failure Assessment.

The patients were evenly matched and outcomes related to predicted mortality were similar for all groups. Patients who received etomidate did not have a higher mortality rate.

### Outcome related to pre-existing risk



Outcome related to Acute Physiology and Chronic Health Evaluation II predicted mortality for patients given etomidate and those given other agents. Horizontal bar represents the median value.

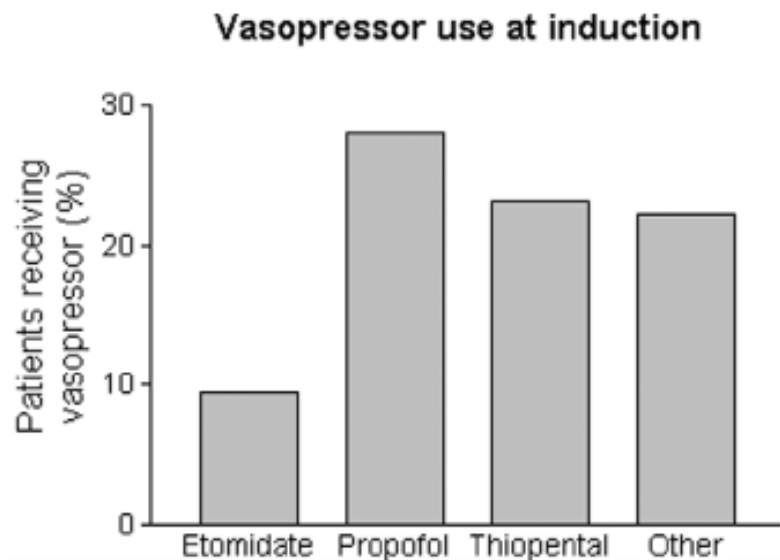
With regard to noradrenalin use, they found no correlation between induction agent used and timing of the start of the infusion ,duration of infusion or dosage .

Details of noradrenaline therapy received by patients in each group

	Etomidate	Propofol	Thiopental	Other	Nil	P value
Number (percentage) receiving	72 (97%)	25 (100%)	26 (100%)	17 (94%)	14 (88%)	
Total dose in milligrams	46	44	52	84	65	0.53
Maximum dose in micrograms per kilogram per minute	0.45	0.40	0.38	0.50	0.46	0.64
Averaged dose in micrograms per kilogram per minute	0.26	0.23	0.19	0.30	0.32	0.29
Duration of infusion in hours	52	59	47	50	40	0.54
Time from intubation to commencing infusion in minutes	68	135	105	15	230	0.49

Data shown are median values.

Patients who were induced with etomidate needed less active management of cardiovascular depression during induction .



Percentage of patients given bolus dose of vasopressor at induction of anaesthesia, grouped by induction agent.

Intensity of cardiovascular management at induction of anaesthesia

	Minor	Moderate	Intensive
Etomidate	●●●●	●●●	
Propofol	●	●	●●●●●
Thiopental	●●●	●	
Midazolam			●●●●

Each dot represents one patient. Minor: less than or equal to 1 mg of metaraminol or less than or equal to 6 mg of ephedrine; moderate: more than 1 mg to less than or equal to 3 mg of metaraminol or more than 6 mg to less than or equal to 18 mg of ephedrine; intensive: more than 3 mg of metaraminol or any dose of adrenaline.

With regard to steroid administration ,

- iv. there was a 67% mortality for patients who received steroids,generally
- v. there was a 60% mortality for those who did not receive steroids,generally
- vi. For patients who received etomidate , there was a higher mortality in patients who received steroids ( 74% vs 58% )

The authors concluded that etomidate did not influence the use of noradrenalin or administration of steroids for the indication of septic shock not responding to vasopressors .They also found that steroid administration did not reduce mortality when administered to patients who had received etomidate.The administration of etomidate was not found to increase mortality .

3. In another study (9) , involving patients undergoing surgery for ruptured abdominal aortic aneurysm , no difference in mortality was found between 32 patients who received Etomidate and 22 matched control subjects who did not .

### 5. The Physiological Role of Cortisol

#### *What is the role of cortisol in critical illness?*

The stress response induces high plasma cortisol levels, despite ACTH levels that return to normal within 2 days.

The reasons for high cortisol in critical illness:

1. Loss of circadian rhythm.
2. Activation of the HPA axis.
3. Reduced cortisol extraction from blood.
4. Reduced binding of cortisol to transcortin.
5. Increased half life of cortisol.
6. Endothelin:  
It is markedly elevated in critical illness.  
It stimulates HPA axis.  
It directly potentiates ACTH at adrenal cortex.

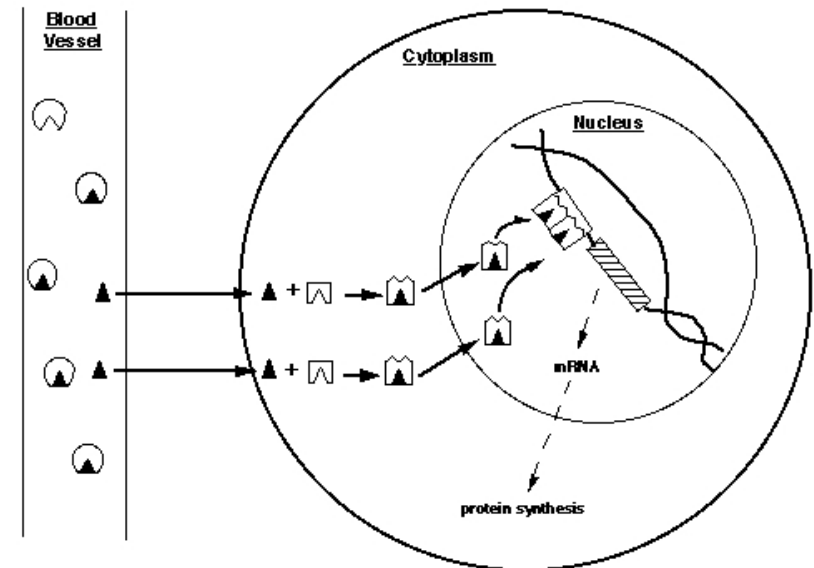
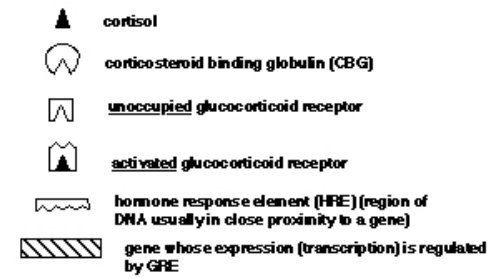
The physiological effects of cortisol include:

1. Increased blood glucose (increased gluconeogenesis in the liver and reduced cell uptake of glucose)
2. Increased plasma proteins
3. Anti inflammatory :
  - reduced capillary permeability
  - reduced leukocyte migration
  - reduced phagocytosis and release of mediators by leucocytes
  - reduced inflammatory mediators
  - stabilization of lysosomes
4. Cardiovascular effects .Cortisol has cardiovascular effects that go beyond its aldosterone – like effects .As discussed earlier, some studies have demonstrated that patients who received etomidate subsequently required more fluids and vasopressors .This warrants looking into the cardiovascular effects of cortisol in a little bit more detail .

**Cardiovascular effects of cortisol :**

Cortisol potentiates the actions of vasopressors through a variety of mechanisms.(24)

**i) Cardiovascular effects mediated through transcription**

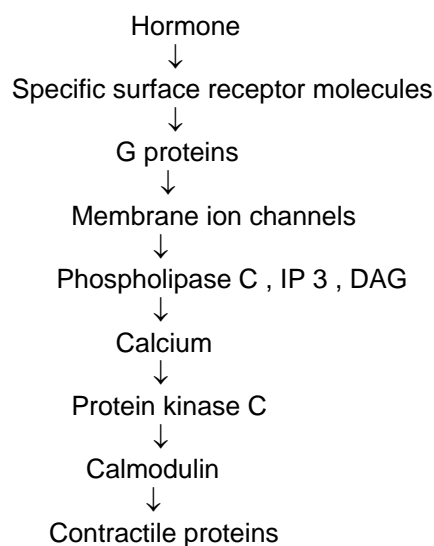


**Traditional mechanism of action of steroid hormones**

These effects take hours to days and are the result of the usual mechanism of action of steroid hormones i.e. activation of intracellular receptors and eventually altered protein synthesis.

Effects include:

- Increased angiotensin II receptor density.
- Increased formation of angiotensinogen and increased activity of ACE.
- Increased activity of angiotensin II.
- Effects on vascular endothelium via nitric oxide and non-nitric oxide dependent pathways.
- The classical vasoconstrictor signal conduction pathway in vascular smooth muscle cells - studies have demonstrated the potentiation of vasopressor action by cortisol acting at different steps along this pathway:



- Enhanced release of endothelin and inhibition of nitric oxide synthesis.
- Increased expression and activity of Na – K – ATPase

## ii.) Acute vascular actions of Cortico-steroids

Rapid responses to cortisol have been elicited in vascular smooth muscle, and other cell types. These responses occur within 5 minutes and include: activation of the sodium-proton exchanger, stimulation of inositol phosphates and cytosolic calcium mobilization – pressor responses within 10 minutes of intravenous hydrocortisone have been demonstrated in animal studies.

Although the receptor density for glucocorticoids(GCC) is 20-30 x greater than that of mineralocorticoids(MCC), the effect occurs at very low concentrations of mineralocorticoids and at much higher concentrations of glucocorticoids leading to the suggestion of cell surface mineralocorticoid receptors. Nevertheless, GCCs and their receptors are more important than mineralocorticoids and their receptors in enhancing vascular tone.

## iii.) Effects on beta receptors:

Glucocorticoids also regulate beta receptor transcription .Methylprednisone has been shown to increase beta receptor density and to counter the downregulation seen with long term catecholamine infusions .(25)

## 6. The Cardiovascular stability of Etomidate

**Let's take a look at the nature of the cardiovascular stability of etomidate.**

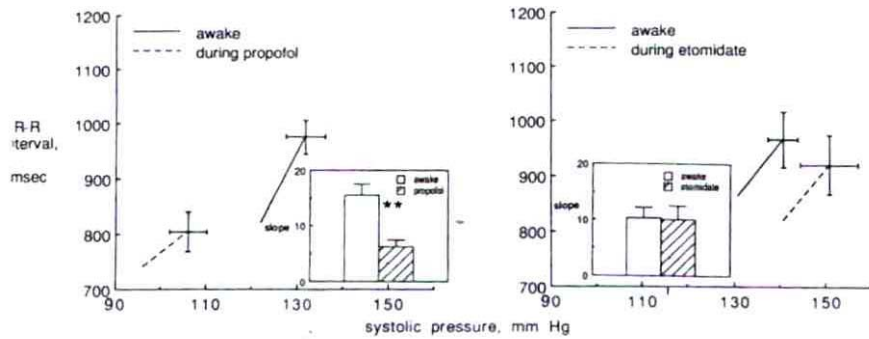
At the usual dose of 0,2 to 0,3 mg/kg etomidate causes a less than 10 % change in heart rate, mean arterial blood pressure (MAP), systolic blood pressure (SBP), diastolic blood pressure (DBP), mean pulmonary arterial pressure, central venous pressure (CVP), pulmonary arterial wedge pressure, stroke volume, cardiac index, peripheral vascular resistance (PVR) and systemic vascular resistance (SVR). Even at 0.45mg/kg (150 % higher than the standard induction dose) produces only a 12% decrease in SBP and MAP, with lesser changes in all other parameters (1).

In patients with valvular heart disease, a dose of 0,3 mg/kg is associated with a less than 20% change in haemodynamic parameters .Etomidate improves the myocardial supply-demand ratio and may improve coronary blood flow up to 19% with no increase in consumption.

Etomidate also maintains tonic sympathetic activity and baroreceptor reflex regulation of sympathetic activity. (3)

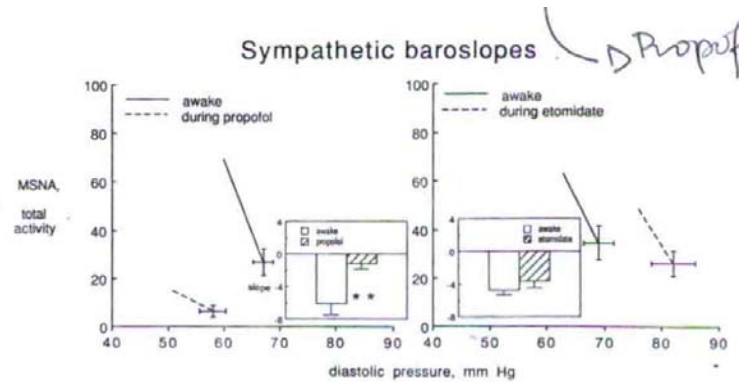


**Fig 1 Cardiac baroslopes – declining pressure response**

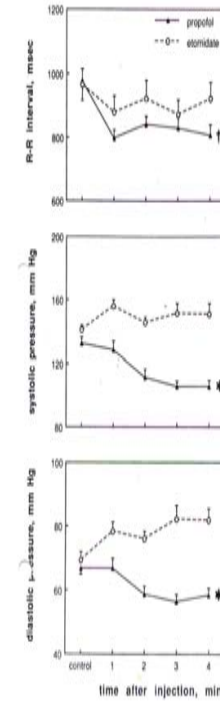


The opposing effects of etomidate and propofol on the cardiovascular system may lie in their effects on the sympathetic nervous system.(4)

**Figure 2. Sympathetic baroslopes .MSNA=Muscle sympathetic nerve activity (MSNA)**



**Fig 3. Haemodynamic responses to etomidate and propofol .**



**7. Options are good...**

Besides using alternate induction agents, there are a few other more interesting options when it comes to overcoming the adrenal suppression of etomidate:

**i) Steroids with etomidate**

It seems logical to administer steroids if one is inducing adrenal suppression .Some authors (5,6) recommend that steroids be given routinely with etomidate .However ,some studies have shown benefit while others have not .

## Hydrocortisone Therapy for Patients with Septic Shock

Sprung, Annane et al

New England Journal of Medicine Vol 358 : 111–124, Jan 10, 2008

This study was very similar to the original study conducted by Annane et al in 2002 (10) in which they found, incidentally, a high incidence of adrenal suppression in patients who received etomidate. Although neither of these studies were primarily investigating etomidate, the discrepancy in the findings is relevant to this discussion: the basis for the recommendation of steroids to patients who have received etomidate is that etomidate causes a failure to respond to corticotropin and that the original study by Annane et al in 2002 showed that steroids reduced mortality in patients who had both septic shock and a failure to increase cortisol secretion in response to corticotropin. (52% mortality in steroid group vs 63% mortality in placebo group).

The above study, published in 2008, showed a 39% mortality in the steroid group and a 36% mortality in the placebo group.

Furthermore, the 2008 study found a higher rate of superinfection including new sepsis and septic shock in the patients who received steroids.

These findings should warn against the indiscriminate use of steroids to counter the adrenal suppression of etomidate.

### ii) Vitamin C for etomidate

The free imidazole radical in etomidate binds cytochrome P450. Other drugs with a free imidazole, such as cimetidine and ketoconazole, may also cause chemical adrenalectomy – the degree of suppression may be as much as that caused by surgical adrenalectomy. (4)

Vitamin C is necessary in the rate limiting step – acting as an electron donor. The rate limiting step in the production of steroid hormones is the hydroxylation of cholesterol to 20-22 dihydrocholesterol. The production of cortisol in response to ACTH stimulation of cells of the adrenal cortex, requires vitamin C and intracellular vitamin C is diminished in response. The reaction involving vitamin C is:



The action of cytochrome p450 is necessary for the reconversion (recycling) of dehydroascorbic acid to ascorbic acid.

A small study testing the response to vitamin C (4), took 2 groups of 5 patients who were scheduled for major abdominal vascular surgery. Both groups were given etomidate and fentanyl infusions. Cortisol and ACTH were measured hourly. An ACTH stimulation test was performed on the 4<sup>th</sup> hour. One group was given vitamin C just before the ACTH stimulation test. This was able to overcome the block in cortisol synthesis.

### a. Furane for Imidazole?

It has also been suggested that substitution of the imidazole group in etomidate with a furane group will overcome this adverse effect. (4)

## 8. Is there a place for Etomidate in Anaesthetics today?

### **Etomidate for Endotracheal Intubation in Sepsis - Acknowledging the Good While Accepting the Bad**

*“The treatment of sepsis at this time is akin to our current understanding of acute myocardial infarction. There is no magic bullet; rather, several therapies must be quickly brought to bear on this complex pathologic state to maximize the benefit of each intervention while limiting the incurred risk. In our minds, the same holds true for the intubation of a septic patient. This is a high-stakes intervention with a large potential cost if it is not performed well. Significant aspiration or a prolonged period of hypotension may well abolish any benefit from all of the above therapies. We think that etomidate is still a very good agent for the induction of unconsciousness, and when combined with muscle relaxation provides the best scenario for rapid, smooth, hemodynamically stable intubation.”*

**Holt Murray and Paul E. Marik. (American College of Chest Physicians) Chest. 2005;127:707-709.**

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