

Etomidate

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State of the Art

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Etomidate – State of the Art

Etomidate has been used in clinical practice for 30 years and during this period extensive experience has been gained. It remains the intravenous hypnotic with the least impact on the cardiovascular system and has even been used in patients with cardiogenic shock. Early difficulties having to do with galenic problems (in particular venous reactions and myocloni) can be largely avoided using relevant techniques and a particular galenic formulation. The blockade of cortisol through etomidate (the "Cortisol Story"), which prompted many anaesthetists to abandon the drug, is irrelevant to the use of the drug for a brief

period of time. Now, 20 years later after the report of Ledingham [1], it is clear etomidate is the induction agent of choice in high-risk patients. Also the galenic problems associated with the original preparation have been overcome, resulting in an important reduction of the adverse effects. In the present paper, the author reviews a range of relevant etomidate issues [Table 1] and presents important properties of the drug that are not generally known and are significant for certain anaesthetic techniques. These issues are given more detailed attention in www.etomidate.schau.de

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Table 1. Issues considered

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1. General pharmacology

Etomidate was introduced as a barbiturate-free anaesthesia agent 30 years ago. Its unique properties in patients with cardiac risks and atypical diseases were readily recognized. Moreover, the following pharmacological hallmarks were found [2]:

- Induction dosage 0.15–0.3 mg/kg BW (adults), and 0.2–0.3 mg/kg (children up to 15 years) effect approx. 20 sec – 5 min.
- Redistribution phases $t_{1/2}$ 2.6 and 29 min, terminal elimination half-life 2.4–5 h
- Protein binding approx. 75%
- Lipophilic substance, nearly insoluble in water
- Cerebral effect presumably through GABA-activation
- High therapeutic index of 26 (safety aspect)

Table 2. Pharmacological hallmarks, see also Table 3

2. Cerebrovascular effects

Etomidate causes a decrease in cerebral oxygen consumption and blood flow [3,4]. Whether etomidate has a pro- or anticonvulsive effect is a matter of dispute; some authors have used it in emergency medicine successfully against convulsions. Myocloni (see below) are generally not accompanied by epileptiform EEG-changes [5]. The cerebrovascular effects of intubation are blunted by etomidate.

3. Cardiac effects

There are no findings associating etomidate with cardiodepressive effects during clinical use. After induction of anaesthesia with etomidate only small, clinically irrelevant changes in blood pressure and heart rate occur [6–9]. In patients with coronary heart disease, coronary blood flow is substantially increased, resulting in a minimal increase in myocardial O_2 -consumption [10,11]. Etomidate has even been used in various types of shock (including cardiogenic shock) without any deleterious effects [12,13]. For such cases, a dose reduction is not recommended, but drugs used in combination must be critically evaluated. Substantial differences are reported, depending on whether noxious stimulation occurred or not. Under clinical conditions (e.g. intubation), heart rate and blood pressure may rise [14]. An

experimental study [15] showed that etomidate, in contrast to thiopental (thiopentone), was inert to cardiac muscle cells. Avoiding the choice of a suitable hypnotic in cardiac risk patients may have serious consequences [16].

4. Histamine release

Histamine release, leading to serious anaphylactoid reactions, is the most common cause of adverse drug reactions in anaesthesia [17]. Etomidate is one of the safest anaesthetics in connection what histamine release is concerned and is for that reason particularly recommended in asthmatic patients [18]. Propofol might also be used in such a situation, but occasionally an associated serious right heart failure may occur unexpectedly.

5. Respiratory effects

Again, clinical and entirely experimental studies yield different results, since noxious stimuli (when present) are modified but still processed [11,19,20] and the absence of such stimuli [21] is clinically irrelevant. This also enables the patient to respond with a respiratory drive to hyperbaric stimulation. It appears, however, that respiratory depression is synergistically expressed when many opioids and all benzodiazepines are used as co-medication to etomidate.

6. The "Cortisol Story"

Etomidate blocks the cortisol synthesis for 4–6 hours after a single dosage [22–24]. Prolonged infusion may lead to clinical signs characteristic of Addison's disease, but even then, this effect is totally reversible. In patients sedated with etomidate, an increased mortality has been suspected. There are, however, no indications for believing this to be related to cortisol levels [25]. In common with other i.v. anaesthetics, etomidate blocks the phagocytic defence in the release of peroxides by leucocytes [26,27], for which effect it has been speculated that they act as "neuroprotective drugs". This property obviously increases susceptibility to fatal infections when these drugs are applied for weeks.

Unfortunately, the "cortisol story" [28] caused many anaesthetists to disregard etomidate totally. Apparently, it

also distracted the initial producer from considering any solution to the galenic problem, influencing some adverse effects henceforth described. Prolonged infusion of etomidate should not be considered, but its use as an induction agent remains justified due to its outstanding properties.

7. Pain on injection

Pain on injection was a prominent feature of the old preparation of etomidate. In addition to the immediately experienced sensations, venous reactions (thrombophlebitis) were also frequent postoperatively, but generally not in the same patients suffering from pain on injection. These adverse effects have been nearly completely eradicated with Etomidate-®Lipuro, as revealed in several clinical trials [29-34]. Also the pain on injection resulting from propofol can be reduced by using MCT/LCT emulsion (Lipofundin® MCT). Should you ask your patient's opinion about this memorable event, the answer will be that there is no reason to utilize a pain-producer when another preparation is available and no arguments, not even economical ones, can be forwarded in favour of the old substance.

8. Etomidate and haemolysis

Etomidate in propylenglycol has an osmolality twelve times as high as Etomidate-®Lipuro, which lies in the range of serum [35]. No wonder, this hyperosmolality leads to haemolysis which may, in turn, cause other adverse effects, e.g. cerebral ones. In contrast, Etomidate-®Lipuro in a dose of 0.3 mg/kg could be shown not to have any haemolytic effects [36].

9. Myocloni

The clinical picture of myocloni leads one to think about grand mal seizures, but EEG recordings do not reveal corresponding findings [5]. It is generally thought that myocloni are an expression of superficial anaesthesia. If myocloni are caused by painful stimulation, this could explain why they are more frequent after etomidate in the old solvent in comparison to Etomidate-®Lipuro. It has also been suggested that myocloni are influenced by haemolysis,

which would result in similar findings. Whatever the reason, the choice of preparation influences the incidence of myocloni [32,33] - but this is not enough, a co-medication is required to remove myocloni from clinical relevance. These vary greatly depending upon the premedication [37] and the timing of opioid administration and it is doubtful whether it is possible to avoid them completely. In contrast to co-medication of opioids or benzodiazepines, any attempts to avoid myocloni by increasing the dosage of etomidate will prove useless. It has been claimed that a pretreatment regimen [38], with injection of subanaesthetic dosages in advance, results in a reduction in the frequency of myocloni. In severely disabled patients, e.g. in shock, the generally deteriorated condition seems to make the sign disappear. This adverse effect may be disturbing to the physician but fortunately not to the patient.

10. Post-operative nausea and vomiting (PONV)

Two studies [34,39] have yielded conflicting results. In one, etomidate caused more emetic problems than propofol, at least among women, who are in any case more susceptible to PONV. The other study gives an equal rate. When utilizing etomidate predominantly for risk patients, even a higher rate of PONV seems an acceptable side effect in view of other advantages.

11. Storage in Emergency Medicine

In a study from the wild prehospital practice [40], Etomidate-®Lipuro ampoules were carried along in rescue ambulances for the summer (May - October) and analysed after up to 6 months of physical and thermic excesses (the temperature within the ambulance varied from 6 to 45°C). No difference in the drug contents and physical properties of the lipid solvent were found. Although etomidate looks like milk, there is no need to keep it in the refrigerator.

12. Prehospital anaesthesia

Emergency patients in need of anaesthesia are often in shock, usually cannot provide information of concomitant diseases, are practically never fasting and have an unknown

body-weight which can only be estimated. These facts point in one direction - that etomidate is the anaesthetic induction agent of choice, although the author's claim about a reduced risk of aspiration (see section 14) remains unsupported in the absence of any studies. Add to this the availability of a ready-to-use ampoule, even in thermally unfavourable conditions.

For induction of anaesthesia in the emergency patient, the rapid sequence induction (RSI) is generally employed, originally described for the combination of thiopental and succinylchloride (suxamethonium). However, for the previously unknown emergency patient, this is preferably now carried out with etomidate as the hypnotic [41]. In the prehospital phase, false or impossible intubation was found so often that two authors [42,43] recommended to forgo the relaxant. How intubation should then take place was not mentioned, but forgoing RSI undoubtedly also has its price. In my own prehospital practice [13], I found a way of performing intubation, employing maintained breathing after etomidate.

After an initial phase also using thiopental, ketamine and no anaesthetic, I have used etomidate for nearly all intubations, including for intubation of comatose patients

- unconsciousness should not serve as a pretext for omitting anaesthesia. It is necessary to protect all patients from the adverse haemodynamic and cerebrovascular responses to the noxious stimulus of intubation. Etomidate possibly also offers some protection for the risk of aspiration through an exceptional impact on the upper airway reflexes.

13. Comparison of i.v. anaesthetics

Table 3 shows the essential properties of a range of anaesthetics for prehospital use, including the varying effect of anaesthetics on the upper airway reflexes. When you compare propofol and etomidate, you find that propofol blocks the laryngeal reflexes better than etomidate - therefore, the laryngeal mask airway is better tolerated in propofol than in etomidate anaesthesia, but the laryngeal defence in the latter may be of importance for preventing aspiration. Many publications are dealing with the haemodynamic response to intubation - a measurable parameter, in contrast to neuromuscular reflexes - but hardly any are considering the neural reflex cause of this response. Even if reflexes are difficult to measure, they are still there.

Property	Thiopental	Etomidate	Propofol	Ketamine	Midazolam
1. Cardiac depression	++	0	++	(+)	+
2. Ventilatory depression	++	0	+	0	+
3. Histamine liberation	++	0	0	0	0
4. Ready-to-use/in ambulance	0	+/+	+/?	+/?	+/?
5. Myocloni ²	0	++	+	0	0
6. Pain on injection	0	0/++ ³	+ ⁶	0	0
7. Pharyngeal reflexes	+	-	-	+	-
8. Laryngeal reflexes	+	(-)	-	+	(-)
9. Dose range (mg/kgBW ⁴)	3-8	0.15-0.3	1.5-2.5	1-2	1-2
10. Term. (elimin.) HL (h) ⁵	11.4	4.6	0.9	0.9	2.5

Table 3: Properties of IV hypnotics and anaesthetics of importance in emergency medicine.

Legends: effect (1-6) evaluated to be: 0 absent, + existent or ++ strongly present; reflex (7-8) : + spasm, - depression or (-) weak depression. ¹Tachycardia may be deleterious to the ischaemic heart; ²Myocloni in the absence of adjuvants (e.g., opioids); ³strong injection pain frequent from old galenic preparation, absent in lipid preparations. ⁴Dosage for anaesthesia induction. ⁵HL=Half-life. ⁶infrequent in MCT/LCT preparation

14. Anaesthesia with maintained breathing

Although previously described by others [44–48], the author's first use of this technique was a matter of necessity engendered by external circumstances, leading to its designation as "pirate anaesthesia". A crucial argument against intubation is summed up in the statement "no vomiting, no aspiration", while laryngoscopy itself may provoke vomiting. However, in certain conditions (ileus, late pregnancy, abdominal compression and oesophageal achalasia), there is a similar danger by this technique, too. Apart from the reflex aspects described above, etomidate – in suitable combination – has the advantage of not depressing spontaneous ventilation in the anaesthetised patient. The author has performed more than 100 emergency pirate anaesthesias, perhaps one third of them out of the hospital, for setting fractures and dislocations. Under more civilized circumstances, the same method has been used on fasting patients for cardioversion, short gastroscopy, forced arthrolysis and other 5-minute procedures. The patient breathes spontaneously, generally without oxygen supply. Also recent studies have dealt with etomidate for short procedures with preserved breathing, although without utilizing any co-medication [49,50].

15. General conclusion: Reconsidering the indications for etomidate

Etomidate remains the safest drug for cardiac risk-cases, and it is reasonable to restrict emergency medicine hypnotics to etomidate. There may be additional, though less frequently used techniques, based on etomidate's unique effect on respiration and reflexes. Finally, it is recommended to get some experience with the drug before suddenly using it for high-risk patients.

This article is based on a more detailed review, to be found at the website

www.etomidate.schau.de

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