

Etomidate
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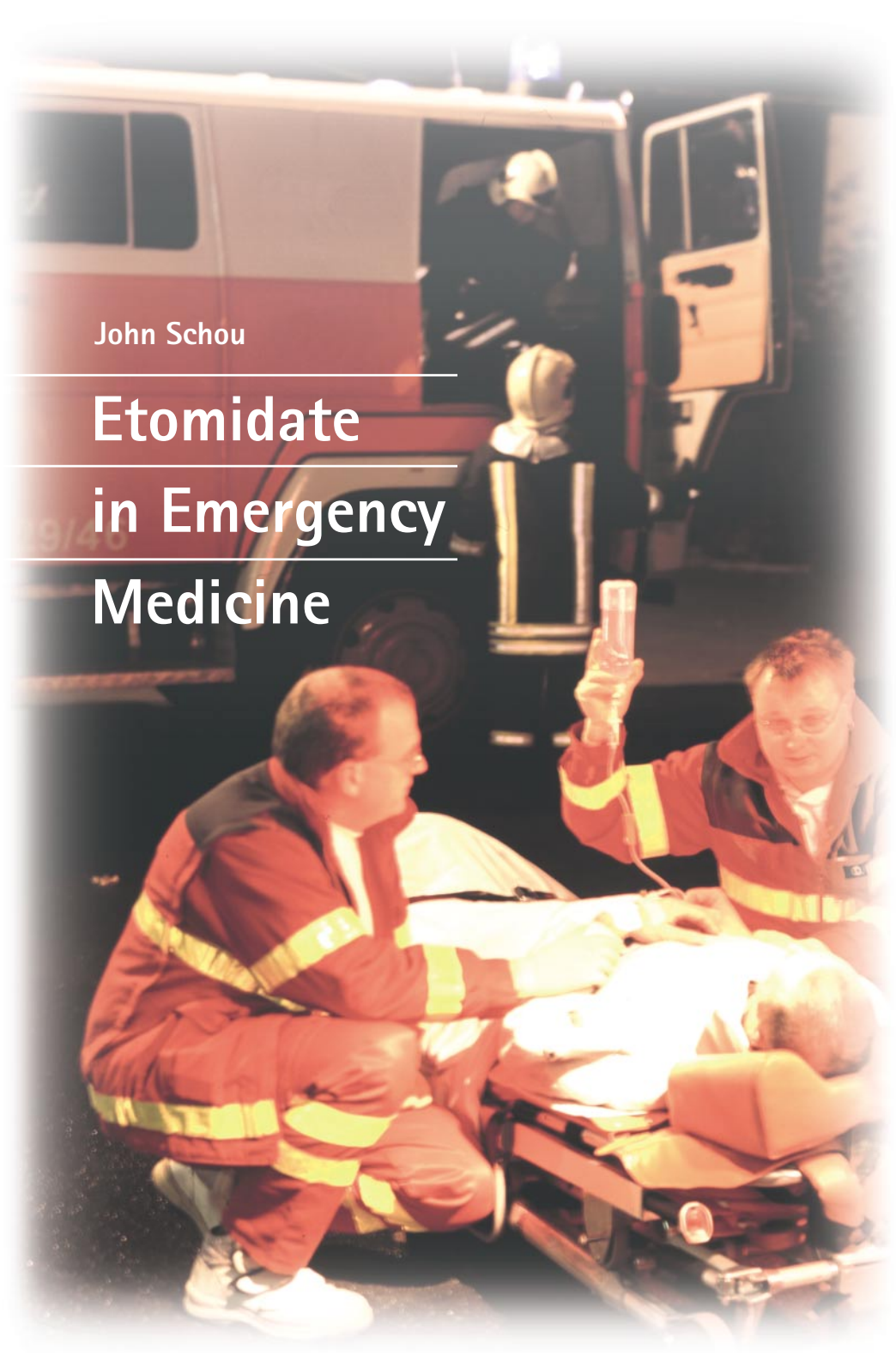
Etomidate

in Emergency
Medicine

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www.etomidate.schou.de

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Etomidate in Emergency Medicine



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A detailed review of the pharmacology and practical use of etomidate can be found at

www.etomidate.schau.de

Pharmacology

Etomidate was introduced into anaesthesia by Alfred Doenicke in 1972. The pharmacological key effects are shown in Table 1.

- 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 predominantly through GABA-activation
- High therapeutic index of 26 (safety aspect)

Table 1. Pharmacological hallmarks.

Etomidate is the intravenous (IV) hypnotic with the least impact on cardiovascular and pulmonary function and it is considered safe as regards histamine release. The impact on various organs is dealt with in the following section. Some adverse effects are considered under galenic aspects.

After venous reactions have been almost eliminated, the most important adverse effect of etomidate is that of myocloni, involuntary muscular movements, which show some clinical resemblance to convulsions. These remain a matter to be dealt with, although their importance in emergency medicine is rather limited.

Etomidate blocks the cortisol-synthesis reversibly for some hours after a single injection [1]. For that reason, any prolonged use beyond one hour is ill-advised. There is, however, no reason to compensate for the (possibly even desired) abolition of the steroid stress response [2]. Moreover, the absolute cortisol levels remain in the normal range following a brief use of etomidate.

Impact on the function of vital organs

Cerebral: Etomidate causes a decrease in cerebral oxygen consumption, blood flow and intracranial pressure [3,4]. Myocloni are generally not accompanied by epileptiform EEG-changes [5], and the drug has been successfully used in emergency medicine against epileptic status [6,7]. There is no reason to forgo using etomidate for the intubation of comatose patients – in particular here, it may be crucial that cerebrovascular effects of intubation are blunted by etomidate [8].

Cardiovascular: Under clinically relevant conditions, etomidate has hardly any effect on cardiac function [9]. Both upward and downward variations in heart rate and blood pressure have been reported, but following intubation, both are apt to increase. Most importantly, etomidate has stood the hardest test by its use in cardiogenic and other types of shock, pulmonary oedema and acute asthma [10,11]. This is in sharp contrast to other hypnotics, which cannot be considered inert to haemodynamics in cardially compromised patients (Table 2). Moreover, an exactly weight-correlated dosage is not essential and there is no need to reduce the dose in shock [12].

Respiratory: Etomidate alone does not cause much impact upon ventilation [13]; however, etomidate is mostly used in a combination with an opioid or a benzodiazepine for suppression of myocloni and augmentation of anaesthesia. These combinations are apt to cause a synergistical respiratory depression. The author's personal recommendation for a suitable combination is a partial antagonist opioid, e.g. nalbuphine, when maintained breathing is required in the anaesthetic technique.

Immunological: Etomidate is considered immunologically safe [14] and can be used in atypical diseases where **histamine release** can be feared or is possibly already present (asthma, anaphylactical incidents).

Renal, hepatic: No adverse effect has been noted. Moreover, there is no need to reduce induction dosage in these conditions although hepatic failure may prolong the duration of action [15].

Galenic improvement and its consequences

A particular problem in the use of etomidate in the past has been **pain on injection**, at a level higher than almost any other anaesthetic. In addition, a considerable proportion of patients developed **thrombophlebitis** at the site of injection, unrelated to the injection pain. This problem was solved by dissolving etomidate in an emulsion consisting of a mixture of medium and long-chain triglycerides (MCT/LCT) as drug carrier for Etomidate-®Lipuro. Now, one could argue that in an emergency, venous reactions are not very important, whereas patients for scheduled surgery could rather demand a painless induction, once such is available. However, it has become evident that other problems are also positively affected by the new preparation.

Etomidate in the original propyleneglycol solution has an **osmolality** twelve times as high as Etomidate-®Lipuro, which has the same osmolality as serum [16]. Etomidate in propyleneglycol causes considerable **haemolysis** and it may in addition be of importance in the generation of **myocloni**. At least, the new formulation causes considerably less myocloni than the old one [17,18].

Still, myocloni calls for additional precautions. Again, there is a difference between use for emergencies and for scheduled cases. The disabled condition of patients in most emergency cases (e. g. shock, coma) requiring anaesthesia potentiates the effect of etomidate and thus tends to decrease myocloni [10]. Many studies confirm that premedication, possibly given IV just before etomidate is injected, decreases the incidence of myocloni [19-22]. This is valid for many drugs and has been investigated predominantly for opioids and benzodiazepines. There is, however, a difference among the possible co-medications used with regards to synergistic respiratory depression (see: respiratory effects). Generally without any consequence in the induction of anaesthesia, this can be of importance for techniques relying on maintained breathing.

Intravenous anaesthetics and emergencies

The emergency patient represents the opposite case of being prepared for an anaesthesia. Cardiovascular problems and shock of various aetiologies are frequent; concomitant diseases, therapies and simply the body weight may be unknown, and the patient is rarely fasting. Add to this the practical problems relating to the assistants and technical aspects. Nevertheless, coping with these obstacles has a fascination of its own [23].

In emergency medicine, the demands placed on drugs seem to differ. It is, of course, important to use drugs with which you have had previous experience. In addition, other properties gain importance in emergencies (Table 2).

The properties which make etomidate seem the logical choice for emergency use can be summarized as follows:

1. Cardiovascular stability
2. No histamine release
3. Broad therapeutical index (of value by unknown body-weight)
4. Maintained breathing and laryngeal defence reflexes for certain techniques
5. Blunting of intracranial pressure rise following intubation.

To this can be added: Etomidate-®Lipuro is the only substance whose stability has been analysed under prehospital conditions.

| Property | Thiopental | Etomidate | Propofol | Ketamine |
|---|------------|-------------------|----------------|----------|
| 1. Cardiac depression | ++ | 0 | ++ | (+) |
| 2. Ventilatory depression | ++ | 0 | + | 0 |
| 3. Histamine liberation | ++ | 0 | 0 | 0 |
| 4. Ready-to-use/ambulance | 0 | +/? | +/? | +/? |
| 5. Myocloni ² | 0 | ++ | + | 0 |
| 6. Pain on injection | 0 | 0/++ ³ | + ⁶ | 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 |
| 10. Term. (elimin.) HL (h) ⁵ | 11.4 | 4.6 | 0.9 | 0.9 |

Table 2: 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

Storage in prehospital emergency medicine

In theory, drugs are kept at a temperature not exceeding 25°C. In prehospital practice, this is absolutely illusory and you must simply hope that the drugs are working in the desired fashion. Occasionally, you may have the suspicion that what you injected was not exactly the intended substance, or at least not in the dose as could be expected from the ampoule. Only one study is known to me concerning the realities of this situation.

Etomidate[®]Lipuro ampoules were carried along in 7 ambulances and mission cars for the summer (May–October) and analysed monthly after up to 6 months of physical and thermic excesses. The mean monthly distances travelled varied between 1200 and 2200 km of generally hard driving, and the temperature within the ambulances varied from 6 to 45°C. No difference in the drug concentration and physical properties of the lipid solvent were found.

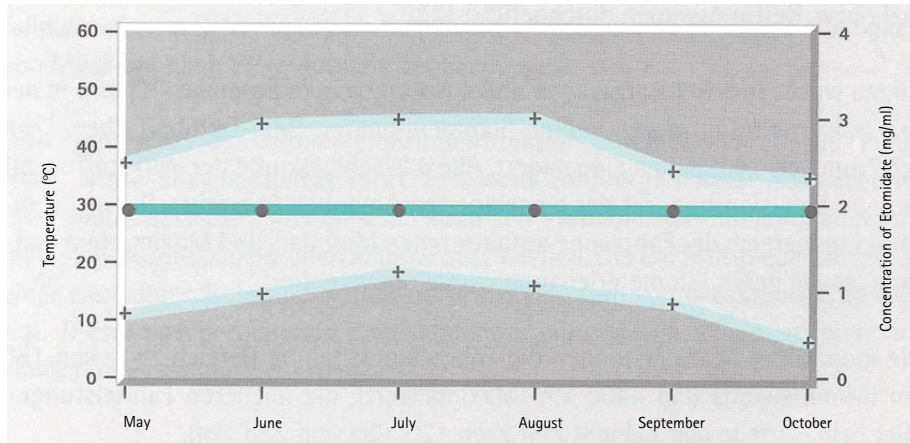


Figure 1. Monthly max. and min. temperatures (+) in the ambulances (left axis) and analysed concentration of etomidate (●) in the ampoules (right axis, middle curve) in the study.

Concerning use in the winter months, the ampoules must be protected from freezing since capillary fractures may be an entry port for contamination. That is, of course, a general precaution and not just restricted to certain drugs.

Emergency intubation anaesthesia

For emergency intubation, two techniques are considered: 1. rapid sequence intubation [RSI] with a concomitantly injected hypnotic and muscular relaxant [MR]; and 2. intubation by maintained breathing. Obviously, the latter is technically more difficult but the consequences of a failed or even oesophageal intubation are not as grave as with the first, where deaths have been caused. With both techniques there is the risk of aspiration of gastric contents to the lungs, possibly resulting in suffocation or Mendelson's syndrome (aspiration pneumonitis).

With RSI attention must be paid to the hypnotic, the MR and the timing of injection and intubation. To my observation, the RSI is generally carried out more rapidly than the MR could work, yielding at best a psychological support, at worst even adverse results from vomiting. Succinylcholine, the most frequently used MR (in any case problematic due to other adverse effects in emergency medicine), causes an increased gastric tonus which then, with relaxation of cardia and vomiting by premature laryngoscopy, may lead to aspiration. The search for a suitable non-depolarizing MR has, unfortunately, not been definitively successful.

For the choice of hypnotic, thiopental was recommended previously but, for the reasons given above, etomidate has been accepted as a gold standard in France and other places and its value for RSI is well documented [24–28], also in children [29,30].

Is it possible to carry out intubation reliably without a MR? In the author's practice it must have been since his equipment was void of any MR. It is, however, quite possible that the route of intubation was of importance since in the author's study of 227 prehospitally intubated patients [10], only 12 were orotracheally intubated and of the remaining, a blind nasotracheal intubation was carried out in 158 cases whereas in 57 patients, a nasal tube was guided laryngoscopically. Controversially, in a study of orotracheal intubation without MR in the hospital [31], only elderly patients with risk factors could be intubated (without the psychological pressure of a necessary success). The explanation may be that the frequently deteriorated conditions of emergency patients augment anaesthesia, while another synergism between etomidate and nalbuphine may account for the rest.

Continued anaesthesia after intubation

The tube alone does not make it an anaesthesia - on the contrary, tracheal reflex stimulation, increased by a badly fixated tube (in turn then augmented by movements of the head, transport disturbances and production of swallowing by the oral route) is apt to cause coughing, which not only is a bad sign but may also be deleterious in cranial trauma. Renewed injection of etomidate may be used for some time to provide temporary relief, but it is not good to control anaesthesia by means of repetitive injection of a short-acting hypnotic under primitive conditions.

Instead, the author recommends the use of midazolam and an opioid. The opioid should be given first (e.g., 0.2 mg fentanyl or 20 mg nalbuphine) and midazolam titrated in repeated doses of 2.5-5.0 mg (at maximum 15 mg). Relaxants should not be used prehospitally at all whereas they can be employed in the emergency department if you are certain to keep the patient intubated for at least the next few hours.



Employing this principle for continued sedation of the intubated patient (with these two substances, it is preferable not to talk of anaesthesia), the physician will soon discover how the dose requirement of midazolam can be anticipated from the patient's general condition.

Figure 2: Nasotracheally intubated entrapped patient. Due to a heavy workload occupying all available hands, the patient was only ventilated after liberation. He was extubated the following day.

Emergency anaesthesia without intubation

The author's own technique, the 'pirate anaesthesia,' was developed when it was required that any anaesthesia in a non-fasting patient (i.e. practically all emergencies) would call for an RSI. One precondition for employing this technique was the assumption that etomidate protects against aspiration by laryngoscopy (no vomiting and an intact laryngeal defence) - with some important exceptions: ileus, late pregnancy, other conditions of high abdominal pressure and the rare condition of oesophageal achalasia. It is, however, also necessary that breathing is maintained and the anaesthetic level is sufficient.

In the literature, a number of publications describe a so-called 'sedation' for brief, painful interventions, using etomidate without any co-medication [32-35]. This is one way to ensure ventilation but the question is, if you can describe the injection of etomidate as 'merely a sedation' (therefore no RSI). Moreover, it is necessary to utilize some co-medication, both in order to avoid any strong myocloni and achieve a sufficient anaesthetic level for really noxious stimulation.

The problem is then, how to augment etomidate without simultaneously causing respiratory depression. Indirectly, the literature supports the existence of such synergism between etomidate on one side and many opioids and benzodiazepines on the other. The author's preference of avoiding this sort of negative synergism with a partial antagonist is only confirmed by one working group [36]. In the author's practise, pentazocine was utilized initially; however, after having precipitated pulmonary oedema in a patient with a heart attack it was replaced with nalbuphine. An equally productive synergism between nalbuphine and midazolam was then found so that these drugs, along with etomidate, were the most frequently used drugs in the last years of the author's activity in prehospital emergency medicine.

A study of the differential synergism between etomidate and various co-medications would pose a suitable challenge for an independent working group.

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