Bispectral index changes following etomidate induction of general anaesthesia and orotracheal intubation


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Background. Etomidate-associated hypnosis has only been studied using standard clinical criteria and raw EEG variables. We conducted a BIS-based investigation of etomidate induction of general anaesthesia.

Methods. Thirty hydroxyzine-premedicated ASA I patients were randomly allocated to receive etomidate 0.2, 0.3, or 0.4 mg kg⁻¹ intravenously over 30 s. The BIS was continuously recorded. A tourniquet was placed on a lower limb to record purposeful movements and myoclonia. Tracheal intubation was facilitated using rocuronium 0.6 mg kg⁻¹ when the BIS value was 50. The times to disappearance of the eyelash reflex, to a decrease in the BIS to 50, and to tracheal intubation were compared. The BIS values 30 s following tracheal intubation, and mean arterial pressure (MAP) and heart rate (HR) at all time points were also recorded.

Results. The BIS value decreased to 50 for tracheal intubation with no purposeful movement in all but one patient in the 0.2 mg kg⁻¹ group. There was no difference between the etomidate groups (0.2, 0.3, and 0.4 mg kg⁻¹) in regards to time to loss of the eyelash reflex (103 (67), 65 (34), 116 (86) s, \( P = 0.2 \)), or to a decrease in BIS to 50 (135 (81), 82 (36), 150 (84) s, \( P = 0.1 \)). Also, the BIS value 30 s after intubation (41 (10), 37 (4), 37 (4), \( P = 0.4 \)), and plasma etomidate concentrations (161 [29–998], 308 [111–730], 310 [90–869] ng ml⁻¹, \( P = 0.2 \)) did not differ between groups. The time to loss of the eyelash reflex was 12–140 s shorter than the time to a decrease in BIS to 50 in three patients in each group who received etomidate 0.2 and 0.4 mg kg⁻¹, and in four patients who received 0.3 mg kg⁻¹. No awareness was recorded. MAP and HR increases following tracheal intubation were comparable between groups.

Conclusions. Etomidate induction doses do not predict the time for BIS to decrease to 50 as this variable varies markedly following three etomidate dose regimen.

Keywords: anaesthesia, depth; anaesthesia, general; anaesthetic techniques, induction; anaesthetics i.v, etomidate; complications, intubation tracheal; analgesia; monitoring, bispectral index

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Etomidate is an imidazole-derived, non-barbiturate hypnotic agent, mainly used for induction of general anaesthesia in haemodynamically compromised patients. Etomidate acts by modulating and mimicking γ-aminobutyric acid type A (GABA<sub>A</sub>) receptors. The pharmacokinetics and pharmacodynamics of etomidate have been described in previous studies. An adequate induction dose is etomidate 0.2–0.4 mg kg⁻¹. Loss of consciousness usually occurs within 10 s following a bolus dose. Plasma etomidate concentrations associated with sedation (100–300 ng ml⁻¹), awakening from anaesthesia (200–300 ng ml⁻¹), and hypnosis allowing minor surgery (300–600 ng ml⁻¹) are within narrow ranges. The pharmacokinetics of etomidate are accounted for by an open three-component model.
However, these studies may have limitations. Significant inter-individual variability in plasma etomidate concentrations was recorded following administration of similar doses. Only small groups of patients and healthy volunteers have been investigated. Also, standard clinical criteria such as haemodynamic responses have been shown to be weak predictors of adequate depth of anaesthesia. In contrast, the EEG bispectral index (BIS) is a computerized EEG-derived variable, closely correlated to sedation and to absence of recall during general anaesthesia. This prospective, double blind study was designed to test three currently used induction doses of etomidate against both BIS values and clinical criteria for adequate depth of general anaesthesia. The follow-up period included the highly stimulating period of tracheal intubation.

Methods

After obtaining Institutional Review Board approval and informed written consent from all participants, 30 consecutive ASA physical status I patients, undergoing elective surgery, received hydroxyzine 1.5 mg kg⁻¹ as oral premedication 90 min before induction of anaesthesia. The patients were prospectively and randomly allocated to receive etomidate 0.2, 0.3, or 0.4 mg kg⁻¹ intravenously as induction doses in a double blind, parallel group study.

Exclusion criteria included: pregnancy; patients who were 25% or more above ideal body weight; patients aged 70 yr or older; intake within the 24 h preceding the study of enzyme-inducing drugs including psychoactive medication, analgesics, excessive alcohol, or of any medication likely to interfere with the assessment criteria.

Lactated Ringer’s solution was infused. Routine intra-operative monitoring included pulse oximetry (\(S_{PO_2}\)), standard lead II electrocardiogram, and non-invasive mean arterial pressure (MAP) measured every minute using an automatic arterial pressure cuff (OmniCare, Hewlett Packard, Boeblingen, Germany). A tourniquet was placed on the upper part of one thigh in order to record any purposeful movement associated with tracheal intubation and/or myoclonus.

A standard BIS monitor strip (BIS Sensor \(^{\circ}\), Aspect Medical Systems, Newton, MA) was placed on the forehead before induction of anaesthesia. The BIS was displayed continuously throughout the procedure, using a model A 2000 Spectral EEG monitor (Aspect Medical Systems, Natick, MA, USA). BIS data were saved on hard disk. Denitrogenation was performed before induction of anaesthesia until expired oxygen was above 90%. Thus, ventilation using a facemask, which might have caused artefacts likely to alter the BIS recording, was not necessary before tracheal intubation.

A nurse not involved in the assessment performed the randomization of the etomidate dose before induction of anaesthesia, using sealed opaque envelopes that contained the group assignments according to a previously randomized computer-generated list. In addition, she prepared individual patient syringes containing an aqueous solution of etomidate (Hypnomidate, Janssen Cilag Laboratory, Issy-les-Moulineaux, France) and started the infusion of the selected etomidate dose. The etomidate dose was infused over a 30-s period through an antecubital vein, using a syringe pump (Pilote Anesthesie 2, Fresenius Vial SA, Brezins, France). The anaesthetist in charge of the patient undertook the BIS monitoring and tracheal intubation, but was unaware of the etomidate dose used. Tracheal intubation was facilitated using rocuronium 0.6 mg kg⁻¹ when the BIS value had decreased to 50, as rocuronium 0.6 mg kg⁻¹ should allow tracheal intubation within 1 min following administration. The anaesthetist in charge of the BIS monitoring performed tracheal intubation when the patient was judged clinically suitable, provided that the BIS was 50 or less. When the BIS had returned to 50 following tracheal intubation, anaesthesia was continued using sufentanil and isoflurane. A propofol 3 mg kg⁻¹ rescue dose was available if the BIS did not decrease below 50 before tracheal intubation. Propofol administration was also allowed if tracheal intubation was impossible and/or a patient showed signs of inadequate anaesthesia such as purposeful movements of the lower limb protected by the tourniquet, swallowing, coughing, sweating, lacrimation, or no loss of consciousness.

Whether tracheal intubation could be easily performed and was associated with purposeful movements was recorded. The time intervals from etomidate administration (T₀) to disappearance of the eyelash reflex (T₁), to a decrease in the BIS to 50 (T₂), and to tracheal intubation (T₃) were recorded and compared. The BIS was also noted 30 s following tracheal intubation (T₃'). MAP and heart rate (HR) were recorded at T₀, T₁, T₂, T₃, and when the BIS returned to 50 (T₄). In order to assess explicit memory, patients were asked about recall or awareness on the day following surgery.

Myoclonus was studied by a trained physician blinded to the treatment groups. Myoclonus has been defined as an involuntary, short contraction of some muscle fibres, of a whole muscle, or of different muscles of one group, leading to a short observable movement of the corresponding body part.

A 5 ml venous blood sample was taken from the arm opposite to that in which the i.v. infusion was established, to measure the plasma etomidate concentration immediately after tracheal intubation. Samples were collected in tubes containing lithium heparinate and immediately centrifuged at 2400 g for 15 min before freezing at −20°C. They were analysed later by a high-performance liquid chromatography assay using a modification of the McIntosh and Rajewski method.

The number of patients for the present study was based on the fact that similar investigations used at the most 30 patients or fewer for data acquisition. Data are
Table 1 Physical characteristics in 30 ASA I patients randomly allocated to receive etomidate 0.2, 0.3, or 0.4 mg kg\(^{-1}\) over 30 s. Values are: age, mean (range); weight and height, mean (SD). Results are mean (SD) except for etomidate concentrations expressed as median (range). In addition, the range is indicated when appropriate. No statistically significant differences occurred between groups (P>0.1) except for weight (P=0.002).

<table>
<thead>
<tr>
<th>Etomidate</th>
<th>0.2 mg kg(^{-1})</th>
<th>0.3 mg kg(^{-1})</th>
<th>0.4 mg kg(^{-1})</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>52 (38–68)</td>
<td>51 (35–78)</td>
<td>47 (32–57)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>64 (9)</td>
<td>74 (12)</td>
<td>56 (7)</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>164 (5)</td>
<td>168 (10)</td>
<td>165 (10)</td>
</tr>
<tr>
<td>Sex ratio (M/F)</td>
<td>1/9</td>
<td>4/6</td>
<td>1/9</td>
</tr>
<tr>
<td>HR at baseline (beat min(^{-1}))</td>
<td>72 (8)</td>
<td>77 (18)</td>
<td>78 (10)</td>
</tr>
<tr>
<td>MAP at baseline (mm Hg)</td>
<td>91 (20)</td>
<td>90 (12)</td>
<td>82 (10)</td>
</tr>
<tr>
<td>Loss of eyelash reflex (T1) (s)</td>
<td>103 (67)</td>
<td>65 (34)</td>
<td>116 (86)</td>
</tr>
<tr>
<td>Time to BIS=50 (T2) (s)</td>
<td>135 (81)</td>
<td>82 (36)</td>
<td>150 (84)</td>
</tr>
<tr>
<td>Time to intubation (T3) (s)</td>
<td>208 (100)</td>
<td>156 (41)</td>
<td>240 (86)</td>
</tr>
<tr>
<td>BIS 30 s after intubation (T‘3)</td>
<td>41 (10)</td>
<td>37 (4)</td>
<td>37 (4)</td>
</tr>
<tr>
<td>Myoclonia (yes/no)</td>
<td>3/7</td>
<td>2/8</td>
<td>1/9</td>
</tr>
<tr>
<td>Etomidate plasma concentration (ng ml(^{-1}))</td>
<td>161 (29–998)</td>
<td>308 (111–730)</td>
<td>310 (90–869)</td>
</tr>
</tbody>
</table>

Fig 1 Times to loss of the eyelash reflex, to a decrease in BIS to 50, to tracheal intubation and BIS values recorded 30 s following tracheal intubation in 30 ASA I patients randomly allocated to receive etomidate 0.2, 0.3 or 0.4 mg kg\(^{-1}\) over 30 s.
Results

The three etomidate groups were comparable in respect of their physical characteristics (except for weight, \( P=0.02 \)). The MAP and HR at baseline, BIS values 30 s following tracheal intubation, and times from etomidate administration (T0) to loss of the eyelash reflex (T1), to a decrease in BIS to 50 (T2), and to tracheal intubation (T3) were similar in the three groups (all \( P \) values \( \geqslant 0.1 \)) (Table 1, Fig. 1). All the time intervals were scattered across a wide range (Fig. 1). The time to loss of the eyelash reflex was significantly correlated with the time to a decrease in BIS to 50 (\( r=0.8, P<0.001 \)). However, the time to loss of the eyelash reflex differed markedly from the time to a decrease in BIS to 50 in three patients who received etomidate 0.2 mg kg\(^{-1}\) (30, 60, 85 s), four patients who received etomidate 0.3 mg kg\(^{-1}\) (12, 21, 43, 60 s), and three patients who received etomidate 0.4 mg kg\(^{-1}\) (60, 105, 140 s).

All except three patients underwent tracheal intubation with no purposeful movement, regardless of the etomidate dose. One patient in the group who received etomidate 0.2 mg kg\(^{-1}\) was still awake 10 min following etomidate administration. This patient was withdrawn from further assessment. In one patient who received etomidate 0.2 mg kg\(^{-1}\), the BIS value increased to 60, 20 s following tracheal intubation whereas in all other patients BIS values remained below 50 for 40–60 s (Fig. 1). One patient who received etomidate 0.4 mg kg\(^{-1}\) did not require any additional drug administration after sufentanil 10 mg had been given in accordance with the study design, and underwent surgery with a BIS value of 30. He recovered consciousness with no recall when nitrous oxide was discontinued. MAP and HR recorded for this patient during recovery when the BIS had returned to 50 were considered as T4 data. BIS values decreased sharply in all patients regardless of the dose regimen (Fig. 2).

Both MAP and HR changed significantly with time (\( P<0.0001 \) for both variables) but were not significantly affected by the etomidate dose (\( P=0.1 \) and \( P=0.2 \) for MAP and HR, respectively). No significant time differences were discovered in the \textit{post hoc} analysis of MAP and HR changes with time, although a trend towards an increase in MAP and HR occurred following tracheal intubation (\( T'3 \)). Myoclonia frequency did not differ significantly between groups (Table 1). No recall or awareness was recorded.

Plasma etomidate concentrations following tracheal intubation were obtained from 28 patients and did not differ significantly between groups (Table 1). Blood samples were not taken from two patients who received etomidate concentrations presented as the mean (SD). The median (range) is only used for non-normally distributed etomidate concentrations, and is provided for selected normally distributed variables for completeness. Categorical data are described as number of patients (\( n \)). Physical characteristics, baseline MAP and HR, BIS values 30 s following tracheal intubation, and all time intervals were compared using a one-way ANOVA after normal distribution had been ascertained. Whether myoclonia was recorded or not was compared using the \( \chi^2 \) test. A two-way ANOVA (time–etomidate dose) was used to investigate the change in MAP and HR over time. The \textit{post hoc} Neumann–Keuls test was used when appropriate. Log-transformation of plasma etomidate concentrations resulted in normal distribution of this variable, which was subsequently submitted to an inter-group comparison using ANOVA. The Spearman correlation coefficient was used to study the relationship between the time to loss of the eyelash reflex and the time for the BIS to decrease to 50. All differences were considered significant at \( P<0.05 \). Statistical analysis was performed using Statview 5 software.
Discussion

In this study, etomidate doses recommended previously for induction of general anaesthesia in clinical practice were investigated for the first time using BIS monitoring. Three main findings are reported. First, tracheal intubation with no purposeful movement was possible following etomidate administration provided the BIS value had decreased to 50. Secondly, etomidate induction doses were not predictive of the times needed to achieve both the BIS-based and the clinical signs of adequate depth of anaesthesia for tracheal intubation. Thirdly, both the BIS-based and the clinical criteria differed markedly in three or four patients out of 10 in each treatment group.

An additional study of etomidate was warranted. Previous etomidate dose–response studies were conducted on small numbers of patients and/or on healthy volunteers and/or were based on unreliable clinical criteria. Furthermore, wide inter-individual variability was reported within and between studies. Currently, volume of distribution, redistribution, effect site concentration, and brain sensitivity are taken into consideration for pharmacokinetic assessment. Also, some clinical criteria used previously to investigate etomidate, mainly MAP and HR changes, and loss of verbal response, are known to be unreliable indicators of adequate depth of anaesthesia when used as sole indices. In contrast, the purposeful movement of a body part in response to a noxious stimulus, a criterion used in the present study, is a reliable clinical indicator of depth of anaesthesia. Furthermore, BIS is highly correlated with level of sedation and loss of consciousness for volatile and most i.v. anaesthetic agents. The only etomidate BIS-based investigation published, sampled only five patients and used a device only providing BIS values with a 75-s delay. Intra-operative recall and awareness are well-defined phenomena not investigated previously after etomidate.

The present study yielded clinically relevant information. In contrast to previous etomidate investigations, the times to loss of the eyelash reflex and to a decrease in BIS to 50 were scattered across a wide range. Three etomidate doses recommended in clinical practice for induction of anaesthesia were predictive neither of the time necessary to achieve a BIS value of 50 nor of the time to loss of the eyelash reflex. The present BIS-based findings suggest that anaesthetists are likely to question the hypnotic effect of etomidate in clinical practice, especially if the induction time is at the upper limit of the recorded range, and BIS monitoring is not used. Within each etomidate group, the time to loss of the eyelash reflex was markedly shorter than the time to a decrease in BIS to 50 in three to four patients out of 10. These findings illustrate the potential with etomidate for unanticipated awareness and recall, as has been demonstrated with other hypnotic agents when only clinical signs are taken into consideration for depth of anaesthesia assessment. When the BIS value decreased, it did so abruptly regardless of the dose regimen, in accordance with Kuigenza’s data. Laryngoscopy and intubation could be performed before opiate agent administration with neither purposeful movement nor recall in all the patients, provided that the BIS value had decreased to 50. However, etomidate administration did not significantly reduce the MAP and HR increases associated with such clinical stimuli as laryngoscopy and intubation, in a similar manner to most hypnotic agents.

Some of the data reported in this investigation differ from previous studies. Times to loss of the eyelash reflex and to a decrease in BIS to 50 are scattered across a wide range. More clustered results have been reported elsewhere. Thus, patients receiving etomidate 0.3 mg kg$^{-1}$ over 30 s were reported to have consistently lost consciousness in 10 s and to have had adequate depth of anaesthesia for 3–5 min. This earlier study may not have been designed accurately enough to allow a conclusion to be drawn. Furthermore, in contrast to previous results collected during stable anaesthesia, plasma etomidate concentrations recorded in the present study after tracheal intubation did not correlate with the administered dose regimen. This is not surprising as induction of general anaesthesia does not occur at steady-state. Moreover, an i.v. bolus of a hypnotic agent rapidly undergoes redistribution and is associated with a rapidly changing plasma drug concentration. Also, drug effect–site concentrations differ from concentrations measured in the venous blood of the forearm.

Some other points should be emphasized. Induction of anaesthesia is currently evaluated in clinical practice by absence of purposeful movements after noxious stimulation. The BIS is highly correlated with adequate depth of anaesthesia and no recall. Comparing these two criteria is of clinical significance. Hypnosis from etomidate was not investigated in a preliminary study of BIS to evaluate a cut-off value of 50. However, BIS is a computerized EEG-derived variable and etomidate consistently produced EEG alterations in humans and in laboratory animals similar to those observed with anaesthetic agents validated previously against BIS values. Myoclonia did not cause epileptic paroxysms or ictal spiking likely to alter BIS recording in the present study, probably because etomidate-associated myoclonia results from subcortical disinhibition. Tracheal intubation producing a highly reproducible reflex response, was used previously to evaluate whether adequate depth of anaesthesia had been provided. In addition the isolated limb technique detects purposeful movements in sedated, paralysed patients. Using this technique, rocuronium would not have suppressed any purposeful movements from inadequate depth of anaesthesia or from myoclonia.

In conclusion, a BIS value of 50 was associated with the absence of purposeful movement during tracheal intubation,
the absence of recall following etomidate administration. The etomidate dose regimen was not predictive of the time taken for the BIS value to decrease to 50. The time to a decrease in BIS to 50 was longer than the time to loss of the eyelash reflex in three to four patients out of 10 in each group studied.

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