PLASMA CONCENTRATION AND E.E.G. AFTER VARIOUS REGIMENS OF ETOMIDATE

A. DOENICKE, B. LÖFFLER, J. KUGLER, H. SUITTMANN AND B. GROTE

SUMMARY

Etoraidate was injected i.v. within 10 or 60 s at various doses. After etomidate 0.3 mg kg\(^{-1}\) the plasma concentration was 1.6 \(\mu\)g ml\(^{-1}\) at 1 min after the end of injection. For about 7 min a good hypnotic effect (stages C\(_2-O\) D\(_2\)) was observed on the e.e.g. recording. For surgical procedures, however, a combination with analgesic drugs appeared to be necessary. When the dose of etomidate was increased (0.1–0.4 mg kg\(^{-1}\)) a linear increase in plasma concentration and slow e.e.g. activity was observed concomitantly. Anaesthesia could be prolonged with additional injections or with continuous infusion. Each additional injection produced a steep increase in concentration of short duration with marked deepening of hypnosis. The infusion induced only a moderate increase in plasma concentration, whereas the depth of sleep during the period of infusion remained nearly the same. E.e.g. changes induced by etomidate are similar to those after barbiturates and other i.v. anaesthetics.

Following the initial animal experiments carried out at Janssen Pharmaceutica (Janssen et al., 1971), etomidate was first used by two of the authors in 1972 in man under e.c.g. and e.e.g. control. After further experimental studies and 8 years of clinical research, this substance became a successful short-acting hypnotic with minimal effects on the circulation (Bruckner et al., 1974; Doenicke et al., 1974; Kettler et al., 1974). The possibility of histamine release can almost be excluded (Doenicke, Lorenz et al., 1973).

That hypnosis could be prolonged by additional injections of etomidate has been known for some time and has been confirmed by e.e.g. recordings (Doenicke, Kugler et al., 1973). However, for such clinical applications there was a lack of information on the plasma concentration.

At the end of 1974 Wynants, Woestenborghs and Heykants published a method enabling investigators to determine etomidate in the plasma by gas chromatography, using the unlabelled drug. By means of this procedure, we have established the plasma concentration occurring after different etomidate regimens and compared these results with the e.e.g. findings (Doenicke et al., 1975).

SUBJECTS AND MATERIALS

Fifteen healthy male volunteers, aged 20–30 yr, took part in this study, giving informed consent.

Group 1

Six subjects received etomidate 0.3 mg kg\(^{-1}\) at 2-week intervals, on the first occasion over 10 s and on the second occasion over 60 s.

Group 2

Six subjects each received etomidate 0.3 mg kg\(^{-1}\) over 60 s followed by 0.15 mg kg\(^{-1}\) over 60 s at 5 min and at 12 min. Two weeks later they received the same initial dose (0.3 mg kg\(^{-1}\)) followed by 0.3 mg kg\(^{-1}\) in 250 ml of glucose as a continuous infusion injected between the 5th and 14th min.

Group 3

Three subjects each received, at 10-day intervals, a total of four anaesthetics. Etomidate was injected in increasing doses, 0.1, 0.2, 0.3 and 0.4 mg kg\(^{-1}\), always within 10 s.

Premedication was the same for all groups: atropine 0.5 mg 15 min before the start of anaesthesia, diazepam 0.05 mg kg\(^{-1}\) 10 min before, and fentanyl 0.1 mg i.v. 5 min before. Diazepam and fentanyl were given to avoid the occurrence of myoclonic movements.

Blood 8 ml was sampled from an arm vein at the
following times: for the anaesthetics with a single injection, 1, 2, 4, 8, 16 and 32 min after the end of injection; for the anaesthetics with additional injections and continuous infusion 1, 2, 4, 7, 9, 14, 16, 20, 28, 44, and 60 min after the end of injection. The blood was stored in cooled test tubes containing sodium citrate and potassium fluoride. Blood samples were centrifuged at 3000 rev min\(^{-1}\) and plasma was separated from the blood.

For gas chromatographic determination propoxate 1\(\mu\)g (propyl-phenyl-ethyl-1H imidazol-5-carboxylate) was added to the plasma and used as internal standard. This standard was used throughout the chemical extraction of the substance.

The gas chromatograph was a Varian 2140 with an alkali flame ionization detector. After the injection of the sample to the gas chromatograph the peak of etomidate appeared first, followed by that of propoxate. The amount of etomidate in the sample was measured by a comparison of these two peaks. Concentrations of etomidate between 0.01 \(\mu\)g ml\(^{-1}\) and 10 \(\mu\)g ml\(^{-1}\) could be measured. The error was 5% for the greater concentration (10 \(\mu\)g ml\(^{-1}\)) and 20% for the lesser concentration (0.01 \(\mu\)g ml\(^{-1}\)) (Wynants, Woestenborghs and Heykants, 1974).

From the time of premedication, the e.e.g. and arterial pressure (Riva-Rocci) were monitored continuously. The e.e.g. was recorded on a 12-channel Hellige-apparatus (Kugler, Doenicke and Laub, 1977).

The e.e.g. curves were evaluated visually and classified according to the e.e.g. stages in each successive 40-s epoch (table I) and then illustrated in a compressed time-scale giving a display of the spectrum of vigilance and sleep (vigilosomnogram).

The following time points of the spectrum were compared with the corresponding plasma concentrations:

(a) period of latency: the period between the start of the injection and the first e.e.g. changes.
(b) end of peak activity: the time when the vigilosomnogram changed from Q to B\(_2\).
(c) end of activity: return to superficial stages of sleep or to awakening (A\(_1\), A\(_2\), B\(_0\)).

## RESULTS

The e.e.g. stages after the administration of etomidate were comparable to the e.e.g. patterns after barbiturates and other i.v. anaesthetics. After a period of latency lasting 10–30 s (depending on the speed of injection), a short initial activation phase of a few seconds occurred with 6–10 s e.e.g. activity (fig. 1).

Subsequently, this e.e.g. changed very rapidly to high, slower activity with superimposed lower rapid waves. When hypnotic activity subsided, mixed activity decreased and more prolonged, slow waves were observed over the posterior region of the brain. Paroxysmal, or burst suppression, activities did not occur.

### Rapid and slow injection (fig. 2)

**Group 1.** Within the first minute after the end of injection, peak plasma concentrations of 1.59 (0.48–2.67) \(\mu\)g ml\(^{-1}\) were reached after rapid injection; 1.30 ± 0.38 \(\mu\)g ml\(^{-1}\) after slow injection. All the data presented here were expressed as mean values

<table>
<thead>
<tr>
<th>TABLE I. Classification of depths of sleep (vigilosomnogram).</th>
<th>L = Loomu; K = Kugler</th>
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<tbody>
<tr>
<td>Mental relaxation</td>
<td>A</td>
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<tr>
<td>Very slight sleep</td>
<td>A(_1)</td>
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<td></td>
<td>A(_2)</td>
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<td>B(_1)</td>
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<td>B(_2)</td>
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<td>Light sleep</td>
<td>C</td>
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<td>C(_1)</td>
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<td>C(_2)</td>
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<tr>
<td>Moderately deep sleep</td>
<td>D</td>
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<td>D(_1)</td>
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<td></td>
<td>D(_2)</td>
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<tr>
<td>Very deep sleep</td>
<td>E</td>
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ETOMIDATE AND E.E.G. CHANGES

Fig. 1. Etomidate-induced e.e.g.-changes (healthy volunteer): 10 s before the end of injection (0.3 mg kg$^{-1}$ within 1 min) relatively fast irregular activity. At the end of the injection (1 min, ↑) small slow waves. One minute later (2 min) high slow activity, superimposed fast waves. The oculogram (OG; right to left epicanthus) shows decreasing rapid eye movements of wakefulness. In the e.c.g. (ECG I) increasing heart rate (up to 88 beat min$^{-1}$). Respiration irregular, relatively fast (22 b.p.m.).

Fig. 2. Vigilosomnogram after a bolus injection of etomidate 0.3 mg kg$^{-1}$ and corresponding etomidate concentrations in the plasma. Premedication: -15 min, atropine 0.5 mg; -10 min, diazepam 0.05 mg kg$^{-1}$; -5 min, fentanyl 0.1 mg.
Fig. 3. Vigilosomnogram (mean values ± SD) of prolonged anaesthesia. Additional injections of etomidate 0.3 mg kg⁻¹ (60 s at 0 min), 0.15 mg kg⁻¹ (60 s at 5 min), 0.15 mg kg⁻¹ (60 s at 12 min), and corresponding etomidate concentrations in the plasma. Premedication: −15 mm, atropine 0.5 mg; −10 mm, diazepam, 0.05 mg kg⁻¹; −5 min, fentanyl 0.1 mg.

± SD. At 1 min plasma concentration was approximately 0.6 µg ml⁻¹, and at 32 min the concentration was approximately 0.075 µg ml⁻¹ with both types of injection.

The end of peak activity occurred after 427 ± 85 s for the rapid injection and after 440 ± 112 s for the slow injection, both read from the e.e.g. (fig. 2). The difference was not statistically significant. The total duration of sleep did not differ substantially either: 770 ± 218 s after the rapid injection vs. 700 ± 185 s after the slow injection. The plasma–time diagrams revealed an etomidate concentration of 0.14 µg ml⁻¹ at the end of peak activity and of 0.11 µg ml⁻¹ at the end of activity.

Prolongation of anaesthesia by additional injections or continuous infusion (fig. 3)

Group 2. Up to the 4th min the same pronounced initial decrease in concentration observed in the first group was noticed. Thereafter, each additional injection, as expected, produced a pronounced, rapid increase in plasma concentration; the subsequent decrease in concentration resembled that of the first injection.

Each additional injection had an effect on the depth of sleep as noted in the e.e.g. (fig. 3, upper part). After 22 min individual values showed considerable variation with a tendency to deep, posthypnotic stages.

No such changes in plasma concentration were noted when etomidate was administered by continuous infusion (fig. 4). From 0.34 ± 0.06 µg ml⁻¹ at the beginning of the infusion, the plasma concentration increased to 0.54 ± 0.12 µg ml⁻¹ at the end of the infusion; at 20 min no difference was apparent between bolus injection and infusion. The peak of activity after both regimens lasted about 22 min whereas the end of activity appeared at about 34 min.

Increasing dose of etomidate

Group 3. The vigilosomnogram (fig. 5A) showed that increasing doses of etomidate produce a deeper and longer hypnotic effect. There was a good relationship between plasma concentration and the observed changes in vigilosomnogram (fig. 5B). The plasma concentration of etomidate at the end of peak activity was 0.12 ± 0.04 µg ml⁻¹ at a dose of 0.1 mg kg⁻¹ and 0.22 ± 0.05 µg ml⁻¹ at 0.4 mg kg⁻¹ (P < 0.05). By increasing the doses of etomidate “acute tolerance” was observed (fig. 6) as it has been described for barbiturates (Brodie et al., 1951; Dundee, Price and Dripps, 1956; Maynert and Klingmann, 1960).
ETOMIDATE AND E.E.G. CHANGES

**Kinetics of etomidate**

The clear biphasic decrease in the plasma concentration curve after a single bolus injection can be explained by means of a two-compartment open model.

After a rapid injection, etomidate immediately entered the central or distribution compartment, represented by the intravascular volume, which is the sole compartment involved in excretion. There is a rapid exchange between this compartment and the effector compartment c.s.f. and specific receptors, where the drug exhibits its activity (Dost, 1968). Both distribution spaces can be regarded as a common reference compartment with a volume of 7.5 litre.

In addition to the plasma, this compartment also comprises well-perfused organs. The half-life of etomidate of 1 min for this compartment correlates well with the short hypnotic activity of the drug.

After 8 min the concentration decreased less rapidly than before, maintaining an equilibrium between plasma and tissue concentrations (zero exchange of drug). The changes in this phase correspond with the elimination of drug.

The distribution volume for etomidate was 145 litre, the elimination constant 0.03 min and the elimination half-life 29 min.

**DISCUSSION**

At pH 7.4 etomidate was 65% bound to albumin, the total binding to human plasma being substantially greater (90%). Etomidate is thus one of the substances with very high protein binding (Mannes and Doenicke, 1977). This might explain why the differences between the effects of rapid and slow injections are so small with regard to plasma concentration and hypnotic activity. A conspicuous feature in this respect is the fluctuation of measured values during the 1st min following a single rapid injection. In some subjects, the processes of distribution probably occur at such a rapid rate that at the time of measuring a large proportion of the drug has already been carried to well perfused organs.

In recent studies, the detection limit for unlabelled etomidate could be lowered still further by perfecting the method devised by Wynants (van Hamme, Ghoneim and Ambre, 1978; Schüttler, Wilms et al., 1980). Thus, Schüttler, Wilms and others (1980) succeeded in following the pathways of etomidate up to 4 h after a bolus injection; van Hamme, Ghoneim and Ambre (1978) extended this to 10 h.

Kinetic data obtained from their studies were different from those obtained by us (Schüttler: \(T_1 = 68\) min, \(V = 161\) litre; van Hamme:
FIG. 5. Vigilosnomogram of increasing doses (left-hand part of figure) corresponding with etomudate concentrations in the plasma (right-hand graphs). Premedication: - 15 min, atropine 0.5 mg, - 10 min, diazepam 0.05 mg kg⁻¹; - 5 min, fentanyl 0.1 mg.
At the dose we chose for continuous infusion (0.3 mg kg\(^{-1}\)) corresponding to 2.4 mg min\(^{-1}\) the plasma concentration 5 min after the first injection increased from 0.34 \(\mu g\) \(ml^{-1}\) to 0.54 \(\mu g\) \(ml^{-1}\) and remained at that value until the end of the infusion. If the concentration becomes less than 0.19 \(\mu g\) \(ml^{-1}\) lighter sleep stages occur with waking at values less than 0.12 \(\mu g\) \(ml^{-1}\) (fig. 4).

Schüttler, Stoeckel and others (1980) reported an infusion regimen with two different doses. Etomidate 80 mg was infused within 10 min to induce sleep. Subsequently, a plasma concentration of 0.5 \(\mu g\) \(ml^{-1}\) was maintained with etomidate 0.8 mg min\(^{-1}\). Plasma concentration on recovery from sleep was approximately 0.3 \(\mu g\) \(ml^{-1}\), 2.5 times greater than in our studies. The apparent reason for these discrepancies must be the absence of premedication in Schüttler’s study. As a consequence, they noticed myoclonia in each volunteer at induction and recovery. It is worthwhile mentioning that the use of an analgesic (fentanyl, nitrous oxide) in clinical practice is very important when etomidate is used as an hypnotic drug.

The bolus injection of etomidate seems to us a safer form of induction than is the infusion, especially since etomidate 80 mg within 10 min represents a very high dose. Subsequently, the continuous infusion is set according to the patient’s requirements, the premedication used and the type of surgery.

The dose we chose is certainly too great for prolonged anaesthesia. After 20 min a dose of 0.5–0.8 mg min\(^{-1}\) appeared to suffice. In a late study Schwilden and co-workers (1981) have shown that, after 30 min, this dose can be further decreased.

REFERENCES


Lorenz, W., Beigl, R., Bezecny, H., Uhlig, G., Kalmar, L.
CONCENTRACIONES PLASMÁTICAS Y E.E.G. DESPUÉS DE VARIOS REGIMENES DE ETOMIDATA

SUMARIO

Se injectingaron por vía intravenosa varias dosis de etomidato a intervalos de 10 ó 60 segundos. Al cabo de un minuto de haber administrado una inyección de 0,3 mg kg⁻¹ de etomidato la concentración plasmática fue de 1,6 μg ml⁻¹. Por espacio de 7 minutos se observó un buen efecto hipnótico (fases C₀ – D₂) en el registro del e.e.g. No obstante, para fines de intervención quirúrgica parece ser necesaria una combinación con drogas analgésicas. Cuando se incrementó la dosis de la droga (0,1 – 0,4 mg kg⁻¹) se observó con carácter concomitante un incremento lineal de la concentración plasmática y del periodo de sueño. La anestesia podria prolongarse mediante inyecciones adicionales o mediante infusión continua. Cada una de las inyecciones adicionales produjo un nuevo incremento de la concentración, de poca duración, junto con un incremento del grado de hipnosis. La infusión produjo tan sólo un incremento moderado de la concentración de plasma, al tiempo que la profundidad del sueño durante el período de infusión permaneció más o menos constante. Los cambios en e.e.g. inducidos por el etomidato fueron similares a los producidos por los barbitúricos y demás anestésicos intravenosos.

CONCENTRATIONS PLASMATIQUES ET E.E.G. APRES DIFFERENTS PROTOCOLES D'ADMINISTRATION DE L'ETOMIDATE

RESUME

De l'etomidate a été injecté en 10 ou 60 s par voie intraveineuse à différentes posologies. Après 0,3 mg kg⁻¹ d'etomidate, la concentration plasmatique était 1,6 μg ml⁻¹ 1 min après la fin de l'injection. On a observé un bon effet hypnotique (états C₀ – D₂) sur les enregistrements e.e.g. pendant environ 7 min. Il semble cependant nécessaire d'associer des analgésiques pour des actes chirurgicaux. Lorsque l'on a augmenté les posologies d'etomidate (0,1 – 0,4 mg kg⁻¹), on a observé simultanément une augmentation linéaire de la concentration plasmatique et de la durée d'action. L'anesthésie pouvait être prolongée par des injections supplémentaires ou une perfusion continue. Chaque injection supplémentaire entraînait une augmentation de concentration de courte durée et un approfondissement marqué de la narcose. La perfusion continue n'entraînait qu'une augmentation modérée de la concentration plasmatique, alors que la profondeur de la narcose restait pratiquement constante pendant la période de perfusion. Les modifications e.g. induites par l'etomidate sont les mêmes que celles observées après injection de barbituriques ou autres anestésiques intraveineux.