PHARMACOKINETICS OF ETOMIDATE ASSOCIATED WITH PROLONGED I.V. INFUSION

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SUMMARY

Plasma concentrations of etomidate have been measured in six patients who required intermittent positive pressure ventilation following surgery. There was an approximately linear relationship between the plasma concentration and the rate of infusion of etomidate. The drug exhibited linear pharmacokinetics over a 10-fold variation in plasma concentration. The decrease in the plasma concentration after discontinuing the infusion was consistent with a three-compartment pharmacokinetic model. The plasma terminal half-life was found to be about 5.5 h, and the clearance calculated to be 0.025 litre kg\(^{-1}\) min\(^{-1}\).

The use of an infusion of etomidate i.v. to provide sedation for patients requiring intermittent positive pressure ventilation in the intensive therapy unit has been described recently (Edbrooke et al., 1982). The technique provides amnesia and sedation in association with stable respiratory and cardiovascular indices and has virtually eliminated the need for neuromuscular blocking drugs in our unit.

Although methods which measure the plasma concentration of etomidate have been described, the pharmacokinetics of the drug, when administered by continuous infusion, have not been investigated. We have measured the plasma concentrations of etomidate and studied the relationship between the plasma concentration and the rate of infusion of this drug.

PATIENTS AND METHODS

Patients and anaesthetic management

Data were obtained during a study of the efficacy of continuous sedation i.v. in the postoperative management of six patients requiring intermittent positive pressure ventilation. All of the patients had undergone maxillofacial surgery (table I) and all had given consent to these procedures. The study was approved by our Ethics Committee.

A cannula was inserted to the radial artery of the non-dominant arm under local anaesthesia. Dexamethasone 4 mg was administered i.v. and anaesthesia induced with thiopentone 4 mg kg\(^{-1}\). Alcuronium 0.2 mg kg\(^{-1}\) was administered and the lungs ventilated mechanically. Normocapnia was maintained. The inspired oxygen and nitrous oxide mixture (\(F_{O,2}\), 0.4) was humidified with a Bennet cascade humidifier at 40°C.

During the operation analgesia was obtained by infusing fentanyl 0.045 \(\mu\)g kg\(^{-1}\) min\(^{-1}\) i.v. supplemented, if necessary, with a single bolus injection of 25 \(\mu\)g (McQuay et al., 1979). Following surgery and throughout the study, analgesia was maintained with a continuous infusion of fentanyl 0.034 \(\mu\)g kg\(^{-1}\) min\(^{-1}\); this was intended to produce a steady state plasma concentration throughout the period of study. Reversal of the neuromuscular blockade was not required.

The patients were transferred to the intensive therapy unit and 10 min was allowed for monitoring to be established. The patients were nursed in a quiet environment and wore ear muffs to reduce auditory stimuli. A bolus injection of etomidate 0.3 mg kg\(^{-1}\) was given, immediately followed by an infusion of etomidate i.v. that was varied between 1 and 25 \(\mu\)g kg\(^{-1}\) min\(^{-1}\), depending on the clinical response of the patient.

Magnesium trisilicate mixture BPC 5 ml h\(^{-1}\) was given through a nasogastric tube to decrease the acidity of the stomach contents. All other drugs were administered i.v. through a central venous catheter. A total fluid load of 1.8 ml kg\(^{-1}\) h\(^{-1}\) was maintained using a solution of 4% dextrose and 0.18% sodium chloride to supplement the infusions of etomidate and fentanyl. Bolus injections of dexamethasone (4 mg every 6 h) were administered to reduce inflammation.

Consciousness was assessed using a slightly modified version of the Glasgow Coma Scale (Teasdale and Jennett, 1974). The modification was imposed
because the patients were unable to make a verbal response on account of the endotracheal intubation. A scale, utilizing eye opening and best motor response, was used. The aim was to produce a level of consciousness such that the patients remained asleep but opened their eyes and obeyed commands when addressed. This scale may be more limited when it is applied to measure sedation than when it is used to measure brain injury, in that we have not seen extensor posturing in any patient recovering from sedation. However, we have used the scale extensively and have found that it provides a simple and readily reproducible guide to the patients’ levels of consciousness.

**Etomidate infusion and plasma concentrations**

As it was anticipated that the patients would require artificial ventilation for about 2 days a solution containing etonidate 750 mg in 500 ml of 5% dextrose was prepared. This volume of solution was sufficient for the entire period of the study and ensured that a constant concentration of drug was given (a solution of 125 mg of etomidate in 1 ml of ethyl alcohol (Janssen Pharmaceuticals) was used). The rate of infusion was controlled with a volumetric infusion pump (Tekmar), and was adjusted as required to achieve appropriate clinical conditions.

Blood samples were drawn from the intra-arterial cannula at frequent intervals for the first 2 h and at 4-hourly intervals thereafter. Approximately 24 h after starting the infusion, the rate of infusion of etomidate was increased to the maximum rate given during the initial period of stabilization and then gradually decreased such that the eventual infusion rate was approximately double that of the previous 24 h. This was intended to achieve quickly a new steady state plasma concentration associated with a rate of infusion that was double associated with the previous steady state. This rate was maintained for a minimum of 16 h. In four patients the effects of a third and in one a fourth incremental increase in the rate of infusion of etomidate were investigated (table I). The decrease in the concentration of etomidate after discontinuing the infusion was measured in blood samples taken at frequent intervals for the first 2 h and thereafter with diminishing frequency for up to 24 h.

Each 4-ml sample of blood was placed in a cooled stoppered tube containing heparin and 10 μl of a saturated solution of potassium fluoride to inhibit blood esterases. Plasma was separated from the blood sample by centrifugation and stored at −20°C until assayed.

**Assay of etomidate**

The etomidate was assayed in duplicate by high pressure liquid chromatography using propoxate as the internal standard. Propoxate hydrochloride 0.8 μg was added to each plasma sample and the etomidate and propoxate extracted into high grade pentane by placing on a vortex mixer for 30 s. The pentane layer was separated by centrifugation and evaporated to dryness by warming to 45°C. The residue was dissolved in 200 μl of the mobile phase that consisted of a mixture of 32.5% methanol, 32.5% water and 35% acetonitrile. A volume of 75 μl of this mixture was injected to an Altex 4.6 × 250-mm ultrasphere 5-μm C-8 column (Anachem) of a high pressure liquid chromatograph (Perkin Elmer series 3B). A flow rate of 1.2 ml min⁻¹ at 14 mPa was used at ambient temperature. The etomidate and propoxate were detected using a spectrophotometer at 248 nm. The co-efficient of variation of this method using a 2-ml sample of plasma was 2.8% at 500 ng litre⁻¹ and 8.3% at 50 ng litre⁻¹ (from 10 samples). The method

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**Table I. Characteristics and status of patients.** Each patient received lorazepam at 10.00 p.m. on the night before the operation and again at 2 h before the start of the operation. Patients indicated * received a third increment and the patient indicated ** received a fourth incremental increase in rate of infusion. These rates of infusion were maintained for at least 8 h.

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>1</th>
<th>2*</th>
<th>3*</th>
<th>4</th>
<th>5*</th>
<th>6**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>38.5</td>
<td>15.25</td>
<td>29.2</td>
<td>16.5</td>
<td>16.2</td>
<td>19.9</td>
</tr>
<tr>
<td>Height (m)</td>
<td>1.65</td>
<td>1.89</td>
<td>1.61</td>
<td>1.63</td>
<td>1.60</td>
<td>1.62</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>58</td>
<td>98</td>
<td>54.5</td>
<td>55</td>
<td>51</td>
<td>57</td>
</tr>
<tr>
<td>Body surface area (m²)</td>
<td>1.63</td>
<td>2.27</td>
<td>1.56</td>
<td>1.58</td>
<td>1.51</td>
<td>1.60</td>
</tr>
<tr>
<td>Sex</td>
<td>F</td>
<td>M</td>
<td>F</td>
<td>F</td>
<td>M</td>
<td>M</td>
</tr>
<tr>
<td>ASA status</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Dose of lorazepam as premedication (mg)</td>
<td>2.5</td>
<td>3.5</td>
<td>2.5</td>
<td>2.5</td>
<td>2.5</td>
<td>2.5</td>
</tr>
</tbody>
</table>
was sufficiently sensitive to detect $8 \mu g \text{ litre}^{-1}$ from a single extraction. There was no interference from the known metabolites of etomidate nor from other drugs which the patients were taking. The plasma concentrations are expressed as total drug and as etomidate base (Ellis and Beck, 1982).

**RESULTS**

The doses and steady state plasma concentrations of etomidate required to produce the desired degree of sedation in these patients are presented in table II. The mean steady state plasma concentration was $158 \pm 36 \mu g \text{ litre}^{-1}$. Although there was an approximately three-fold variation in both the dose and the plasma concentration of etomidate, the plasma clearance of etomidate was much less variable. In figure 1, the results from one patient during the first 24 h are shown. It took 4–5 h to achieve steady state.

**Table II. Individual plasma concentrations of etomidate at steady state.** $C^\text{SS}$ is the steady state plasma concentration (mean ± SEM, number of samples in parentheses) derived from data taken between 6 and 24 h after starting the infusion. Clearance is calculated as the ratio of the rate of infusion to $C^\text{SS}$.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Dose ($\mu g \text{ kg}^{-1} \text{ min}^{-1}$)</th>
<th>$C^\text{SS}$ ($\mu g \text{ litre}^{-1}$)</th>
<th>Clearance (litre $\text{ kg}^{-1} \text{ min}^{-1}$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5.1</td>
<td>203 ± 14.8 (5)</td>
<td>0.025</td>
</tr>
<tr>
<td>2</td>
<td>2.7</td>
<td>119 ± 5.1 (6)</td>
<td>0.023</td>
</tr>
<tr>
<td>3</td>
<td>3.3</td>
<td>118 ± 6.4 (5)</td>
<td>0.028</td>
</tr>
<tr>
<td>4</td>
<td>6.1</td>
<td>320 ± 17.0 (5)</td>
<td>0.019</td>
</tr>
<tr>
<td>5</td>
<td>2.8</td>
<td>107 ± 8.3 (7)</td>
<td>0.026</td>
</tr>
<tr>
<td>6</td>
<td>2.2</td>
<td>82 ± 5.8 (5)</td>
<td>0.027</td>
</tr>
<tr>
<td>Mean ± SEM</td>
<td>3.7 ± 0.6</td>
<td>158 ± 36.4</td>
<td>0.025 ± 0.0013</td>
</tr>
</tbody>
</table>

![Graph](image)

**Fig. 1.** The response of one patient (No. 6) and the dose and plasma concentration of etomidate during the first day. The response of the patient was measured using a modified Glasgow Coma Scale where motor corresponds to the best motor response and eye corresponds to eye opening. $\ast$ = plasma concentration; $\circ$ = rate of infusion of etomidate.
The plasma concentrations and the degree of sedation remained unchanged thereafter.

In every patient there was an approximately linear relationship between the rate of infusion of etomidate and the plasma concentration of etomidate. Linear regression analysis was used to determine the regression equation between the infusion rate and the plasma concentration for each patient \( (r > 0.9; P < 0.01) \). There was no significant difference between the slopes of these regression lines. The pooled results from all of the patients are shown in figure 2, from which it can be seen that doubling the infusion rate, approximately doubles the plasma concentration of the drug.

The decrease in the plasma concentration of etomidate after discontinuing the infusion is shown in figure 3. The results appear to fit into three phases: an initial fast decline was followed by a more gradual decrease, which was then followed by a much slower decrease; these are indicative of a three-compartment open pharmacokinetic model.

The plasma concentration for each patient was fitted to an exponential function using a computer program. In this program, kinetic rate constants are calculated using non-linear least squares regression analysis. The polyexponential equations that describe these curves, together with the rates of drug transfer between the different compartments, are shown in table III.

![Figure 2](image2.png)  
**FIG. 2.** The plasma concentration at different rates of infusion of etomidate in the six patients \((r = 0.96; t = 11.178; P < 0.01)\).

![Figure 3](image3.png)  
**FIG. 3.** The plasma concentration of etomidate, as a function of time in the six patients, after discontinuing the infusion.
DISCUSSION

Plasma concentrations following a bolus injection of etomidate have been studied in animals and man. Analysis of the experimental data has provided evidence for the presence of three compartments, one of which is a large central compartment that includes the plasma and the brain (Lewi, Heykants and Janssen, 1976). These results were supported in man by Van Hamme, Ghoneim and Ambre (1978) and more recently by De Ruiter and his colleagues (1981) who gave their patients a bolus injection of etomidate 0.2 or 0.3 mg kg⁻¹. This dose produced loss of consciousness within about 10 s and anaesthesia, followed by sleep, that lasted for 3–5 min. However, during the first 5 min the plasma concentration was changing most rapidly, and made it difficult to identify accurately the plasma concentration associated with sedation.

Patients undergoing major maxillofacial surgery represent an almost ideal group in whom to study the pharmacokinetics of appropriate drugs in order to improve treatment. Following operation they require intermittent positive pressure ventilation, sedation and analgesia for about 48 h and this provides sufficient time to achieve steady state conditions.

At steady state we found that there was very little interpatient variation in the clearance of etomidate from the plasma. The mean plasma clearance was 0.025 ± 0.001 (SEM) litre kg⁻¹ min⁻¹. This rapid clearance is typical of a drug that is eliminated by metabolism rather than by renal excretion. The plasma concentration necessary to induce a suitable degree of sedation was more variable and the approximately three-fold variation was reflected in a similar variation in the rate of infusion. From our results, there appeared to be a direct linear relationship between the dose and the plasma concentration of etomidate at steady state—doubling the dose approximately doubled the plasma concentration.

On stopping the infusion, we found that the decrease in the plasma concentration was consistent with a three-compartment pharmacokinetic model. The exponents derived from the best curves through our experimental points were similar to those reported by other workers. However, our terminal exponent of 0.00218 min⁻¹, which corresponds to a terminal half-life of 322 min, is somewhat longer than previously reported. Our estimate of the terminal half-life may be more accurate than previous estimates, as we were able to measure the concentration of etomidate for almost 24 h after discontinuing the infusion, whereas other workers reached their
limit of detection approximately 6–8 h after giving a bolus injection. It is desirable to measure plasma concentrations for at least four half-lives to ensure accurate estimations.

The calculated rates of drug transfer between the compartments reported here are different from those reported following a bolus of the drug i.v. This may be attributable to the use of an infusion. For example, infusions tend to maximize the effects of tissue uptake through tissue: blood partition, whereas following a bolus injection, the amount of drug in the tissues is more sensitive to changes in perfusion of the tissues. The ratio of $\gamma/k_{10}$ of about 0.19 indicates that only about 19% of the drug in the body is in the central compartment and available for elimination. This compares with a ratio of 0.15 reported by Van Hamme, Ghoneim and Ambre (1978), after a bolus injection.

Our patients took about 40 min to awaken and this was longer than the time to recovery following an i.v. bolus dose. We could not detect any association with a specific plasma concentration. This delay may be partly attributable to a residual effect of the infusion of fentanyl, which was discontinued at the same time as the infusion of etomidate.

It is interesting to compare the elimination of etomidate with that of other drugs that have been used for sedation in the intensive therapy unit. The terminal half-life of etomidate may be shorter than that of chlormethiazole, but is considerably longer than that of alphaxalone. Moore and colleagues (1975) found the terminal half-life of chlormethiazole to be about 4 h in young adult volunteers and this value was subsequently confirmed by Jostell and colleagues (1978). However, the pharmacokinetics of chlormethiazole are age-dependent and the terminal half-life increases to about 8.5 h in the elderly (Nation et al., 1976). The influence of age on the pharmacokinetics of etomidate has not been studied.

Although chlormethiazole may be suitable for short-term sedation of a few hours (Scow et al., 1981), prolonged infusion for up to 48 h, in patients requiring intensive therapy, was shown to be associated with delayed recovery (Scott et al., 1980). This suggests a cumulative effect of the drug.

Althesin is probably the drug that has been most widely used for prolonged i.v. sedation (Ramsey et al., 1974). Simpson (1978) calculated the terminal half-life of alphaxalone as 34 min, deriving the value from a two-compartment model, but from plasma concentrations taken for only 2 h following a bolus dose. The pharmacokinetics of alphadolone, which is formulated with alphaxalone, have not been studied.

Sear and Prys-Roberts (1979) have noted that some patients with liver disease extract alphaxalone from the circulation more quickly than others and they suggest that this may be a result of changes in hepatic blood flow. In contrast, patients with liver disease remove chlormethiazole more slowly from the plasma (Pentikäinen, Neuvonen and Jostell, 1980) and in these patients the dose may require adjustment. The effects of liver disease on the pharmacokinetics of etomidate have not been studied, but the rapid clearance of the drug from the plasma is typical of drugs that are metabolized in the liver and the clearance may be subject to changes in hepatic blood flow or hepatic function.

Changes in hepatic blood flow may also arise as a consequence of cardiovascular changes that result in a decrease in cardiac output. However, throughout the whole period of the study little variation in heart rate, or systolic and diastolic arterial pressures, was discernible. Further studies are in progress to assess in more detail the effects of etomidate on the cardiovascular system.

ACKNOWLEDGEMENTS

We thank Mr P. G. McAndrew, Consultant Maxillofacial Surgeon, for his help and encouragement, Mr N. G. Kenyon (Department of Medical Physics) for developing the computer programs and help with the statistical analyses, and Mr E. O. Ellis who assayed the etomidate. We also thank Mrs J. F. Heath who typed the manuscript, and Janssen Pharmaceuticals for supplies of etomidate.

REFERENCES


**PHARMACOCINETIQUE DE L’ETOMIDATE EN PERFUSION INTRAVENEUSE PROLONGEE**

**RESUME**

Les concentrations plasmatiques d’etomidate ont été mesurées chez six patients dont l’état nécessitait une ventilation en pression positive intermittente dans la période post-opératoire. Il y avait une relation approximativement linéaire entre la concentration plasmatique et la vitesse de perfusion de l’étomidate. Il existait pour cet agent une relation pharmacocinétique linéaire pour des valeurs de concentrations plasmatiques variant de 1 à 10. La décroissance de la concentration plasmatique à l’arrêt de la perfusion était compatible avec un modèle pharmacocinétique à trois compartiments. Les valeurs retrouvées de la demi-vie plasmatique terminale étaient d’environ 5,5 h et la clairance calculée de 0,025 litre kg$^{-1}$ min$^{-1}$.

**PHARMAKOKINETIK VON ETOMIDATE BEI INTRAVENÖSER LANGZEITINFUSION**

**ZUSAMMENFASSUNG**


**FARMACOCINÉTICA DEL ETOMIDATO ASOCIADO CON INFUSIÓN I.V. PROLONGADA**

**SUMARIO**

Se midieron las concentraciones de etomidato en el plasma en seis pacientes que exigian una ventilación intermitente de presión positiva después de la cirugía. Existía una relación aproximadamente lineal entre la concentración en el plasma y el ritmo de infusión del etomidato. La substancia demostraba una farmacocinética lineal en una variación hasta de diez veces en la concentración en el plasma. La disminución de la concentración en el plasma después de parar la infusión era constante para con el modelo farmacocinético de tres compartimentos. Se halló que la media-vida terminal del plasma era de alrededor de 5,5 h y la eliminación se calculó en 0,025 litro kg$^{-1}$ min$^{-1}$.