A DOSE-RESPONSE RELATIONSHIP FOR ETOMIDATE, WITH SOME OBSERVATIONS ON CUMULATION

B. Kay

SUMMARY
In a within-patient comparison in 30 subjects, sleep was induced before e.c.t. by different doses of etomidate or methohexitone: etomidate 0.1 mg/kg, 0.2 mg/kg, 0.4 mg/kg or methohexitone 1.5 mg/kg. The duration of hypnotic effect was assessed by recording the time of spontaneous waking and, later, of recovery of normal ocular muscle tone. Doubling the dose of etomidate produced a significant increase in both sleeping time and late recovery. Compared with methohexitone 1.5 mg/kg, etomidate 0.2 mg/kg provides an equal duration of sleep, but allows faster late recovery. In eight patients in whom sleep was maintained by repeated injections of etomidate 0.1 mg/kg as required, little evidence of cumulation was seen up to 27.5 min duration of sleep.

Etomidate is a new non-barbiturate i.v. induction agent with a rapid onset of action. In rats, guineapigs and dogs, the duration of hypnosis after etomidate is dose-dependent, sleeping time being doubled when the dose is doubled (Reneman and Janssen, 1975). In man, a dose of 0.3 mg/kg body weight has been recommended for induction of anaesthesia by Doenicke (1974), who found that the duration of action of this dose corresponded to that following methohexitone 1.5 mg/kg. Kettler and Sonntag (1974) compared etomidate 0.3 mg/kg with Althesin 0.9 mg/kg, ketamine 5 mg/kg, methohexitone 2 mg/kg, propanidid 7 mg/kg and thiopentone 4 mg/kg.

It is difficult to estimate equipotent dosage of different drugs, even in relation to their main therapeutic action. The purpose of the present investigation was to determine by a within-patient trial the duration of sleep produced by etomidate 0.1 mg/kg, 0.2 mg/kg and 0.4 mg/kg, and to demonstrate a dose-response relationship. The duration of sleep following methohexitone 1.5 mg/kg was determined also in the same patients, to provide a reference point.

A dose-response relationship was investigated similarly in relation to a later stage of recovery from the hypnotic effect of etomidate, again comparing recovery after methohexitone.

METHOD
Thirty unselected outpatients undergoing electroconvulsant therapy were studied. No premedication was given and no other medications were taken by the patients before treatment. Normal procedures and precautions were observed before anaesthesia. The mean age of the patients was 35 yr 8 months (26-70 yr) and the mean weight 62.6 kg (49-97 kg). There were nine men and 21 women in the series. All the anaesthetics were given by the author. Anaesthesia was induced by injecting the induction agent i.v. during 30 sec, followed, after a 15-sec pause, by a rapid injection of suxethonium bromide 50-80 mg according to the patient’s weight and previous response. The patients were then ventilated with oxygen using Waters’ apparatus until 2 min after the completion of injection of the induction agent, when the electroconvulsant shock was given. All the patients began breathing spontaneously a few seconds after the convulsions had ceased. They were observed closely until they opened their eyes spontaneously. They were then asked, “Are you awake?” and as soon as a response was obtained the number of minutes after the injection of the induction agent was recorded.

The induction agents and doses used were etomidate 0.1 mg/kg, etomidate 0.2 mg/kg, etomidate 0.4 mg/kg and methohexitone 1.5 mg/kg. These were given in random order to each of the patients, so that the majority received all four treatments at different times. For the purpose of establishing a later point of recovery, all patients were asked before treatment to use a Maddox Wing in order to determine the resting ocular muscle position. After waking, serial determinations were made at 1-min intervals until the pre-treatment measurement was obtained, as suggested by Hannington-Kiff (1970). A large minority of patients were unable to co-operate with this test because of poor ocular or mental function.

In a separate small group of patients an attempt was made to assess the cumulative effects of etomidate. Because of its lack of analgesic effect, it was not
possible to use the drug as the sole anaesthetic agent over considerable periods, a method used by Clarke and Dundee (1966). Instead, etomidate 0.1 mg/kg was used to induce sleep before caudal block in eight women undergoing vaginal repair. This dose was repeated each time the woman responded to her name, and the time interval from the previous injection was recorded. The observations were abandoned when the patients were taken into the operating theatre (an average of 33 min after induction of sleep), as stimuli of varying intensity occurred after that time.

RESULTS

Twenty-six patients received all four induction regimens. The mean waking times after etomidate are shown in table I. The increase in duration of effects with each doubling of dose is highly significant ($P<0.001$).

Mean late recovery times, as estimated by the Maddox Wing test, are shown in table I also. Eight patients were unable to complete this test. Statistically significant ($P<0.01$) increases in the duration of action occurred each time the dose of etomidate was doubled.

Figure 1 shows these results in a graphic form, with the times of recovery after methohexitone 1.5 mg/kg displayed on the appropriate curve. The mean waking time after methohexitone was 10.45 min, a point on the curve close to that of etomidate 0.2 mg/kg. However, the late recovery point after methohexitone (35.44 min) is close to that of etomidate 0.35 mg/kg. Apparently late recovery after methohexitone is delayed compared with a dose of etomidate producing the same duration of sleep. The ratio of mean times to waking and late recovery is 1:2.75 for etomidate 0.2 mg/kg and 1:3.39 for methohexitone 1.5 mg/kg (taken from the dose-response curve, not mean observations).

The result of repeated injections of etomidate 0.1 mg/kg in the second group of patients is shown in

Table I. Mean waking times and late recovery times after etomidate and methohexitone (± SEM)

<table>
<thead>
<tr>
<th>Etomidate (mg/kg)</th>
<th>Methohexitone 1.5 mg/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.1</td>
<td>0.2</td>
</tr>
<tr>
<td>Mean waking time (min)</td>
<td>7.52 ± 1.07</td>
</tr>
<tr>
<td>Late recovery time (min)</td>
<td>20.41 ± 1.17</td>
</tr>
</tbody>
</table>

Fig. 1. Mean times of waking, and late recovery (judged by Hannington-Kiff’s ocular test) after etomidate 0.1 mg/kg, 0.2 mg/kg and 0.4 mg/kg and methohexitone 1.5 mg/kg. ×—× waking time after etomidate; ×—× late recovery time after etomidate; ⊗ reference point (methohexitone 1.5 mg/kg).

Fig. 2. Mean total cumulative dose of etomidate 0.1 mg/kg repeated as necessary to maintain sleep. The outer lines indicate the range of individual dose requirements.
figure 2. Eight separate graphs were constructed of the time at which each patient required a further dose of etomidate to maintain sleep. A mean cumulative dose at each 2.5-min interval was then calculated from the individual graphs. Figure 2 could not be constructed for times beyond 27.5 min as measurements in two patients did not continue after this time. It is apparent that there is very little cumulation of etomidate during this time.

**DISCUSSION**

Etomidate is a new i.v. induction agent with apparent advantages over established drugs in that it does not release histamine (Doenicke et al., 1973) and has a lesser effect on the cardiovascular system (Bruckner et al., 1974). However, such comparison can be of relevance only if doses with the same therapeutic effect are compared. So far, most of the doses compared have been those estimated by personal experience and have differed in different trials.

The present report relates only to the duration of sleep and to a more prolonged hypnotic effect of etomidate; not to the ability of etomidate to suppress reaction to a stimulus. Etomidate has no analgesic effect, and even the stimulation of the application of a mask and inhalation of 2% halothane vapour might be expected to produce more reaction after etomidate 0.2 mg/kg than after methohexitone 1.5 mg/kg. As an agent for induction of anaesthesia, therefore, Doenicke's estimation of etomidate 0.3 mg/kg as equivalent to methohexitone 1.5 mg/kg may be more acceptable. Much depends upon the drugs used concurrently. When an analgesic is administered as premedication, or as part of the technique of i.v. induction of anaesthesia, the lower dosage of etomidate will provide hypnosis with a shorter duration of action and presumably smaller degree of any side-effects produced. Therefore the particular advantages of etomidate would seem to be utilized best in combination with an analgesic drug for premedication or as a supplement to anaesthesia, allowing minimal dosage of this apparently very safe intravenous hypnotic agent.

**REFERENCES**


**RELATION DOSE–RECEPTIVITE POUR L’ETOMIDATE AVEC QUELQUES OBSERVATIONS SUR LE CUMUL**

Au cours d'une comparaison des effets de divers traitements chez un même sujet, effectuée sur 30 personnes, le sommeil a été obtenu, avant le traitement par les électro-convulsivants, par diverses doses d'etomidate ou de méthohexitone: etomidate 0,1 mg/kg, 0,2 mg/kg, 0,4 mg/kg ou méthohexitone 1,5 mg/kg. La durée de l'effet hypnotique a été estimée en enregistrant le moment du réveil spontané et plus tard la récupération du tonus normal du muscle oculaire. En doublant la dose d’étomidate on a provoqué une augmentation significative du temps de sommeil et un retard dans la récupération. Par comparaison avec 1,5 mg/kg de méthohexitone et 0,2 mg/kg d'étomidate on a trouvé que le sommeil était de durée égale, mais que la récupération était plus rapide. Sur huit patients chez lesquels on a maintenu le sommeil par des injections répétées d'étonidate à 0,1 mg/kg, en fonction des besoins, il n'y a eu que peu d'évidence de cumul jusqu'à une durée de sommeil de 27,5 minutes.

**BEOBACHTUNGEN BEZÜGLICH DOSIERSUMMIERUNG BEI ANWENDUNG VON ETOMIDAT**

Innerhalb einer Vergleichsgruppe von 30 Patienten, bei denen Etomidat 0,1, 0,2, 0,4 mg/kg oder Methohexiton 1,5 mg/kg verschiedentlich dosiert, als Schlafmittel vor der Elektrokonvulsion-Schockbehandlung verwendet wurde, ergaben sich die folgenden Resultate. Die Dauer der Schlafwirkung wurde erstens mittels des spontanen Erwachens ermittelt, danach dem Auftreten normaler Muskeltonus. Bei Verdopplung der Etomidatdosis erwies sich eine bedeutende Verlängerung der Schlafzeit, sowie Normalisierung. Im Vergleich zu Methohexiton 1,5 mg/kg zeigte Etomidat 0,2 mg/kg sich als gleich, was die Schlafdauer anbelangt, doch erreichten die Patienten im schnelleren Maasse, wenn auch später, das Bewusstsein. Bei acht Patienten wurde das Schlafstadium mittels
wiederholter Injektionen von Etomidat 0,1 mg/kg angehalten. Es ergaben sich wenige Zeichen von Dosen-Summierung während einer bis zu 27,5 Minuten Schlafdauer.

RELACION DE UNA DOSIS-RESPUESTA PARA EL ETOMIDATO CON ALGUNAS OBSERVACIONES SOBRE CUMULACION

SUMARIO

En una comparación dentro del paciente, en 30 personas, se provocó el sueño antes de la terapia electroconvulsionante por medio de distintas dosis de etomidato o metohexitona: etomidato 0,1 mg/kg, 0,2 mg/kg, 0,4 mg/kg o metohexitona 1,5 mg/kg. La duración del efecto hipnótico se evaluó registrando el tiempo del despertar espontáneo y, más tarde, de la recuperación del tono muscular ocular normal. El doble de la dosis de etomidato produjo un incremento significativo tanto en el período del sueño como en una recuperación lenta. Comparándolo con la metohexitona 1,5 mg/kg, el etomidato 0,2 mg/kg proporciona una duración igual del sueño, pero permite una recuperación tardía más rápida. En ocho pacientes en que se mantuvo el sueño mediante inyecciones repetidas de etomidato 0,1 mg/kg según lo requerido, se apreció poca evidencia de cumulación hasta 27,5 min de duración del sueño.