EVALUATION OF THREE PREPARATIONS OF ETOMIDATE

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SUMMARY

Three formulations of etomidate were evaluated in unpremedicated patients undergoing minor gynaecological procedures. There was a high frequency of pain on injection (up to 50%) and excitatory phenomena (up to 95%) with all formulations. The frequency of excitatory phenomena was significantly greater than that after methohexitone. Recovery was rapid, but emetic sequelae were frequent and significantly more marked than after methohexitone.

Etomidate, an imidazole derivative, is a potent water-soluble i.v. anaesthetic agent which has been undergoing clinical trials in Europe since 1972 (Doenicke, Wagner and Beetz, 1973; Doenicke et al., 1973). More recently it has been studied in Britain (Morgan, Lumley and Whitwam, 1975; Holdcroft et al., 1976; Kay, 1976a, b) and North America (Ghoneim et al., 1976; Gooding and Crossen, 1976).

It is claimed that etomidate has minimal effects on the cardiovascular system (Doenicke et al., 1973) and is metabolized in blood and liver to form an inert derivative (Janssen et al., 1971). Unlike most of the other i.v. anaesthetics tested, Doenicke and his colleagues (1973) showed that it does not release histamine. Although it is water-soluble, it does not form a stable solution and dispensing of small quantities presents difficulties. The aqueous solution causes a high frequency of pain on injection (Morgan, Lumley and Whitwam, 1975; Kay, 1976a, b) and efforts have been made to produce a commercial preparation in an organic solution which will be stable, non-irritant and cause less pain on injection.

We have compared the effects of the three solutions which have been available for study, in unpremedicated patients at a standard dose of 0.3 mg kg\(^{-1}\) as recommended by Doenicke, Wagner and Beetz (1973). Two rates of injection were used to see if the side-effects, like those of the barbiturates and Althesin (Barron, 1968; Samuel and Dundee, 1973), were influenced by this factor.

METHOD

The three preparations of etomidate studied were:

- Aqueous: The form used since 1972 in most published reports. Dispensed in a vial containing 30 mg of etomidate sulphate with phosphate buffer and 20 ml of water to make a 0.15% solution of pH 3.3 (Kay, 1976a).
- Polyethylene glycol solution (PEG): Available since 1976. Dispensed as 5 ml of a 0.2% solution.
- Propylene glycol solution (PG): Available since 1977. Dispensed as 10 ml of a 0.2% solution.

Unpremedicated patients undergoing minor gynaecological surgery were anaesthetized with the three preparations (table I). The mean age, weight and duration of anaesthesia in the three groups were broadly comparable. The injection (0.3 mg kg\(^{-1}\)) was given at either 2 mg s\(^{-1}\) (fast) or 1 mg s\(^{-1}\) (slow). Anaesthesia was continued with 70% nitrous oxide in oxygen with incremental doses of etomidate as required. During injection the patients were asked if the arm was comfortable proximal to the site of venepuncture. The presence of spontaneous involuntary muscle movements, tremor, hypertonus, cough, hiccup and marked respiratory depression was noted and the systolic arterial pressure and heart rate were recorded as described by Dundee, Moore and Nichol. (1962). Anaesthesia was graded on the basis of these features as: Uneventful. Minor upset: not interfering with the course of anaesthesia. More severe or prolonged upset interfering with the course of anaesthesia. Severe upset: endangering the patient's life or making surgery impossible (often requiring a major change in the anaesthetic technique such as the use of suxamethonium or halothane).

At the end of surgery the nitrous oxide was discontinued and 2 min later the patients were classified as awake, safe (presence of active protective reflexes) or unsafe. They were not allowed food or fluid for the following 6 h and enquiries were made at 1 and 6 h after surgery on the occurrence of nausea or vomiting.

Although the main object of this study was to compare the action of the three preparations of
etomidate at two rates of injection, results of previously published studies from this department with methohexitone in similar patients (Dundee, 1963) have been included in the analysis. The induction dose of methohexitone reported in that study (1.6 mg kg\(^{-1}\)) is approximately equipotent with etomidate 0.3 mg kg\(^{-1}\).

RESULTS

**Pain on injection**

Pain occurred in approximately 30\% of all patients receiving etomidate (table II). In most instances this was slight and elicited only on questioning. There was no significant difference between the frequency in any of the groups, although it occurred more frequently with the aqueous solution. Even when the findings with the two speeds of injection were pooled there was no significant difference between the three preparations. However, with each preparation there were more complaints of pain with the slow compared with the fast rate of injection, but this difference was not significant, even when data from all three preparations were pooled.

**Induction side-effects**

Tremor and involuntary muscle activity, often apparently semi-purposeful in nature, were the most notable features of anaesthesia with etomidate. These began as the patient became unconscious and often persisted throughout the anaesthetic though only rarely did they interfere with the performance of surgery. An excitatory effect occurred during induction in 70-95\% of patients (table II), but there was no significant difference in frequency between the aqueous and PEG formulations. However, there was a higher frequency with the PG formulation than with the aqueous form. This was significant when data for the two speeds of injection were pooled (\(\chi^2 = 4.02; P<0.05\)). The occurrence of muscle movements was not influenced consistently by the speed of injection and is much more frequent with any preparation of etomidate than with methohexitone. Comparing the lowest frequency for etomidate in table II (aqueous solution) with that following methohexitone 2\%, both given at the faster speed, the difference is highly significant (\(\chi^2 = 11.237; P<0.001\)).

Respiratory upset, mainly cough and hiccup, with occasional laryngospasm, occurred in 10-30\% of patients and was least common with the PEG preparation.

Apnoea of sufficient duration to require ventilatory assistance was no more frequent with etomidate than with methohexitone.

### TABLE II. Percentage frequency of pain on injection and induction side-effects in each group

<table>
<thead>
<tr>
<th>I.v. anaesthetic</th>
<th>Speed of injection</th>
<th>Pain on injection</th>
<th>Excitatory phenomena</th>
<th>Respiratory upset</th>
<th>Marked respiratory depression</th>
<th>Decrease in systolic arterial pressure (&gt; 20 mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Etomidate aqueous</td>
<td>Slow</td>
<td>50</td>
<td>75</td>
<td>25</td>
<td>5</td>
<td>20</td>
</tr>
<tr>
<td></td>
<td>Fast</td>
<td>40</td>
<td>70</td>
<td>30</td>
<td>10</td>
<td>0</td>
</tr>
<tr>
<td>Etomidate PEG</td>
<td>Slow</td>
<td>30</td>
<td>80</td>
<td>13</td>
<td>0</td>
<td>27</td>
</tr>
<tr>
<td></td>
<td>Fast</td>
<td>24</td>
<td>82</td>
<td>9</td>
<td>3</td>
<td>12</td>
</tr>
<tr>
<td>Etomidate PG</td>
<td>Slow</td>
<td>35</td>
<td>85</td>
<td>20</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>Fast</td>
<td>25</td>
<td>95</td>
<td>30</td>
<td>5</td>
<td>15</td>
</tr>
<tr>
<td>Methohexitone 2%*</td>
<td>Fast</td>
<td>33</td>
<td>26</td>
<td>2</td>
<td>13</td>
<td></td>
</tr>
</tbody>
</table>

* Data from Dundee (1963).
THREE PREPARATIONS OF ETOMIDATE

A decrease in arterial systolic pressure greater than 20 mm Hg was rare following etomidate and appeared to be unrelated to the solvent or speed of injection, and its frequency was not different from that following methohexitone.

In respect of the grading system for induction, the preparation in PEG appeared to be better than either of the others (fig. 1), but even with pooling of uneventful and slight upset categories, differences failed to reach statistical significance. The frequency of satisfactory anaesthesia (uneventful or with minor upset) with methohexitone was significantly greater than with any of the etomidate preparations ($\chi^2 = 9.3-21.9; P<0.005$).

Recovery

Recovery from all three formulations was rapid and there were no significant differences related to solvent or rate of administration (fig. 2). It was also very similar to that after methohexitone.

Postoperative sickness was assessed separately at 1 h and 6 h after the end of anaesthesia, but since there was little sickness after the 1st hour only the total has been shown in figure 3. The frequency varied from 35% to 50% and neither the formulation used nor the speed of injection had any influence. There was more sickness after etomidate than after methohexitone ($\chi^2 = 9.98; P<0.005$ for pooled etomidate cases). Most of this difference appeared to result from vomiting in the few minutes after wakening from anaesthesia.

DISCUSSION

Previous studies of etomidate have utilized a buffered aqueous solution and one of the main criticisms has been that of pain on injection (Morgan, Lumley and Whitwam, 1975; Gooding and Corssen, 1976; Kay, 1976a). It seemed possible that the use of organic solvents might reduce this since Kay (1976a) reported no pain with etomidate in Cremophor EL, although i.v. injection of diazepam in propylene glycol is painful (Dundee and Wyant, 1974). It was hoped also that by reducing the frequency of pain on injection the frequency of involuntary muscle movements might be diminished also. However, there was no marked decrease in pain or muscle movements with the organic preparations. Pain is encountered also...
with methohexitone and it is claimed that its frequency is reduced by the addition of lignocaine to the solution (Rowlands, 1969). Kay (1976a) has not confirmed the advantages of this combination for etomidate.

Excitatory effects are a feature of all i.v. anaesthetics studied so far. They vary from small involuntary muscle movements, seen also with thiopentone but more so with the methylated barbiturates, to true convulsions as described by Goldman (1965), Uppington (1973) and Male and Allen (1977). Hypertonus is a related variant, especially with ketamine. All these have been seen with etomidate, but the commonest type is myoclonia (repeated jerky movements sometimes accompanied by reflex semi-purposeful actions). The frequency described, in the absence of sedative premedication, varies; Kay (1976) reported 10–25% but Holdcroft and her colleagues (1976) reported about 70%, which is close to our own figure. Since these excitatory effects appear to be a feature of all i.v. anaesthetic agents it is not surprising that altering the solvent had no significant effect on their frequency and it seems unlikely that they are related to pain on injection. A fast rate of injection did not increase the frequency of muscle movement as was found by Barron (1968) with methohexitone and Samuel and Dundee (1973) with Althesin. However, it is claimed that the frequency can be reduced by sedative premedication (Holdcroft et al., 1976) and further studies to examine this aspect are in progress.

The occurrence of hiccup, laryngospasm, respiratory depression or cardiovascular changes were not problems with etomidate. However, the present studies were not designed to detect small degrees of arterial hypotension and it remains to be seen if etomidate causes less hypotension than thiopentone, methohexitone, Althesin or propanidid, as claimed by Doenicke and his colleagues (Doenicke, Wagner and Beetz, 1973; Doenicke et al., 1973).

Delayed recovery was not a problem with etomidate and a study is in progress to assess the speed of return of mental clarity and ability to balance. Kay (1976b) suggested that late recovery is better after etomidate than following methohexitone. Vomiting accompanied the rapid recovery in about 30% of all patients. This high frequency is known to be a feature of minor gynaecological operations, but it is possible to detect marked differences between induction agents (Clarke et al., 1971). On the basis of its emetic properties etomidate resembles propanidid more than Althesin or the barbiturates.

One of the differences between etomidate and other anaesthetic drugs studied by Doenicke and his colleagues (1973) was the absence of histamine liberation. Although these workers advise caution in interpreting their findings this would seem to be a safety factor, since histamine is implicated in anaphylactoid reactions. No-one can be certain that a drug will not sensitize a patient, so that on repeated administration a hypersensitivity reaction would occur. On the basis of this study and subsequent experience we would not agree with Doenicke’s comment: "regarding the absence of clinical side-effects etomidate therefore appears to be superior to the other substances examined". However, it does seem to have a high margin of safety regarding histamine-mediated effects and from the many thousands of patients anaesthetized in Germany and Great Britain no manifestations of histamine liberation have been described.

Since the introduction of etomidate, it has been apparent that the drug by itself is not a satisfactory induction agent. The frequency of pain on injection is unacceptable and is not offset by any real benefits in terms of cardiovascular stability or recovery. Kay (1976a) has shown that the pain cannot be reduced by the addition of lignocaine. Doenicke and his colleagues (1973) precede etomidate with i.v. diazepam. These additions may make the drug more acceptable, but an agent should possess clear advantages over established drugs to gain popularity when such adjuvants are required.

ACKNOWLEDGEMENTS

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REFERENCES


THREE PREPARATIONS OF ETOMIDATE


EVALUATION DE TROIS PREPARATIONS D’ETOMIDATE

RESUME
Trois formules d’etomidate ont été évaluées sur des malades non prétraitées soumises à des interventions gynécologiques mineures. On a constaté un fort pourcentage (50%) de douleurs au moment de l’injection ainsi qu’un phénomène excitatoire (95 %) avec toutes les formules. La fréquence du phénomène excitatoire a été sensiblement plus forte que celle constatée après le méthohexiton. La récupération a été rapide, mais il y a eu de fréquentes séquelles émétiques, celles-ci étant nettement plus marquées qu’après le méthohexiton.

AUSWERTUNG VON DREI ETOMIDATPRÄPARATIONEN

ZUSAMMENFASSUNG
Drei Etomidatenformeln wurden in nicht vorbehandelten Patienten während leichter, gynäkologischer Behandlungen ausgewertet. Es kam zu einer starken Schmerzanhäufung nach der Injektion (bis zu 50%) und Anzeichen von Erregung (bis zu 95%) bei allen drei Formeln. Die Frequenz der Erregungssphänomene war bedeutend größer als die nach Methohexiton. Die Erholung trat sehr schnell ein, aber der nachfolgende Brechreiz trat öfter in Erscheinung und war bedeutend stärker als nach Methohexiton.

EVALUACION DE TRES PREPARACIONES DE ETOMIDATA

SUMARIO
Se evaluaron tres formulaciones de etomidata en pacientes no premedicados sometidos a procedimientos ginecológicos menores. Se produjo una elevada frecuencia de dolor durante la inyección (hasta 50%) y fenómenos excitativos (hasta 95%) con todas las formulaciones. La frecuencia de los fenómenos excitativos resultó significativamente superior a la que se produce después de methohexiton. La recuperación fue rápida, pero los accesos de vómito fueron frecuentes y significativamente más fuertes que después de methohexiton.