AN INVESTIGATION OF THE CENTRALLY AND PERIPHERALLY MEDIATED CARDIOVASCULAR EFFECTS OF ETOMIDATE IN THE RABBIT

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SUMMARY
In the decerebrate rabbit etomidate caused dose-related decreases in mean arterial pressure and preganglionic sympathetic nerve activity. There were no significant alterations in heart rate. Etomidate was found to have no effect on the baroreceptor reflex. In pithed animals the effects of etomidate were of short duration and of a lesser magnitude than in the decerebrate animal. It was concluded that the additional effects in the decerebrate rabbit were a result of depression of central cardiovascular control. It was found that etomidate was largely without effect on the cardiovascular system at normal anaesthetic doses (0.5–1 mg kg⁻¹). However, larger doses (2–8 mg kg⁻¹) produced marked depression of central cardiovascular control, the myocardium and the peripheral vasculature.

Etomidate (R-(+)-ethyl-L-(1-pentethyl)-1H-imidazole-5-carboxylate sulphate) is a recently introduced i.v. anaesthetic induction agent. Reports of studies in animals (Weymar et al., 1974; Janssen, Niemegeers and Marsboom, 1975) and man (Doenicke et al., 1973; Morgan, Lumley and Whitwam, 1975; Kay, 1976) have emphasized the absence of cardiovascular effects. Nonetheless, Rifat, Gamulin and Gemperle (1976) have observed significant decreases in mean arterial pressure and stroke volume following the administration of etomidate to a group of elderly patients.

Detailed studies of the action of etomidate on the cardiovascular system and on cardiovascular reflex mechanisms are lacking. We have studied its effects on decerebrate and on pithed rabbit preparations. These preparations are suitable for cardiovascular investigation as they enable differentiation of the peripheral cardiovascular effects and those mediated by actions on the hind brain, vasomotor centres and the baroreflex. The present study complements previous studies of the effects of thiopentone, Althesin and ketamine on these preparations (McGrath, MacKenzie and Millar, 1975; MacKenzie et al., 1976; McGrath and MacKenzie, 1978).

METHODS
Male New Zealand white rabbits (weights 3.0–3.3 kg) were either decerebrated or pithed.

The decerebrate animals were anaesthetized with 3% halothane in oxygen. The experimental protocol was essentially that described by McGrath, MacKenzie and Millar (1975). A tracheostomy was made and femoral arterial and venous cannulae were inserted. A 13-mm trephine hole, made in the parietal bone, was enlarged with bone nibblers and a midcollicular decerebration was performed by suction. The administration of halothane was discontinued and the lungs were ventilated mechanically with 100% oxygen (Harvard Instruments ventilator Model 613). Gallamine 1 mg kg⁻¹ was given every 40 min and the ventilation was adjusted to maintain the end-tidal carbon dioxide at 4% (LB2 Beckman analyser).

Both aortic depressor nerves were divided in the neck. The desheathed central end of the left aortic depressor nerve was placed over a pair of silver wire electrodes and was stimulated supramaximally using a Devices gated pulse generator and isolated stimulator (0.1 ms pulse width, 50 Hz for 20 s).

Nerve activity was recorded from multifibre strands of the central end of the divided left preganglionic cervical sympathetic nerve using bipolar platinum electrodes. The amplified signal (Tektronix 122) was then passed via a dual beam oscilloscope (Tektronix D12) to a pulse height selector and thence to a Panax ratemeter. The mean integrated sympathetic discharge rate was displayed on a Devices MX19 recorder.

The pithed animals were anaesthetized also with 3% halothane in oxygen and the trachea was intubated via a tracheostomy. Anaesthesia was
maintained with 1% halothane in oxygen. The left carotid artery was cannulated with a concentric double cannula, each lumen being connected to a Statham pressure transducer. The inner cannula was introduced until its tip lay in the left ventricle as demonstrated by the characteristic pulse wave. The outer cannula remained with its tip in the carotid artery until its tip lay in midstream in the aorta. A thermistor-tipped probe was introduced into the right carotid artery until its tip lay in midstream in the aorta. A cannula was introduced into the right external jugular vein for the administration of drugs and of the cold saline used in the measurement of cardiac output by the cold dilution method (Fegler, 1954).

The rabbit was decerebrated as above, gallamine was administered and the lungs were ventilated mechanically. The rabbit was pithed fully via the trephine hole. The pithing rod was made of stainless steel (2 mm diameter), covered with a Teflon sheath (o.d. 3.6 mm) except for 12 mm at its tip. An indifferent electrode of silver wire was placed subcutaneously dorsal and parallel to the cervical vertebrae. The rod was withdrawn to the level of T8, at which point stimulation produced no change in heart rate but produced an increase in arterial pressure, solely a result of the direct vasopressor effect of the stimulated sympathetic nerves (McGrath and MacKenzie, 1978).

Etomidate was given (a) during a 5-min cycle of electrical stimulation (1 ms at supramaximal voltage (~90 V) at 10 Hz for 20 s), (b) during a 12-min cycle of noradrenaline 0.3 μg kg⁻¹ injections, (c) during a period of sustained electrical stimulation (stimulation parameters as before but at only 5 Hz).

Each dose of etomidate 0.5–4 mg kg⁻¹ was given 2 min before the electrical stimulation or injection of noradrenaline. (AD₅₀ of etomidate in rabbits is 0.5 mg kg⁻¹ (Janssen, Niemegeers and Marsboom, 1975).) The particular cycle was continued until recovery. In the case of continuous stimulation, etomidate was given after a stable arterial pressure was achieved (usually 1–2 min), the pressure being maintained at an increased value for a further 4 min. Cardiac output was measured about 1 min before and after the addition of the drug in (a) and (c). From the mean arterial pressure (MAP), heart rate (HR) and cardiac output (CO), peripheral resistance (PR) and stroke volume (SV) (PR = MAP/CO and SV = CO/HR) were calculated. Left ventricular systolic and end-diastolic pressures were measured and left ventricular dP/dt max was taken from these results.

Throughout all experiments arterial blood was sampled at least every 60 min, for analysis of the acid–base state and for measurements of $P_{aO_2}$ and $P_{aCO_2}$ (IL Model 213). Base excess was calculated and any deficit was corrected with the appropriate amount of sodium bicarbonate.

Rectal temperature was maintained at 38 ± 0.5 °C by using a homoeothermic blanket (C. F. Palmer).

The indices measured were recorded on a Devices MX19 eight-channel recorder. Heart rate was obtained from the pressure channel by means of an instantaneous ratemeter (Devices). Cardiac output curves were recorded on a pen recorder (Servo-scribe).

A test-dose of the solvent (sodium biphosphate; sodium phosphate, sodium chloride and water) equivalent in volume to the highest dose produced no measurable response.

Analysis of results

In each rabbit resting values of mean arterial pressure, heart rate, sympathetic nerve discharge and, when measured, cardiac output, stroke volume, peripheral resistance and left ventricular $dP/dt$ max have been used as their own control values and expressed as 100%. Changes in these indices following the administration of etomidate have been expressed as a percentage of their own control values. The data were analysed for significance by means of Student's $t$ test. $P<0.05$ was taken as the level of significance.

RESULTS

Decerebrate rabbit

The control values are shown in table I. The administration of etomidate produced dose-related decreases in arterial pressure and sympathetic nerve activity which were significantly different from the control values at all doses (fig. 1). The changes in heart rate were much less pronounced, being statistically significant only at the highest dose (8 mg kg⁻¹) (fig. 1).

The baroreceptor reflex was largely intact after the administration of etomidate. Stimulation of the depressor nerve decreased mean arterial pressure and sympathetic nerve activity to a level slightly less than the control at each dose, although as mean arterial pressure and sympathetic nerve activity were decreased already following the administration of the drug, the absolute decreases were smaller than the control decreases (figs 1 and 2).
Table I. Mean resting/baseline values (±SEM) in the decerebrate rabbit, unstimulated pithed rabbit and continuously stimulated pithed rabbit

<table>
<thead>
<tr>
<th>Preparation</th>
<th>Mean arterial pressure (mm Hg)</th>
<th>Heart rate (beat min⁻¹)</th>
<th>Sympathetic nerve activity (impulses s⁻¹)</th>
<th>Cardiac output (ml min⁻¹)</th>
<th>Stroke volume (ml)</th>
<th>Peripheral resistance (ml min⁻¹ per mm Hg)</th>
<th>Left ventricular dP/dt max (mm Hg s⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decerebrate</td>
<td>86 ± 8.6</td>
<td>221 ± 7.3</td>
<td>45.3 ± 13</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Pithed unstimulated</td>
<td>27.6 ± 1.7</td>
<td>232 ± 3.47</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Pithed continuously stimulated</td>
<td>57.8 ± 4.8</td>
<td>234 ± 4.7</td>
<td>—</td>
<td>207 ± 8.4</td>
<td>0.87 ± 0.04</td>
<td>0.28 ± 0.03</td>
<td>2539 ± 468</td>
</tr>
</tbody>
</table>

The heart rate component of the reflex was unaltered by doses of 0.05–4 mg kg⁻¹ and the decrease with the highest dose (8 mg kg⁻¹) was associated with a marked decrease of values before stimulation of the baroreceptor reflex (fig. 1).

**Pithed rabbit**

Baseline values obtained in the unstimulated pithed rabbit and in the continuously stimulated pithed rabbit are presented in table I.

**Unstimulated rabbit.** The administration of etomidate produced dose-related decreases in mean arterial pressure and left ventricular dP/dt max which were significant at the higher doses (2 mg and 4 mg kg⁻¹). These values had returned to baseline within 7 min (fig. 3A). Heart rate was decreased by up to 5%, a small but statistically significant reduction (fig. 3A). Left ventricular end-diastolic pressure was increased only by the 4-mg kg⁻¹ dose.

It was impracticable to measure the cardiac output.
when arterial pressure was changing rapidly. However, 1 min after the injection of etomidate, cardiac output was relatively stable and, although not maximal, the effects of etomidate were still very much in evidence (fig. 3).

Cardiac output and stroke volume increased significantly at the 1-mg kg\(^{-1}\) dose, but at the higher doses no significant effect was seen (fig. 4A). Peripheral resistance decreased significantly at the 4-mg kg\(^{-1}\) dose (fig. 4A).

The effect of brief electrical stimulation. Brief electrical stimulation in the pithed animal (70 V at 10 Hz for 20 s) produced a marked increase in mean arterial pressure and left ventricular \(dP/dt\) max (the pithing rod was positioned so that there was no effect on heart rate). Etomidate administered before brief electrical stimulation produced no significant change in the increase in mean arterial pressure. On the other hand, a significant diminution in the increase of left ventricular \(dP/dt\) max produced by brief electrical stimulation was noted following the administration of etomidate (control increases = 100%; 1 mg and 2 mg kg\(^{-1}\) (fig. 5A)).

The effect of noradrenaline. Marked increases in mean arterial pressure and left ventricular \(dP/dt\) max were produced by the administration of noradrenaline 0.3 \(\mu\)g kg\(^{-1}\). Etomidate produced no significant effect on this response at any dose (fig. 5A).

The effect of continuous stimulation. Sustained electrical stimulation produced higher control arterial pressures because of stimulation of peripheral sympathetic nerves, resulting in increased vasomotor tone. Etomidate produced a significant decrease in left ventricular \(dP/dt\) max at all doses and a significant decrease in mean arterial pressure at all but the smallest dose. A small but significant decrease in heart rate was noted at all doses. However, this never exceeded 4% of the control value (fig. 3B). The cardiac output and stroke volume increased significantly at the 0.5–mg kg\(^{-1}\) dose only. There was a significant decrease in peripheral resistance at all doses (fig. 4B). Figure 6 compares the effects of etomidate 2 mg kg\(^{-1}\) on basal activity in the unstimulated pithed rabbit with that found in the continuously stimulated pithed rabbit.

Comparison of the effects of etomidate on mean arterial pressure in the pithed and decerebrate rabbit. The effects of etomidate on the mean arterial pressure in unstimulated pithed rabbits, pithed rabbits subjected to continuous stimulation and decerebrate rabbits can be seen in figure 7. At higher doses etomidate produced a more profound decrease in arterial
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FIG. 3. The effects of four doses of etomidate on heart rate, mean arterial pressure and left ventricular dP/dt max in the pithed rabbit: (A) in the absence of sympathetic nerve stimulation, (B) in the presence of continuous stimulation of the sympathetic outflow at T8 (5 Hz). Each value is expressed as a percentage of pre-injection. The values at "m" represent the maximum decrease which occurred between 15 and 30 s after injection. Doses: • = 0.5 mg kg\(^{-1}\); A = 1 mg kg\(^{-1}\); • = 2 mg kg\(^{-1}\); O = 4 mg kg\(^{-1}\). n = 6; bars indicate ± SEM.

pressure in the decerebrate rabbit than in the continuously stimulated pithed rabbit.

DISCUSSION

Decerebrate rabbit

In the decerebrate rabbit the administration of etomidate produced simultaneous decreases in mean arterial pressure and sympathetic nerve activity. Similar results were seen previously in this preparation following the administration of ketamine (McGrath, MacKenzie and Millar, 1975), Althesin and thiopentone (MacKenzie et al., 1976).

Etomidate produced negligible effects on the baroreceptor reflex and thus contrasts with the effects of ketamine, Althesin and thiopentone, with which there was a marked diminution of the heart rate component of the reflex. Thus, etomidate can be said to preserve the baroreceptor reflex pathways intact.

Fig. 4. The effects of increasing doses of etomidate on cardiac output (CO), stroke volume (SV) and peripheral resistance (PR) (A) in the absence of sympathetic nerve stimulation and (B) in the presence of continuous stimulation of the sympathetic outflow at T8. Each value is expressed as a percentage of pre-injection. n = 6; bars are ± SEM.

Fig. 5. The effects of etomidate on the increase in mean arterial pressure and left ventricular dP/dt max produced by (A) noradrenaline given before etomidate and 2 and 12 min after, and (B) short electrical stimulation given before etomidate and 2, 7 and 12 min after etomidate. Each value is expressed as a percentage of the change caused by the stimulus before etomidate. Doses • = 0.5 mg kg\(^{-1}\); A = 1 mg kg\(^{-1}\); • = 2 mg kg\(^{-1}\); O = 4 mg kg\(^{-1}\). n = 6; bars are ± SEM.
Pithed rabbit

In the pithed rabbit the decrease in mean arterial pressure was significant only at the 2-mg and 4-mg kg\(^{-1}\) doses, in contrast to the decerebrate rabbit, in which there was a decrease in mean arterial pressure at all doses. This suggests that the decrease in sympathetic nerve activity noted at all doses in the decerebrate rabbit mediates a central cardiovascular depressant effect of etomidate.

The significant decrease in left ventricular \(dP/dt\) max produced by etomidate indicates that the drug has the property of decreasing myocardial contractility directly. While this may be in part a result of a decrease in the peripheral resistance decreasing left ventricular \(dP/dt\) max as expected from Starling’s Law, the decreases in left ventricular \(dP/dt\) max are much greater than that expected from this cause alone.

When measured 1 min after the smaller doses of etomidate, small increases in cardiac output and stroke volume were noted, probably an effect of an overshoot related to changing venous return in the unbuffered pithed rabbit.

Etomidate decreased the peripheral resistance at all doses during continuous stimulation but only with the 4-mg kg\(^{-1}\) dose in the unstimulated rabbit. This was to be expected, as vascular tone is greater in the continuously stimulated rabbit and is likely, therefore, to be more sensitive to the depressant effects of etomidate.

The responses of mean arterial pressure and left ventricular \(dP/dt\) max to noradrenaline were virtually unaffected by etomidate, although there was a slight potentiation at the smaller doses and a decrease with the greater doses of etomidate. Similar effects
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were produced by ketamine, Althesin and pentobarbitone (McGrath and MacKenzie, 1978) and have been ascribed, in the case of ketamine, to blockade of neuronal noradrenaline uptake (Montel et al., 1973; Nedergaard, 1973), an action that may be attributable also to etomidate.

The responses of mean arterial pressure and left ventricular dP/dt max to a short train of electrical stimuli were noted both before and after the administration of etomidate. As we wished to observe the maximal effects of etomidate and the trend to recovery, the stimulus was not produced until 2 min after the drug had been given. Following etomidate, no effect was seen on the response of the mean arterial pressure, but there was a significant decrease in the response of left ventricular dP/dt max. This could have been a result of a small reduction in the increase of peripheral resistance because of interference with sympathetic nerve conduction or sympathetic ganglia leading to a measurable reduction of left ventricular dP/dt max via the Starling effect.

Etomidate produced a small but significant decrease in heart rate in the pithed rabbit, but no change in heart rate in the decerebrate rabbit. This may be peculiar to the decerebrate animal, with unaffected baroreceptor mechanisms, responding to the decrease in mean arterial pressure by maintaining its heart rate, while the unbuffered animal demonstrated the negative chronotropic action of etomidate.

In conclusion, the comparison of the effects of etomidate on the pithed and decerebrate rabbit allowed us to demonstrate that the drug has both a central and a peripheral depressant effect on the cardiovascular system, while maintaining baroreceptor pathways intact. In clinical doses it has a small cardiovascular depressant effect, while being unique, apparently, among the i.v. anaesthetic agents in preserving the baroreceptor-mediated responses to hypotension and hypertension.

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REFERENCES


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RECHERCHE SUR LES EFFETS CARDIOVASCULAIRES CENTRAUX ET PERIPHERIQUES MEDIATS DE L'ETOMIDATE SUR LES LAPINS

RÉSUMÉ
L'étomidate a provoqué sur le lapin décérébré des diminutions, en fonction de la dose, de la tension artérielle moyenne et de l'activité préganglionique du nerf sympathique. Il n'y a eu aucune altération importante de la fréquence cardiaque. On a trouvé que l'étomidate n'avait aucun effet sur le réflexe barorécepteur. Les effets de l'étomidate sur les animaux énervés ont été de courte durée et d'une moins grande importance que ceux constatés sur les animaux décérébrés. On en a conclu que les effets supplémentaires observés sur le lapin décérébré provenaient de la dépression du contrôle cardiovasculaire central. On a trouvé que l'étomidate restait essentiellement sans effet sur le système cardiovasculaire aux doses anesthésiantes normales (0,5-1 mg kg⁻¹). Cependant les doses plus fortes (2-8 mg kg⁻¹) ont produit une dépression plus prononcée du contrôle cardiovasculaire central, du myocarde et du système vasculaire périphérique.

EINE UNTERSUCHUNG DER MITTELBAREN ZENTRALEN UND PERIPHEREN KARDIOVASKULÄREN EFFEKTE VON ETOMIDAT BEIM KANINCHEN

ZUSAMMENFASSUNG

UNA INVESTIGACION DE LOS EFECTOS CARDIOVASCULARES MEDIADOS CENTRALMENTE Y PERIFERICAMENTE DE ETOMIDATA EN EL CONEJO

SUMARIO
En el conejo descerebrado se produjeron mediante etomidata disminuciones relacionadas con la dosis en la presión arterial media y la actividad nerviosa simpática pręganglionica. No se produjeron alteraciones significativas en los latidos del corazón. Se descubrió que la etomidata no ejerce efecto alguno sobre el reflejo baroreceptor. Los efectos de la etomidata sobre animales sin médula espinal fueron de corta duración y de menor consideración que en los animales descerebrados. Se concluyó que los efectos adicionales en el conejo descerebrado fueron un resultado de la depresión del control cardiovascular central. Se descubrió que la etomidata ejercía poco efecto sobre el sistema cardiovascular con dosis anestésicas normales (0,5-1 mg kg⁻¹). Sin embargo, las dosis mayores (2-8 mg kg⁻¹) produjeron una marcada depresión del control cardiovascular central, el miocardio y la vasculatura periférica.