ETOMIDATE FOR INDUCTION OF ANAESTHESIA AT CAESAREAN SECTION: COMPARISON WITH THIOPENTONE

J. W. Downing, R. J. R. Buley, J. G. Brock-Utne and P. C. Houlton

SUMMARY

Thirty mothers undergoing elective Caesarean section received thiopentone 3.5 mg kg$^{-1}$ and 30 received etomidate 0.3 mg kg$^{-1}$ for induction of anaesthesia. Subsequent management of anaesthesia was identical in both groups. Maternal to fetal base excess differences and the degree of biochemical correlation between mother and infant were more favourable following etomidate than following thiopentone. The clinical status of the newborn was considered superior with etomidate.

Thiopentone is a standard induction agent in obstetric anaesthesia (Bradford and Moir, 1969; Baraka et al., 1971; Peltz and Sinclair, 1973; Downing et al., 1976; Mahomedy et al., 1976). However, barbiturates cause some degree of cardiorespiratory depression, influencing maternal–fetal haemodynamics and transplacental exchange (Dundee and Wyant, 1974). Thiopentone crosses the placental barrier and drug-induced depression of the newborn may result if a large dose is given to the mother (Finster and Poppers, 1968).

It has been suggested that current investigations of various induction agents for Caesarean section are inappropriate in view of the extremely low frequency of drug-induced neonatal depression at elective section (Crawford, 1977). However, these considerations may not apply if the fetus is at risk.

Etomidate, the new imidazole i.v. induction agent, has an action rapid in onset and of short duration. There is minimal alteration in cardiorespiratory function and recovery is uneventful (Morgan, Lumley and Whitwam, 1975; Fragen, Caldwell and Brunner, 1976). It does not cause detectable histamine release (Doenicke et al., 1973). Initially, etomidate possessed two undesirable side-effects: pain on injection and excessive involuntary movements during induction. The introduction of a new preparation of etomidate (Hendry, Miller and Lees, 1977) and the use of a rapid induction sequence (Downing et al., 1974) has reduced the frequency of both problems.

We describe the use of etomidate for anaesthesia at Caesarean section. The results are contrasted with those obtained from a control series receiving thiopentone (Buley et al., 1977).

PATIENTS AND METHODS

Sixty mothers who conformed to the criteria of the “clinically acceptable ideal case” (Crawford, 1962) gave consent to the investigation. The patients were not in labour and the membranes were intact. In every patient, placental function was judged to be normal on clinical grounds. Gestational age was 38–42 weeks, confirmed by a positive foam test and an amniotic fluid lecithin–sphingomyelin ratio greater than 2.5; the fetus was a singleton with vertex presenting. The mother lay on her left side during transfer to the operating theatre for elective Caesarean section.

During anaesthesia and surgery a 15° foam rubber wedge was placed under the right buttock, providing left lateral tilt. A standard anaesthetic technique was used similar to that described by Buley and others (1977). In 30 mothers, etomidate was used as the i.v. induction agent in a dose of 0.3 mg kg$^{-1}$ and the remaining 30 received thiopentone 3.5 mg kg$^{-1}$ (control series). The control series includes 23 patients described in our previous report (Buley et al., 1977).

Patients weighing more than 85 kg were excluded from the trial and the dose of the induction agent related to weight was not corrected for pregnancy. Tracheal intubation was facilitated by the simultaneous administration of suxamethonium 1.75 mg kg$^{-1}$ or 1 mg kg$^{-1}$ with thiopentone or etomidate from the same syringe (Downing et al., 1974). Manual pressure was applied to the cricoid cartilage by an assistant until the tracheal tube cuff was inflated.

Ventilation of the lungs was controlled using a Manley ventilator delivering an expired minute
volume of 130 ml kg\(^{-1}\) designed to maintain maternal \(P_{\text{aCO}_2}\) within a range 3.7–4.8 kPa.

Anaesthesia was maintained with 50% nitrous oxide in oxygen (monitored with an Ohio Airco Model 600 Oxygen Analyser) and enflurane 0.5–0.8%. Further muscle relaxation was provided by i.v. injection of pancuronium 2–4 mg. Following delivery of the infant, pethidine 50 mg was administered i.v. The residual effects of the non-depolarizing drug were antagonized at the end of the procedure with neostigmine 5 mg mixed with atropine 1.2 mg i.v. (Brock-Utne et al., 1978).

At the time of delivery maternal arterial and fetal umbilical cord blood samples were obtained and analysed using an IL 413 blood-gas analyser. Results were verified using a Radiometer B.M.S. Mk II blood-gas apparatus. The electrodes were calibrated using standard buffer solutions and certified gases or a Radiometer gas-mixing device. Base excess values were calculated. Student’s \(t\) test for unpaired data was used in analysing the results. In calculating fetal base excess values, corrections were made for the degree of haemoglobin desaturation in the umbilical cord blood samples (Buley et al., 1977).

RESULTS

Mothers

The average maternal age of the etomidate group (23.9 yr, SEM 1.0) was younger than that of the thiopentone control group (26.8 yr, SEM 0.5) \((P<0.05)\). The mean body weights of the two groups were comparable; etomidate 71.6 kg, SEM 1.9, v. thiopentone 70.0 kg, SEM 1.9.

The arterial blood-gas status of the mothers at delivery (table I) showed respiratory alkalosis with a compensatory metabolic acidosis (more marked in the etomidate group \((P<0.005)\)) in the majority at delivery.

Infants

The average induction to delivery (I-D) and uterine incision to delivery (U-D) intervals were similar in both groups (table II). The time to sustained breathing (TSR) by the infants was slightly shorter with etomidate \((0.1>P>0.05)\), but much shorter than in our previously published left lateral tilt series \((TSR \text{ thiopentone: left tilt } 27.3 \text{ s } \pm 5.7 \text{ v. etomidate } 10.8 \text{ s } \pm 1.5 \text{ (}P<0.005\)) (Buley et al., 1977). Apgar scores at 1, 2 and 5 min were similar (table II), a mild degree of neonatal depression \((A—C 4–6)\) being encountered in the first 2 min of life in only three infants of the two groups.

The acid–base and blood-gas values obtained from

<table>
<thead>
<tr>
<th>Group</th>
<th>Thiopentone</th>
<th>Etomidate</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>[H(^+)] ((\text{nmol litre}^{-1}))</td>
<td>Mean SEM</td>
<td>Mean SEM</td>
<td>(P&lt;0.05)</td>
</tr>
<tr>
<td>(P_{\text{aCO}_2}) (kPa)</td>
<td>4.23 0.06</td>
<td>4.16 0.05</td>
<td>n.s.</td>
</tr>
<tr>
<td>(P_{\text{o2}}) (kPa)</td>
<td>23.7 1.3</td>
<td>22.4 1.1</td>
<td>n.s.</td>
</tr>
<tr>
<td>Base excess ((\text{mmol litre}^{-1}))</td>
<td>(-3.6 0.5)</td>
<td>(-5.6 0.3)</td>
<td>(P&lt;0.005)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Table II. Time intervals and clinical status of the infants whose mothers received thiopentone with nitrous oxide, oxygen and enflurane or etomidate with nitrous oxide, oxygen and enflurane. (Mean ± SEM)</th>
</tr>
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<tbody>
<tr>
<td></td>
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<tr>
<td>I-D (min)</td>
</tr>
<tr>
<td>U-D (s)</td>
</tr>
<tr>
<td>TSR (s)</td>
</tr>
<tr>
<td>Apgar score</td>
</tr>
<tr>
<td>1–3</td>
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<tr>
<td>4–6</td>
</tr>
<tr>
<td>7–8</td>
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</tbody>
</table>

\*Original thiopentone left lateral tilt series (Buley et al., 1977); 27.3 s \(\pm 5.7\) v. 10.8 s \(\pm 1.5\) etomidate, \(P<0.005\).
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TABLE III. Comparison of umbilical venous (Uv) and arterial (Ua) biochemical values, of infants whose mothers received either thiopentone with nitrous oxide, oxygen and enflurane or etomidate with nitrous oxide, oxygen and enflurane. (Mean ± SEM)

<table>
<thead>
<tr>
<th>Group</th>
<th>Thiopentone Mean</th>
<th>Etomidate Mean</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>[H⁺] (nmol litre⁻¹)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Uv</td>
<td>45.3 1.1</td>
<td>47.6 0.6</td>
<td>n.s.</td>
</tr>
<tr>
<td>Ua</td>
<td>51.0 1.3</td>
<td>53.3 0.7</td>
<td>n.s.</td>
</tr>
<tr>
<td>Pco₂ (kPa)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Uv</td>
<td>5.34 0.1</td>
<td>5.33 0.09</td>
<td>n.s.</td>
</tr>
<tr>
<td>Ua</td>
<td>6.42 0.14</td>
<td>6.43 0.12</td>
<td>n.s.</td>
</tr>
<tr>
<td>Po₂ (kPa)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Uv</td>
<td>4.4 0.17</td>
<td>4.30 0.10</td>
<td>n.s.</td>
</tr>
<tr>
<td>Ua</td>
<td>2.66 0.14</td>
<td>2.68 0.08</td>
<td>n.s.</td>
</tr>
<tr>
<td>O₂ saturation (%)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Uv</td>
<td>71.9 2.8</td>
<td>71.1 1.6</td>
<td>n.s.</td>
</tr>
<tr>
<td>Ua</td>
<td>39.9 3.2</td>
<td>39.3 2.1</td>
<td>n.s.</td>
</tr>
<tr>
<td>Base excess (mmol litre⁻¹)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Uv</td>
<td>-4.7 0.7</td>
<td>-6.5 0.3</td>
<td>P&lt;0.05</td>
</tr>
<tr>
<td>Ua</td>
<td>-6.8 0.7</td>
<td>-8.0 0.3</td>
<td>n.s.</td>
</tr>
</tbody>
</table>

n.s. = not significant.

Blood-gas and acid–base differences between mother and fetus Δ(Ma–Ua) and Δ(Ma–Uv) are presented in table IV. BE values are significantly smaller for etomidate than for thiopentone.

Umbilical venous to arterial differences Δ(Uv–Ua) representing the fetal internal environment (Dawes, Mott and Widdicombe, 1974) were similar with both drugs.

Biochemical interrelationships

Correlation coefficients (r) for maternal arterial v. fetal blood-gas results are shown in table V. The expected close correlation between Ma and Ua hydrogen ion concentration [H⁺] and base excess (BE) values was not seen with etomidate. However, r values for Ma v. Uv/Ua Pco₂ were greater with etomidate. With etomidate, a negative correlation emerged between Ma and Δ(Ma–Uv)/Δ(Ma–Ua) [H⁺] and an unusual relationship was apparent between Ma and Δ(Ma–Ua) BE.

DISCUSSION

The first clinical trials of etomidate were encouraging (Doenicke et al., 1973; Morgan, Lumley and Whitman, 1975), and, in view of the increasing number of adverse reactions associated with the administration of other i.v. induction agents (Dundee,
1976), the drug could represent a useful addition to the obstetric anaesthetist's armamentarium.

Etomidate produces rapid anaesthesia in one arm-brain circulation time and, unlike thiopentone, it is hydrolysed rapidly to an inactive substance so that recovery is faster than that following barbiturates (Hendry, Miller and Lees, 1977; Lees and Hendry, 1977).

Etomidate causes minimal alteration in the cardio-respiratory state (Morgan, Lumley and Whitwam, 1975; Fragen, Caldwell and Brunner, 1976; Gooding and Corsen, 1976), and does not appear to release histamine in detectable quantities (Doenicke et al., 1973).

The advent of a new polyethylene glycol solvent for etomidate has decreased significantly the frequency of pain on i.v. injection (Hendry, Miller and Lees, 1977), and our routine induction technique for Caesarean section (Downing et al., 1974) allows little time for excess movement at induction to be a problem.

Mother and fetus

Both groups of patients in this study were placed in the left lateral tilt position (Buley et al., 1977). Although the mothers in the etomidate group were younger on average than the control patients, the mean parity in the two series was comparable. Any advantage accruing to the infants of the etomidate group because of maternal age differences should be offset by the relatively greater degree of maternal acidaemia present in the etomidate group.

Unfortunately, blood-gas and acid-base measurements obtained from the umbilical vessels are indicative of the fetal biochemical state only at the time of sampling, and, although our programme attempted to ensure that the only difference in the two groups was the induction agent, we should not disregard other factors which may influence maternal to fetal exchange.

Preoperative placental function is important in this regard, but clinical data did not indicate any major differences between the groups. Blood flow through the uterus and placenta is impeded during uterine contraction and is influenced by posture. None of our patients was in labour and the effects of posture on chorio-decidual haemodynamics (Downing et al., 1974; Buley et al., 1977) were standardized. Surgical interference and rupture of the membranes also disturb fetal blood-gas homeostasis and this can be difficult to evaluate (Fothergill, Robertson and Bond, 1971). However, all the Caesarean sections were performed by the same group of surgeons using the same technique, as indicated by the similar I-D and U-D intervals in both groups.

Fetal state at delivery, as indicated by Ua sample (Dawes, Mott and Widdicombe, 1954; James et al., 1958), was similar in both groups, except for the decrease in Uv BE with etomidate. When the blood-gas status of the mother is related specifically to the fetal state using the indices $\Delta(Ma - Uv)$ and $\Delta(Ma - Ua)$, etomidate would appear to provide advantages over thiopentone. This was not reflected in the Apgar scores at 1 min. Marx, Mahajan and Miclat (1977) have demonstrated that a correlation exists between the Ua sample and the $A(C - A)$ Apgar score only at the moment of birth. The clinical impression that the etomidate group of infants responded more favourably to introduction to the outside environment was reflected to some extent by differences in the time to spontaneous respiration.

To evaluate further the cause of this improved fetal tissue perfusion, we examined the effect of etomidate on the biochemical state of umbilical venous (Uv) blood. There was an improvement in Uv BE of the etomidate group. Furthermore, the $\Delta(Ma - Uv)$ BE difference was significantly smaller with etomidate than with thiopentone. Thus there would appear to be improved matching of maternal to placental circulation after the administration of etomidate. This statement is supported further by the close correlation between Ma $v.$ Uv/Us $Paco_2$ with etomidate.

The absence of a correlation between Ma and Ua $[H^+]$ and BE in the etomidate series, coupled with the emergence of a significant negative relationship, Ma $v.$ $\Delta(Ma - Uv) / \Delta(Ma - Ua)$ $[H^+]$ and the positive correlation noted for Ma $v.$ $\Delta(Ma - Ua)$ BE (table V) with etomidate, deserves further comment. On pharmacological grounds, fetal cardiovascular haemodynamics and organ perfusion should be maintained better following the injection of etomidate, relative to thiopentone. This may improve the transport of fetal circulating fixed acids to the placenta.

A review of the literature reveals that no induction agent investigated for Caesarean section has proved manifestly superior to thiopentone (Bradford and Moir, 1969; Baraka et al., 1971; Peltz and Sinclair, 1973; Downing et al., 1976; Mahomedy et al., 1976; Crawford, 1977). Indeed, James and others (1977) and Magno (1976) were unable to recommend lumbar extradural analgesia over a thiopentone, nitrous oxide, oxygen, volatile agent and relaxant anaesthesia for Caesarean section.

Our study of etomidate suggests that this drug may be of particular value in obstetric anaesthesia,
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especially in the clinically ill fetus whose biochemical status may be served better. Further testing of this hypothesis is indicated.

REFERENCES


ETOMIDATE ZUR EINLEITUNG DER NARKOSE FÜR KAISERSCHRITT: EIN VERGLEICH MIT THIOPENTON

ZUSAMMENFASSUNG

Von 60 Müttern, die sich für einen Kaiserschnitt entschieden hatten, erhielten 30 3,5 mg kg⁻¹ Thiopentone und 30 0,3 mg kg⁻¹ Etomidate zur Einführung der Narkose. Danach wurde die Narkose in beiden Gruppen identisch weitergeführt. Die von der Mutter zum Fetus übergegangenen Basenexzessen und der Grad der biochemischen Wechselbeziehung zwischen Mutter und Kind waren nach Etomidat günstiger als nach Thiopentone. Der klinische Zustand der Neugeborenen wurde nach Etomidat für überlegen erachtet.
ETOMIDATA PARA LA INDUCCION DE ANESTESIA EN SECCION CESAREA: COMPARACION CON TIOPENTONA

SUMARIO

Treinta madres sometidas a sección cesárea electiva recibieron 3,5 mg kg⁻¹ de tiopentona y 30 recibieron 0,3 mg kg⁻¹ de etomidata para inducción de anestesia. La administración posterior de anestesia fue idéntica para ambos grupos. Las diferencias entre el exceso básico materno y fetal y el grado de correlación bioquímica entre madre e infante fueron más favorables tras la administración de etomidata que tras la administración de tiopentona. El estado clínico del recién nacido fue considerado superior con etomidata.