British Journal of Anaesthesia 1992; **69**: 586–588

THIOPENTONE AND ETOMIDATE CONCENTRATIONS IN MATERNAL AND UMBILICAL PLASMA, AND IN COLOSTRUM

Z. ESENER, B. SARIHASAN, H. GÜVEN AND E. ÜSTÜN

SUMMARY

We have measured concentrations of etomidate and thiopentone in maternal plasma, umbilical venous plasma and colostrum after induction of anaesthesia in 40 patients undergoing Caesarean section. Mean plasma etomidate concentration declined rapidly (1242.0 ng ml^{-1} at 5 min, 434.0 ng ml^{-1} at 15 min, 64.2 ng ml^{-1} at 30 min, 7.0 ng ml^{-1} at 60 min and undetectable 2 h after the injection). Mean plasma concentrations of thiopentone declined more slowly (6.09 μg ml^{-1} at 5 min, 2.64 μg ml^{-1} at 2 h, 1.35 μg ml^{-1} at 4 h, 0.86 μg ml^{-1} at 9 h and 0.59 μg ml^{-1} at 12 h). Mean umbilical venous thiopentone concentration was 4.72 μg ml^{-1}, whereas the thiopentone concentration in the maternal sample at 5 min was 6.09 μg ml^{-1}, giving an umbilical:maternal vein ratio of 1:1.3. Mean umbilical etomidate concentration was 51.7 ng ml^{-1} and the corresponding maternal vein sample (5 min) was 1242.0 ng ml^{-1} ($P < 0.001$), giving an umbilical:maternal vein ratio of 1:24. Mean concentrations of thiopentone in colostrum were 1.98 μg ml^{-1} at 30 min, 0.91 μg ml^{-1} at 4 h and 0.59 μg ml^{-1} at 9 h, colostrum:plasma ratios at 4 h and 9 h being 0.67 and 0.68, respectively. Mean concentrations of etomidate in colostrum were 79.3 ng ml^{-1} at 30 min and 16.3 ng ml^{-1} at 2 h, being undetectable at 4 h. The colostrum:plasma etomidate concentration ratio was 1.2 at 30 min. We conclude that, although plasma and colostrum concentrations of thiopentone and etomidate declined rapidly, the decrease was faster with etomidate. (Br. J. Anaesth. 1992; **69**: 586–588)

KEY WORDS

Anaesthetics, intravenous: thiopentone, etomidate. Anaesthesia: obstetric. Pharmacokinetics: plasma, umbilical vein cord and colostrum concentrations.

Thiopentone is used extensively for induction of anaesthesia in obstetrics [1]. However, barbiturates cause cardiorespiratory depression. There is abundant evidence that thiopentone crosses the placenta easily and is found in significant concentrations in umbilical cord blood. Etomidate is associated with little or no cardiovascular or respiratory effects [2–4] and the clinical status of the newborn after Caesarean section has been shown to be satisfactory [3, 5–7].

In some departments it is common practice to discard the first portions of milk after general anaesthesia, to avoid any side effects of the anaesthetic agents. Reports of the excretion of etomidate in colostrum after induction of anaesthesia have, to our knowledge, not been published.

The aim of this study was to determine the post-anaesthetic concentrations of thiopentone and etomidate in maternal and neonatal plasma, and in colostrum after induction doses of thiopentone and etomidate.

PATIENTS AND METHODS

We studied 40 healthy pregnant women at term undergoing Caesarean section. Each patient received a single i.v. injection of either thiopentone 5 mg kg^{-1} ($n = 20$) or etomidate 0.3 mg kg^{-1} ($n = 20$) for induction of anaesthesia.

Patients were premedicated with atropine 0.5 mg i.m. or 0.25 mg i.v. Left lateral tilt was used and the lungs were preoxygenated for 3–4 min. After thiopentone or etomidate, suxamethonium 1.5 mg kg^{-1} was given and the trachea was intubated, using cricoid pressure. Anaesthesia was maintained with 50% nitrous oxide in oxygen with halothane not exceeding 0.5%, until delivery of the infant. After delivery the nitrous oxide concentration was increased to 66% and halothane was increased as needed. Neuromuscular block was maintained with additional increments of suxamethonium.

The end of the injection of thiopentone or etomidate was taken as the starting point for obtaining blood samples.

In the thiopentone group, maternal blood samples were obtained at 5 min, 2, 4, 9 and 12 h, and colostrum samples at 30 min, 4 and 9 h after induction.

In the etomidate group, maternal blood samples were obtained at 5, 15, 30 and 60 min and 2 h, and colostrum samples at 30 min, 2 and 4 h after induction.

Umbilical cord blood (umbilical vein) was obtained immediately after delivery.

Plasma was separated immediately and samples for thiopentone were stored at −18 °C. Samples

ZEYNEP ESENER*, M.D.; BINNUR SARIHASAN, M.D.; EMRE ÜSTÜN, M.D.; Department of Anaesthetics, Ondokuz Mayis University, Medical School, Samsun, Turkey. HÜLYA GÜVEN, M.D., Department of Pharmacology, Dokuzeylül Univ, Medical School, Izmir, Turkey. Accepted for Publication: April 27, 1992.

*Address for correspondence: PK 29, 55001, Samsun, Turkey.

TABLE I. *Patient characteristics (mean (range or SEM)): age, weight, gestational age and induction to delivery (I–D) interval in the thiopentone and etomidate groups*

Group	Age (yr)	Weight (kg)	Gestational age (weeks)	I–D interval (min)
Thiopentone	28.3 (22–38)	75 (2)	39.9 (0.6)	7.3 (2.1)
Etomidate	28.2 (19–41)	74 (2)	40.1 (0.7)	7.0 (0.9)

were thawed at room temperature before the extraction process. Thiopentone was extracted from plasma and colostrum with n-hexane containing 1.5% iso-amyl alcohol and re-extracted into sodium hydroxide 2.5 mol litre^{-1} [8]. Thiopentone concentrations were measured using a spectrophotometric method (SIM AMINCO SMF 500) with absorbance at 305–505 μm [9].

To each 1-ml aliquot of plasma for etomidate measurement, heparin 0.002 g and potassium fluoride 10 μl (to inhibit esterase activity) were added and stored at −18 °C. After the samples were thawed and etomidate extracted from plasma or colostrum (with pentane, by mixing on a vortex mixer and discarding the upper layer twice), spectrophotometric (VARIAN DMS 100) measurement of etomidate was carried out using the absorbance at 235 μm.

Colostrum samples also were stored at −18 °C until analysis.

Results are given as mean (SEM). Student's *t* test was used for statistical analysis of the data within each group.

RESULTS

The two groups were similar in mean age, weight, gestational age and induction–delivery (I–D) interval (table I).

Thiopentone group. Maternal concentrations of thiopentone at 5 min (sample closest to delivery) were in the range 4–12.1 μg ml^{-1} (mean 6.09 (SEM 0.4) μg ml^{-1}). Mean maternal plasma concentration was 2.64 (0.3) μg ml^{-1} (range 0.8–7.0 μg ml^{-1}) at 2 h, 1.35 (0.2) μg ml^{-1} (range 0.1–3.7 μg ml^{-1}) at 4 h, 0.86 (0.1) μg ml^{-1} (range 0.4–1.4 μg ml^{-1}) at 9 h and 0.59 (0.1) μg ml^{-1} (range 0.2–1.2 μg ml^{-1}) at 12 h.

In the umbilical vein, thiopentone concentrations ranged from 2.3 to 10.2 μg ml^{-1} (mean 4.72 (0.4) μg ml^{-1}).

Mean concentrations of thiopentone in colostrum at 30 min, 4 h and 9 h after the injection were 1.98 (0.2) μg ml^{-1} (range 0.6–4.7 μg ml^{-1}), 0.91 (0.1) μg ml^{-1} (range 0.4–1.9 μg ml^{-1}) and 0.59 (0.1) μg ml^{-1} (range 0.3–1.4 μg ml^{-1}), respectively.

Etomidate group. Maternal concentrations of etomidate at 5 min (sample closest to delivery) were in the range 340–2500 ng ml^{-1} (mean 1242.0 (SEM 146) ng ml^{-1}). Mean maternal plasma concentrations at 5 min, 15 min, 30 min and 1 h after the injection of etomidate were 434.0 (82) ng ml^{-1} (range 0–1400 ng ml^{-1}), 64.2 (10) ng ml^{-1} (range 0–145 ng ml^{-1}), 7.0 (2.6) ng ml^{-1} (range 0–35 ng ml^{-1}) and 0.5 (0.1) ng ml^{-1} (range 0.2–1.2 ng ml^{-1}), respectively. There was no detectable etomidate in any of the 2-h samples.

In the umbilical vein, etomidate concentrations were in the range 0–190 ng ml^{-1} (mean 51.7 (10.3) ng ml^{-1}).

Mean concentrations of etomidate in colostrum at 30 min and 2 h after the injection were 79.3 (21.5) ng ml^{-1} (range 0–420 ng ml^{-1}) and 16.2 (4.1) ng ml^{-1} (range 0–60 ng ml^{-1}), respectively. No etomidate could be detected in any of the 4-h samples.

DISCUSSION

Although the measurement of plasma etomidate concentrations can be carried out accurately by several methods including gas chromatography (GC) [10–13], gas–liquid chromatography (GLC) [14] or high performance liquid chromatography (HPLC) [15], GC and GLC require considerably longer and are more laborious than HPLC [13]. We used an extraction method described for HPLC by Ellis and Beck [15] and u.v. spectrophotometry [16] based, like HPLC, on ultraviolet detection for estimation of the substrate. It was therefore possible to complete the extraction and estimation process in 1–1.5 h.

Etomidate is metabolized largely by esteratic breakdown [9, 17]. Continuing esteratic activity causes a decrease in etomidate concentration in blood samples also [18]. Therefore saturated potassium fluoride 10 μl was added to 10 ml of blood as a preservative.

We found that plasma etomidate concentrations declined rapidly. Doenicke and colleagues [11] found a plasma etomidate concentration at 30 min similar to our data. In Gregory and Davidson's study [7], in contrast, maternal etomidate concentrations at delivery were found to be smaller than the present data. This could be attributable to the greater I–D interval in their study.

Plasma thiopentone concentration decreased more slowly than etomidate concentration. Brodie and colleagues [19] reported that thiopentone concentrations decreased rapidly for the first 30 min then more slowly, with mean concentrations similar to those in our study. Andersen and colleagues [20] reported also that thiopentone was detected in plasma for up to 36 h. Although we did not obtain 36 h samples, thiopentone was detected in all the samples at 12 h (approximately 10% of the mean concentration at 5 min).

Thiopentone crosses the placental barrier readily, fetal and maternal concentrations equilibrating within 2–3 min [21, 22]. We did not obtain fetal blood in this study, but the umbilical plasma concentration of thiopentone in the blood sample obtained immediately after the cord had been clamped (mean 7.3 (2.1) min after the injection of thiopentone) was 4.72 (0.4) μg ml^{-1}. Mean con-

centration in the closest maternal sample (5 min) was 6.09 (0.4) μg ml^{-1}, giving an umbilical : maternal ratio of 1:1.3. Data on umbilical concentrations of thiopentone were in agreement with those of Finster and colleagues [23] and Flowers and Hill [21].

We found an umbilical : maternal venous etomidate concentration ratio of 1:24; Gregory and Davidson [7] reported this ratio as 1:2. This difference may be explained by the differences in doses of etomidate (0.4 mg kg^{-1} *vs* 0.3 mg kg^{-1}), I–D intervals (15.2 min *vs* 7.0 min) and the fact that, in our study, umbilical samples were taken later than maternal samples (7.0 min *vs* 5 min).

Drugs present in maternal circulation reach the mammary gland and milk by passive diffusion through glandular epithelium [20]. Colostrum : plasma ratios of thiopentone at 4 h and 9 h were 0.67 and 0.68, respectively. Andersen and colleagues [20] also found this ratio to be less than 1. The colostrum : plasma etomidate ratio was 1.2 at 30 min. While no etomidate could be detected in any of the 2-h plasma samples, etomidate was still detectable in nine of 20 colostrum samples, with a mean value of 16.2 (4) ng ml^{-1} at 2 h. Rapid decline in etomidate concentrations in colostrum may be an advantage in early feeding of the newborn after Caesarean section.

In conclusion, our results indicate that, although plasma concentrations of thiopentone and etomidate declined rapidly, this decrease was faster for etomidate.

REFERENCES

1. Datta S, Alper MH. Anesthesia for Cesarean section. *Anesthesiology* 1980; **53**: 142–160.
2. Fragen RJ, Caldwell N, Brunner EA. Clinical use of etomidate for anesthesia induction: A preliminary report. *Anesthesia and Analgesia* 1976; **55**: 730–733.
3. Giese JL, Stanley TH. Etomidate: A new intravenous anesthetic induction agent. *Pharmacotherapy* 1983; **3**: 251–258.
4. Nimmo WS, Miller M. Pharmacology of etomidate. *New Pharmacological Vistas in Anesthesia* 1983; **7**: 83–93.
5. Downing JW, Buley BJR, Brock-Utne JG, Houlton PC. Etomidate for induction of anaesthesia at Caesarean section: comparison with thiopentone. *British Journal of Anaesthesia* 1979; **51**: 135–140.
6. Gregoriades SA. Etomidate pour l'opération césarienne. *Cahiers d'Anesthésiologie* 1990; **38**: 275–276.
7. Gregory MA, Davidson DG. Plasma etomidate levels in mother and fetus. *Anaesthesia* 1991; **46**: 716–718.
8. Brodie BB, Mark LC, Papper EM, Lief PA, Bernstein E, Rovenstine EA. The fate of thiopental and a method for its estimation in biological material. *Journal of Pharmaceutical Sciences* 1949; **168**: 85–96.
9. Dayton PG, Peral JM, Landrau MA, Brand L, Mark LC. The relationship between binding of thiopental to plasma and its distribution into adipose tissue in man, as measured by a spectrophotofluorimetric method. *Biochemical Pharmacology* 1967; **16**: 2321–2326.
10. Avram MJ, Fragen RJ, Linde HW. HPLC assay for etomidate in human plasma: results of preliminary clinical studies using etomidate for hypnosis in total intravenous anesthesia. *Journal of Pharmaceutical Sciences* 1983; **72**: 1424–1426.
11. Doenicke A, Löffler B, Kugler J, Suttmann H, Grote B. Plasma concentration and EEG after various regimens of etomidate. *British Journal of Anaesthesia* 1982; **54**: 393–400.
12. Haring CMM, Dijkhuis IC. A rapid method of determining serum levels of etomidate by gas chromatography with the aid of a nitrogen detector. *Acta Anaesthesiologica Belgica* 1980; **31**: 107–112.
13. Shaw J, Kay B, Keegan M, Healy TEJ. Quantitative estimation of etomidate in water, plasma and blood. A comparison between high performance liquid chromatography and gas chromatography. *Journal of Pharmacological Methods* 1982; **7**: 311–319.
14. Wynants J, Woestenborghs R, Heykants J. A gas chromatographic assay method for etomidate in human plasma. Janssen Research Products Information Service, Section II: *Biological Research Reports*, Serial No: R26490/13. Beerse, Belgium: Janssen Pharmaceutica, 1974.
15. Ellis CO, Beck PR. Determination of etomidate in human plasma by high-performance liquid chromatography. *Journal of Chromatography* 1982; **232**: 207–211.
16. Skoag DA, West DM. *Principles of Instrumental Analysis*. New York: Holt, Rinehart and Winston Inc., 1971.
17. Corssen G, Reves JG, Stanley TH. *Intravenous Anesthesia and Analgesia*. Philadelphia: Lea & Febiger, 1988.
18. Van Hamme MJ, Ambre JJ, Conheim MM. Mass fragmentographic determination of plasma etomidate concentrations. *Journal of Pharmaceutical Sciences* 1977; **66**: 1344–1346.
19. Brodie BB, Mark LC, Papper EM, Lief PA, Bernstein E, Rovenstine EA. The fate of thiopental in man and method for its estimation in biological material. *Journal of Pharmaceutical Sciences* 1949; **168**: 85–96.
20. Andersen LW, Qvist T, Hertz J, Mogenson F. Concentrations of thiopentone in mature breast milk and colostrum following an induction dose. *Acta Anaesthesiologica Scandinavica* 1987; **31**: 30–32.
21. Flowers CE, Hill C. The placental transmission of barbiturates and their pharmacological action on the mother and infant. *American Journal of Obstetrics and Gynecology* 1959; **78**: 730–741.
22. Kosaka Y, Takahashi T, Mark LC. Intravenous thiobarbiturate anesthesia for Cesarean section. *Anesthesiology* 1969; **31**: 489–505.
23. Finster M, Mark LC, Morishima HO, Moya F, Perel JM, James LS, Dayton PG. Plasma thiopental concentrations in the newborn following delivery under thiopental–nitrous oxide anesthesia. *American Journal of Obstetrics and Gynecology* 1966; **95**: 621–629.