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Clinical investigations concerning the use of Ethrane for Cesarean section

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In obstetrical anesthesia – beyond the field of general operative medicine – the effects of and adverse reactions to an anesthetic agent must always be evaluated with reference to two individuals, the mother and the infant, before a judgement can be made about the suitability or inadequacy of a new drug for obstetrical purposes [2, 5].
Once the pharmacological and general clinical-anesthetic properties of the inhalation anesthetic, Ethrane, had been extensively documented. [1, 3, 8, 9, 11, 12, 13, 15, 16, 17, 19, 22, 24, 25, 26, 27] it became necessary to investigate the adequacy or unsuitability of the drug for obstetrical procedures. In this connection it should be noted that chemically Ethrane is similar to Methoxyflurane, while pharmacologically it resembles Halothane more closely [11].
In contrast to the numerous papers dealing with its surgical-anesthetic properties, reports on the use of Ethrane for obstetrical anesthesia are relatively scarce. In addition to papers from South America, DEVOGHEL, [5] COLEMAN' [4] and MAGNO [21] have reported their special findings in the obstetrical field. It thus appears that Ethrane relaxes the uterus, but the effects on uterus and fetal heart rate are promptly reversible [5]. COLEMAN [4] and MAGNO [21] have also reported satisfactory results with Ethrane. On our part, we have been publishing partial results in preliminary papers [6, 7].

Our aim has been:

1. to obtain information on the diaplacental passage of Ethrane by measuring maternal and neonatal Ethrane blood concentrations;
2. to evaluate postnatal adjustment of the infant by the APGAR scoring system, acid-base balance and blood gas analysis.

1 Method

To study possible adverse effects of anesthetic agent in the field of obstetrics, standardized anesthesia for primary Cesarean section appears to be particularly suitable, since other factors that might be mistaken for effects induced by the anesthetic agent are eliminated to a large extent. Consequently, 50 healthy mothers undergoing primary Cesarean section were given Ethrane instead of Halothane for anesthesia. Selection of the patients was based in part on the fact that the fetuses showed no evidence of imminent or manifest intrauterine manifestations.
After administration of Atropine (= 0.5 mg) and pre-oxygenation in left lateral position, anesthesia was induced with 150 to 250 mg Thiopental and 1 mg/kg Succinylcholine. Under endotracheal intubation anesthesia was maintained until delivery of the infant, using N_2O/O_2 in a 1:1 ratio, and Ethrane in a concentration of 1% by vol. on the

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average; Alcuronium Dichloride (Alloferin) was given for additional muscle relaxation. Proper gas exchange was assured by controlled hyperventilation using 9 liters/minute on the average. The maternal ECG was continuously monitored. Blood pressure and pulse rate were checked every five minutes. After delivery of the infant, the Ethrane concentration was increased to 2% by vol., and the N_2O/O_2 ratio was changed to the usual value of 2:1.

The Ethrane concentrations in the maternal blood, as well as maternal blood gases and acid-base balance were determined at the time of birth. Simultaneously, arterial and venous blood was collected from the umbilical cord for determining Ethrane concentrations, blood gases and acid-base balance. Condition of the newborn was assessed by the APGAR scoring system. All parameters were redetermined 5, 10 and 15 minutes after delivery.

Ethrane concentrations were determined by gas-chromatography; blood gases and acid-base balance were measured using the ASTRUP method and the SIGGAARD-ANDERSON nomogram, respectively. The newborn acid-base parameters were not corrected for the individual oxygen saturation.

2 Results

2.1 Maternal parameters

From a total of 50 available protocols, 31 were selected which provided all parameters for all points in time.

The age of the patients averaged 25.6 years, mean body weight was 71.3 kg. In 50% of cases the Cesarean section involved primiparae.

Continuous ECG monitoring showed no particular features. Following induction, blood pressure dropped by an average of 10 to 20 mm Hg, corresponding to a decrease of approx. 10 to 15% from base line.

2.2 Ethrane concentrations, blood gases and acid-base balance of mothers and infants

Of a total of 50 protocols, one was excluded for being incomplete with reference to one reading; thus, 49 complete protocols were available for evaluation.

2.2.1 Ethrane concentrations in maternal and infant blood

Ethrane concentrations in maternal arterial blood at the time of birth averaged 6.60 mg/100 ml. Ethrane concentrations in the umbilical artery at this time were 3.03 mg/100 ml, those of the umbilical vein were 3.94 mg/100 ml. Consequently, maternal Ethrane concentrations were approximately 50% higher than the umbilical venous and more than twice as high as the umbilical arterial Ethrane concentrations. The umbilical venous exceeded the umbilical arterial Ethrane concentrations by 0.92 mg/100 ml (Fig. 1).

Five minutes after birth, the umbilical venous Ethrane concentrations of the infants dropped to 0.91 mg/100 ml, 10 minutes after birth to 0.57, and 15 minutes after birth to 0.35 mg/100 ml. Thus, the Ethrane concentrations 15 minutes after birth were only 1/10 those of the initial concentrations.

If we try to correlate the maternal and the neonatal Ethrane concentrations with reference to the time of delivery we find merely a positive correlation between umbilical venous and umbilical arterial concentrations. While other correlations might be suspected, their statistical significance is not distinct enough to be used with sufficient clinical relevance (Fig. 2).

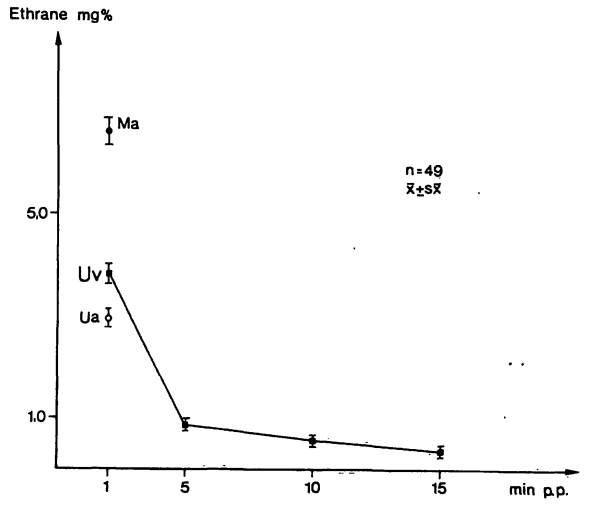

Fig. 1. Maternal (Ma), umbilical venous (Uv) and umbilical arterial (Ua) Ethrane concentrations 1, 5, 10 and 15 min post partum.

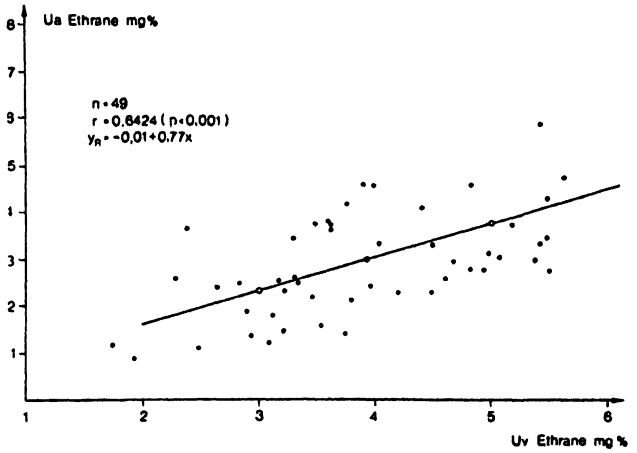

Fig. 2. Correlation between umbilical venous (Uv) and umbilical arterial Ethrane concentrations at birth.

2.2.2 Blood gases and acid-base balance of maternal and infant blood

The maternal pH values at the time of birth averaged 7.38, the umbilical venous pH was 7.28, and the umbilical arterial pH was 7.24. The umbilical venous pH dropped five minutes after birth to 7.2, and then rose to 7.24 and – 15 minutes after birth – to 7.30 (Fig. 3).

The average maternal PCO_2 at the time of birth was 31.83 mm Hg, the umbilical venous PCO_2 was 38.78, and the umbilical arterial PCO_2 was 41.87 mm HG. Five minutes after birth, the umbilical venous PCO_2 of the infant was 57.5 mm Hg; it then dropped to 53.4 and finally to 46.4 mm Hg (Fig. 4).

The maternal PO_2 at the time of birth averaged 149.3 mm Hg, the umbilical venous PO_2 was 36.4, and the umbilical arterial PO_2 was 25.1 mm HG. Five minutes after birth, the PO2 in the umbilical vein was 36.1, 10 minutes after birth it was 45,5 and 15 minutes after birth it was 50.6 mm Hg (Fig. 4)

The induction-delivery-interval (IDI) averaged 17.24 minutes.

Correlating once more the various maternal and infant parameters with reference to the time of delivery, we obtain the following picture:

A positive correlation exists between maternal pH on the one hand, and umbilical venous and umbilical arterial pH on the other hand. In addition, we find a significant correlation between umbilical venous and umbilical arterial pH (Figs. 5, 6, 7).

A further positive correlation is obtained between maternal PCO_2 on the one hand, and umbilical venous and umbilical arterial PCO_2 on the other (Figs. 8, 9).

Maternal PO_2 may be significantly correlated with umbilical venous PO_2, while a statistically conspicuous relationship exists between umbilical venous and umbilical arterial PO_2 (Figs. 10, 11).

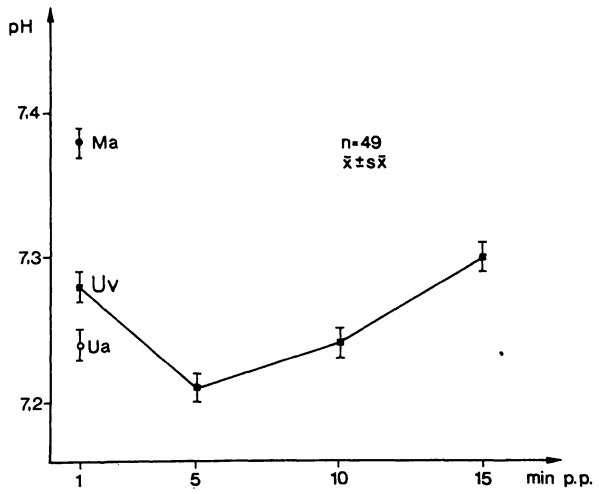

Fig. 3. Maternal (Ma), umbilical venous (Uv) and umbilical arterial (Ua) pH at birth as well as umbilical venous (Uv) pH 5, 10 and 15 min p.p.

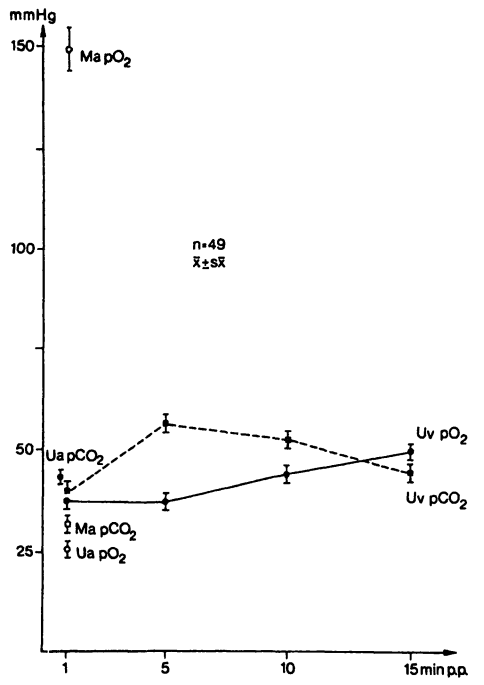

Fig. 4. Maternal (Ma), umbilical venous (Uv) and umbilical arterial (Ua) PO_2 and PCO_2 at birth and 5, 10 and 15 min post partum.

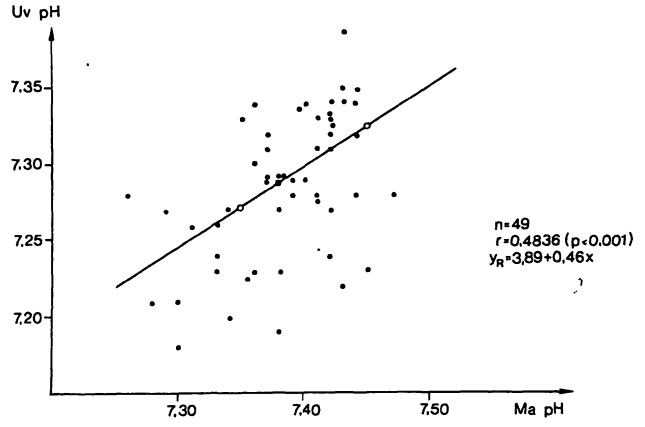

Fig. 5. Correlation between maternal (Ma) and umbilical venous (Uv) pH.

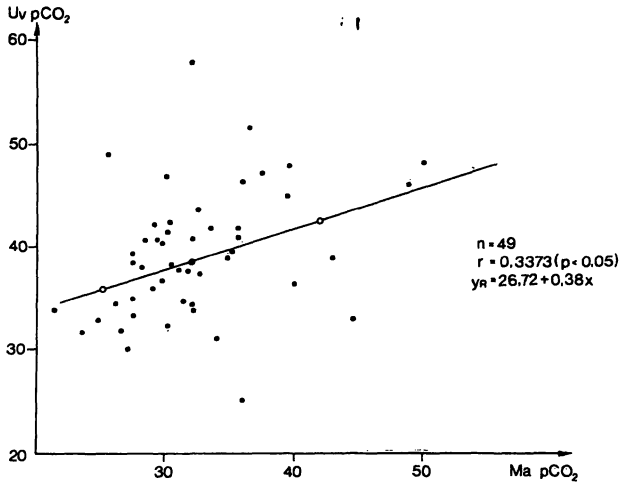

Fig. 8. Correlation between maternal (Ma) and umbilical venous (Uv) PCO_2.

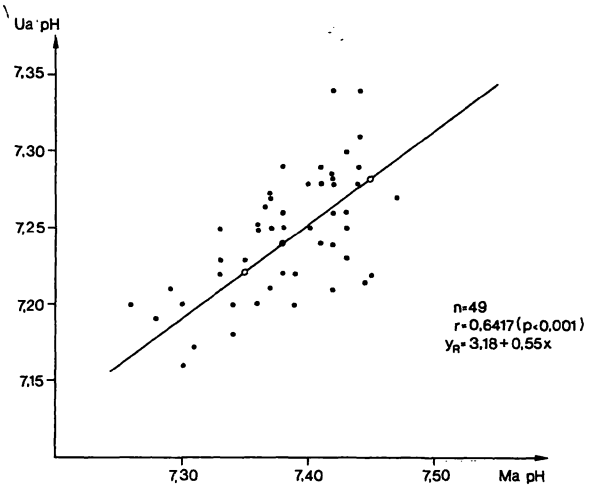

Fig. 6. Correlation between maternal (Ma) and umbilical arterial (Ua) pH.

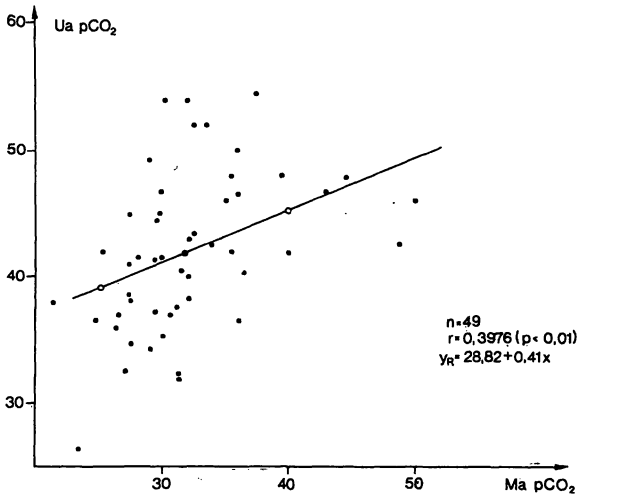

Fig. 9. Correlation between maternal (Ma) and umbilical arterial (Ua) PCO_2.

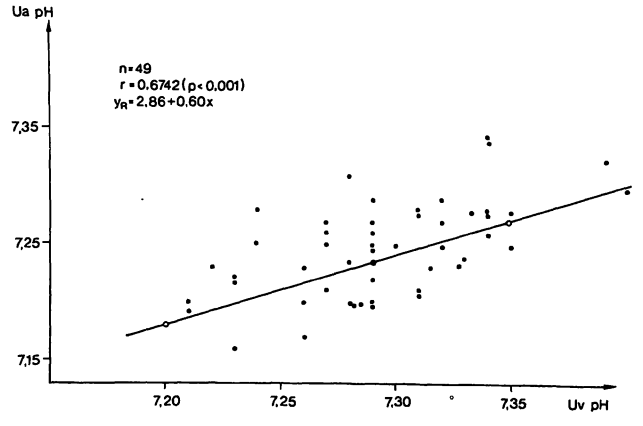

Fig. 7. Correlation between umbilical venous (Uv) and umbilical arterial (Ua) pH.

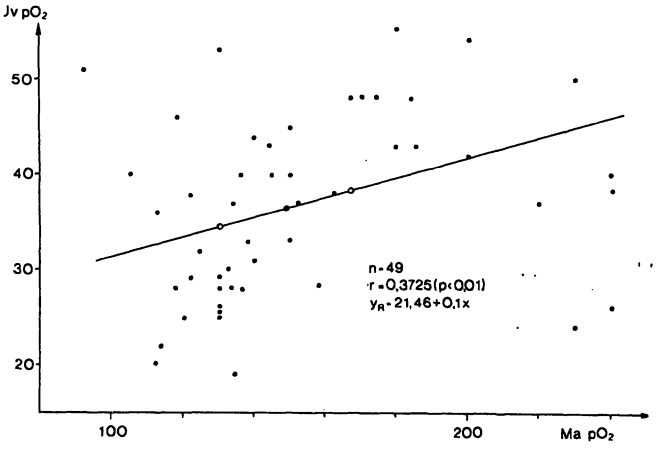

Fig. 10. Correlation between maternal (Ma) and umbilical venous (Uv) PO_2.

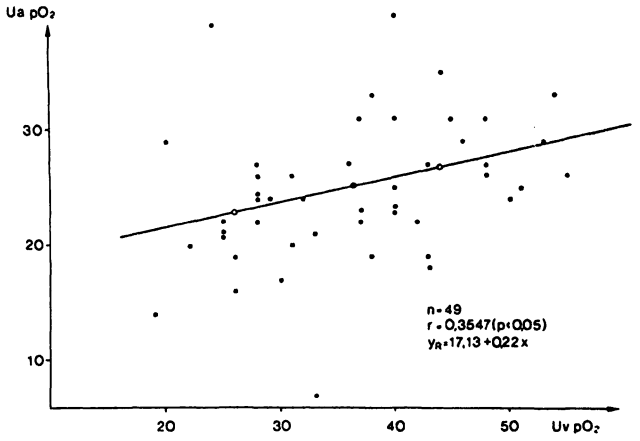

Fig. 11. Correlation between umbilical venous (Uv) and umbilical arterial (Ua) PO_2.

Base excess or base deficit in the infant blood after delivery shows the following picture:
From –8.05 at the time of birth, the negative base excess improved to –7.9, –6.7, and finally to –4.6 mEq/ liter 15 minutes after birth (Fig. 12).
Buffer base at the time of birth was 40.78, five minutes after birth it was 43.28, 10 minutes after birth 43.45, and 15 minutes after birth 46.03 mEq/liter (Fig. 12).

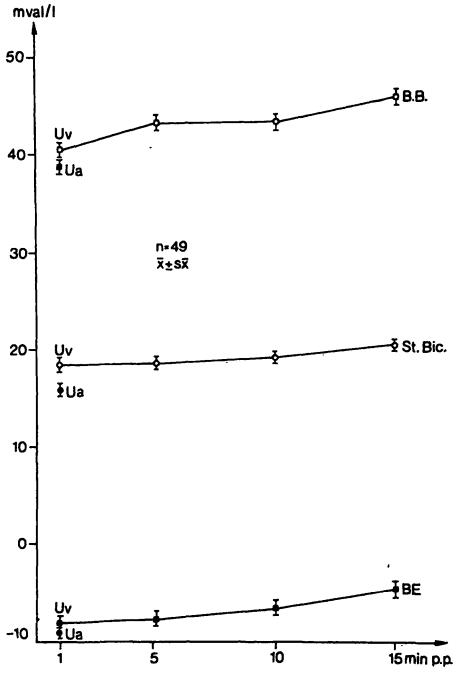

Fig. 12. Umbilical venous (Uv) and umbilical arterial (Ua) Base excess (BE), Standard-Bicarbonate (St. Bic) and Buffer Base (BB) at birth and 5, 10 and 15 min post partum.

Standard bicarbonate increased from 18.21 mEq/ liter at the time of birth to 18.41, 19.02, and finally to 20.60 mEq/liter 15 minutes after birth (Fig. 12).

3 Discussion

Major results of our investigation may be summarized in various groups.
From the clinical point of view, the prospective study of Ethrane anesthesia for Cesarean section has given satisfactory results. Drops in blood pressure exceeding 15% of base line readings did not occur with cautious dosage of Ethrane; likewise, bradycardia, tachycardia, or disorders of heart rhythm were not detected in the ECG records. Similar findings are found in the literature [e.g. 1, 12, 25, 26, etc.].
Mean induction-delivery-interval (IDI) was approximately 17 minutes. After this time, 6.6 mg/100 ml Ethrane were found in the maternal blood. At this same point in time, Ethrane concentrations in the umbilical venous blood were approximately 60% of the maternal concentrations (3.94 mg/100 ml), and the umbilical arterial concentrations were 46% of maternal concentrations (3.02), and 77% of umbilical venous concentrations. In contrast to evaluations based on a limited number of patients, [6, 7] we have been unable to detect any statistically relevant correlation between IDI, and umbilical venous Ethrane concentrations, as well as between maternal and umbilical venous Ethrane concentrations. This absence of a theoretically expected relationship may mean that the umbilical venous concentration depends on the maternal concentrations only at certain points in time until delivery, while it is determined by other criteria beyond the seven minute range. If we calculate the feto-maternal Ethrane concentration coefficient we find that this latter – practically independently of IDI – is situated between 0.59 and 0.63, the shortest IDI amounting to 7 minutes. This means that between 7 and 36 minutes, approximately 60% of the maternal Ethrane concentration became detectable in the umbilical venous blood of the fetuses.
There was, however, a significant correlation between umbilical venous and umbilical arterial

Ethrane concentrations. The concentration ratio rose from 0.69 to 0.77 for an IDI between 11 and 18 minutes. Subsequently, between 19 and 25 minutes, it dropped again to 0.7 and 0.68 (over a period of 26 minutes), respectively.

These findings suggest that at least for IDI exceeding 7 minutes, neither IDI nor maternal concentrations play any significant role with reference to the diaplacental passage of Ethrane. Equalization of concentrations must have taken place already before 7 minutes. Undoubtedly dependent on a number of factors, the feto-maternal concentration ratio varies between 0.33 and 0.96, with a mean value of 0.6. This means that from 30 to 96% of maternal Ethrane concentrations is transferred to the fetus. The umbilical arterial/umbilical venous ratio averages 0.77, ranging from 0.37 to 0.99.

Just as quickly as diaplacental passage of Ethrane occurs, the agent is eliminated from the body of the infant. Postpartum concentration patterns show that already after five minutes 23%, after 10 minutes 14%, and after 15 minutes 9% of the initial postpartum concentration can be detected.

The condition of the infants was assessed by the APGAR scoring system, by the blood gas and acid-base balance values. At the time of birth, the usual gradients for pH, PCO_2 and PO_2 were found. These parameters are at least partly (blood gases) dependent on the controlled ventilation of the mother, as demonstrated by, among other things, the fact that there was a highly significant relationship between maternal pH and umbilical venous pH, and also between maternal PCO_2, and umbilical venous and umbilical arterial PCO_2 of the infants. The umbilical venous PO_2 depended directly on the maternal PO_2. Similarly, there is an inverse correlation between ID-time and umbilical venous PCO_2 – the longer the time until delivery, the lower is the umbilical venous PCO_2. Since simultaneously the umbilical venous PCO_2, depends directly on the maternal PCO_2, this correlation may be best explained by the decreasing maternal PCO_2 during the time until delivery.

Finally, a highly significant correlation was found between umbilical venous and umbilical arterial pH values, as well as between venous PO_2 and arterial PO_2 readings. These correlations are a direct or indirect consequence of maternal-fetal and fetal-maternal gas exchanges, and in this sense they should not be directly related to the use of Ethrane. As measured by blood gases and acid-base balance, the infants have adjusted normally during the immediate postpartum phase (up to 15 minutes). The pH increased up 7.3; PCO_2 and PO_2 reached approximately normal levels. The initial slight metabolic acidosis gradually faded out in the course of the observation period.

Summarizing, we may conclude from our findings that in the area of obstetrics Ethrane provides satisfactory clinical results; that Ethrane is rapidly transferred from mother to fetus, induction-delivery-interval and maternal concentrations apparently playing a significant role only in the initial phase of Ethrane administration; that the Ethrane concentration in the postpartum phase decreases rapidly, since 15 minutes after birth the Ethrane concentration in the infants amounted only to 1/10 of the initial concentration at the time of birth; that postpartum adjustment of the infants as measured by the APGAR scores, blood gases and acid-base balance followed normal patterns.

These conclusions refer to the mean values as well as to the individual cases. Even extreme values range within tolerable limits; they belong to different patients.

Summary

1. In a prospective study 50 patients were anesthetized with Ethrane for Cesarean section. During anesthesia continuous ECG monitoring showed no particular features. Blood pressure decreased by an average 10 to 15% of initial value.

2. Ethrane concentrations in the maternal arterial blood were 6.6 mg/100 ml at the time of birth, in the umbilical artery they averaged 3.03 mg/100 ml, in the umbilical vein 3.94 mg/100 ml. In the postpartum phase, Ethrane concentrations in the infants dropped

to 0.91 mg/100 ml five minutes after birth, to 0.57 mg/100 ml 10 minutes after birth, and to 0.53 mg/100 ml 15 minutes after birth. A positive correlation between umbilical venous and umbilical arterial Ethrane concentrations was found.

3. Postpartum adjustment of the infants – assessed by the APGAR scores, blood gases and acid-base balance – followed normal patterns. A positive correlation was found between maternal pH on the one hand, and umbilical venous and umbilical arterial pH of the infants on the other. In addition, there was a significant correlation between umbilical venous and umbilical arterial pH.
4. Maternal PCO_2 correlated with the umbilical venous and umbilical arterial PCO_2 values. The induction-delivery-interval showed an inverse correlation with reference to the umbilical venous PCO_2 values.
5. Maternal PO_2 significantly influenced the umbilical venous PO_2, and a conspicuous relationship was found between the umbilical venous and umbilical arterial PO_2.
6. By and large, the use of Ethrane in the field of obstetrical anesthesia can be called satisfactory. The anesthetic agent is rapidly transferred from mother to fetus, but the newborn just as quickly eliminates the agent if respiratory function in the postpartum phase is adequate. Postpartum adjustment of the infants follows normal patterns.

Keywords: Caesarean section, Ethrane, general anaesthesia, induction-delivery interval, neonatal acid base balance, neonatal blood gases, neonatal conditions, obstetric anaesthesia.

Zusammenfassung

Klinische Untersuchungen zur Anwendung von Ethrane bei der Sektionarkose

1. In einer prospektiven Studie wurde bei 50 Patientinnen Ethrane zur Anästhesie bei der Sectio caesarea verwendet. Über den gesamten Anästhesieverlauf zeigten die fortlaufenden EKG-Kontrollen keine Besonderheiten. Die Blutdruckwerte fielen im Mittel um 10–15% des Ausgangswertes ab.
2. Die Ethranekonzentrationen im mütterlichen Arterienblut betrugen zum Zeitpunkt der Geburt 6,6 mg/100 ml, die Konzentrationen in der Arteria umbilicalis lagen im Mittel bei 3,03 mg/100 ml, die in der Vena umbilicalis bei 3,94 mg/100 ml. In der postpartalen Phase fielen die neonatalen Ethranekonzentrationen 5 min nach der Geburt auf 0,91 mg/100 ml, 10 min nach der Geburt auf 0,57 und 15 min nach der Geburt auf 0,53 mg/100 ml. Es bestand eine positive Korrelation zwischen umbilikalvenösen und umbilikalarteriellen Ethranekonzentrationen.
3. Die postpartale Adaptation der Neugeborenen – beurteilt am APGAR-Status sowie den Blutgasen und dem Säuren-Basen-Haushalt – verlief regelrecht. Dabei bestanden positive Korrelationnen zwischen mütterlichem pH einerseits sowie umbilikalvenösem und umbilikalarteriellem pH der Neugeborenen andererseits. Weiterhin zeigten sich signifikante Korrelationen zwischen umbilikalvenösem und umbilikalarteriellem pH.
4. Die mütterlichen PCO_2-Werte korrelierten mit den umbilikalvenösen und umbilikalarteriellen PCO_2-Werten. Die Einleitungs-Entwicklungs-Zeiten zeigten eine inverse Korrelation zu den umbilikalvenösen PCO_2-Werten.
5. Der mütterliche PO_2 beeinflußte signifikant den umbilikalvenösen PO_2, eine auffällige Beziehung bestand zwischen umbilikalvenösen und umbilikalarteriellen PO_2-Werten.
6. Insgesamt ist die Verwendung von Ethrane im Bereich der geburtshilflichen Anästhesie zufriedenstellend. Die Substanz wird zwar rasch von der Mutter auf den Feten übertragen, jedoch ebenso rasch aus dem Organismus des Neugeborenen bei adäquater postpartaler Atemfunktion eliminiert. Die postpartale Adaptation der Neugeborenen verläuft regelrecht.

Schlüsselwörter: Allgemeinanästhesie, Einleitungs-Entwicklungs-Zeit, Ethrane, geburtshilfliche Anästhesie, neonatale Blutgase, neonataler Säuren-Basen-Status, Neugeborenenstatus, Sectio caesarea.

Résumé

Investigations cliniques concernant l'emploi d'éthrane pour les césariennes

Dans une étude prospective, 50 parturientes ont été anesthésiées à l'éthrane pour une césarienne. Durant l'anesthésie l'enregistrement continu d'ECG n'a montré aucune particularité. La tension a baissé en moyenne de 10 à 15% par rapport à la valeur initiale.

Les concentrations d'éthrane dans le sang artériel maternel ont été de 6,6 mg/100 ml au moment de la naissance, de 3,03 mg/100 ml dans l'artère ombilicale et de 3,94 mg/100 ml dans la veine ombilicale. Dans la phase postpartale, les concentrations d'éthrane chez les bébés ont baissé de 0,91 mg/100 ml 5 minutes après la naissance à 0,57 mg/100 ml 10 min. après la naissance et à 0,53 mg/100 ml 15 min. après la naissance. Une corrélation positive a été observée entre les concentrations d'éthrane dans la veine et l'artère ombilicales.

L'ajustement postpartum des bébés – évalué par les scores APGAR, les gaz sanguins et l'équilibre acido-

basique – a suivi les normes. Une corrélation positive a été observée entre le pH maternel d'une part et le pH de la veine et de l'artère ombilicales des bébés d'autre part. De plus, on a relevé une corrélation significative entre le pH de la veine et de l'artère ombilicales.

Il y a eu également corrélation entre le PCO_2 maternel et les valeurs de PCO_2 de la veine et de l'artère ombilicales. L'intervalle induction-accouchement a montré une corrélation inverse avec référence aux valeurs PCO_2 de la veine ombilicale.

Le PO_2 maternel a influencé de façon significative le PO_2 de la veine ombilicale et unr relation évidente a été observée entre le PO_2 de la veine et de l'artère ombilicales.

D'une façon générale, on peut conclure que l'emploi d'éthrane est satisfaisant en ce qui concerne l'anesthésie obstétrique. L'agent anesthésique est rapidement transféré de la mère au foetus, mais le nouveau-né élimine cet agent tout aussi rapidement si la fonction respiratoire est conforme dans la phase postpartale. L'ajustement postpartum des bébés suit les normes.

Mots-clés: Anesthésie générale, anesthésie obstétrique, conditions, césarienne, néonatales, équilibre acido-basique néonatals, éthrane, gaz sanguins néonatals, intervalle induction-accouchement.

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