Postpartum Changes in the Minimum Alveolar Concentration of Isoflurane

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Background: Minimum alveolar concentration (MAC) is decreased in pregnancy, but it is not known how quickly after delivery MAC returns to normal. We measured the MAC of isoflurane in a group of women undergoing elective tubal ligation after delivery.

Methods: After delivery, 20 patients underwent inhalational induction of anesthesia with isoflurane and tracheal intubation. MAC was determined in each patient by observing the response to a 10-s, 50-Hz, 80-mA transcutaneous tetanic electric stimulus to the ulnar nerve at various concentrations of isoflurane. The end-tidal concentration of isoflurane was kept constant for at least 10 min before each stimulus, and the concentration of isoflurane was ultimately varied in steps of 0.05 vol\% until we obtained a sequence of three alternate responses: move–not move–move or move–not move–not move. The MAC for each subject was taken as the mean of the two concentrations just permitting and just preventing movement. A venous blood sample was taken immediately before induction of anesthesia for measurement of progesterone concentration. MAC was compared with time after delivery and plasma progesterone concentrations by Kendall’s rank correlation.

Results: There was a positive correlation between MAC and the time after delivery (P < 0.001). The median MAC of isoflurane was 0.775 vol\% (range 0.675–0.775 vol\%) in five women 24–36 h postpartum. MAC was more variable, 0.825 vol\% (0.675–0.975 vol\%) in nine women 36–72 h postpartum, whereas six patients more than 72 h postpartum had a MAC of 1.125 vol\% (1.025–1.175 vol\%). The correlation between MAC and plasma progesterone concentration was almost statistically significant (P = 0.060).

Conclusions: The MAC of isoflurane was reduced in women 24–36 h postpartum and gradually increased to normal values by 72 h postpartum. (Key words: Anesthesia, obstetric: postpartum. Anesthetics, volatile: isoflurane. Hormones: progesterone. Potency, anesthetic: minimum alveolar concentration.)

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The minimum alveolar concentration (MAC) of isoflurane has been shown to be reduced by 28% in pregnant women at 8–12 weeks’ gestation,1 confirming earlier studies that showed a reduction in MAC in pregnant ewes2 and rats.3 The reduction in MAC may be a result of increased progesterone concentrations,4 but our study in pregnant women did not directly support this hypothesis.

In female Sprague-Dawley rats, the MAC of halothane was decreased by 16% in midgestation and 19% at term (days 21–23), but by the 5th day postpartum it had returned to values found in the nonpregnant state.5 Because there are no data from humans on the changes in MAC during the postpartum period, we measured the MAC of isoflurane in a group of patients undergoing elective tubal ligation after delivery.

Materials and Methods

The study was approved by the local clinical research ethics committee. Twenty patients, American Society of Anesthesiologists physical status I, undergoing tubal ligation after delivery were studied. Patients were excluded if less than 24 h had elapsed since delivery, if they had symptoms of esophageal reflux, or if they were taking any medications. Written informed consent was given by all patients.

No preanesthetic medication was given. Anesthesia was induced with isoflurane in oxygen using a standard Magill breathing system with a fresh gas flow rate of 150 mL·kg⁻¹·min⁻¹. The trachea was intubated with a 7.5-mm (ID) cuffed gas monitoring endotracheal tube (Portex Limited, Hythe, England) without the use of a neuromuscular blocking agent. End-tidal gas samples were aspirated at a rate of 90 mL·min⁻¹ from the sampling port at the distal end of the endotracheal tube. The concentrations of isoflurane, carbon dioxide and oxygen were measured continuously using a photoacoustic and magnetoacoustic gas monitor (type 1304, Bruel and Kjaer, Nærum, Denmark).6 The monitor was calibrated with a commercially available reference gas source (QMA<sub>13</sub>) and was allowed to stabilize for 10 min. MAC was adjusted to maintain the end-tidal isoflurane concentration between 4.5 and 5 vol\% with electrical stimuli to the ulnar nerve.

The investigators were blinded to the MAC. We observed the response to electrical stimuli by using a constant current source. All patients agreed to the use of electrical stimuli.

To the end, we were allowed an electric stimulus to the ulnar nerve at the frequency of 50 Hz, 80 mA. The voltage was maintained at 30 V, 50 Hz, 80 mA, and the duration was 20 s.

The volar surface of the forearm was stimulated by a 2-cm-long, 2-mm-wide, noninvasive electrode attached to the skin. The first response was any movement of the fingers of the hand in the stimulated arm or any other movement of the face, head, or neck. A positive response was any withdrawal of the extremities from the stimulus, or any other movement in the stimulated arm, such as tightening of the muscles of the arm or the face. A negative response was no response at all. If the patient had no response to the first stimulus, a second stimulus was given, and the response was recorded as positive or negative.

The initial stimulus to each hand was delivered with the isoflurane concentration maintained at 0.1 vol\%. If no response was obtained, the concentration was increased by 0.1 vol\% and the initial stimulus was repeated. If a response was obtained, the concentration was decreased by 0.1 vol\% and the response was recorded as positive or negative.

A 10-min period was allowed before each increase in isoflurane concentration, and each concentration was administered for 10 min. The concentration just prior to the increase was recorded as the MAC. Postpartum Changes in the Minimum Alveolar Concentration of Isoflurane

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POSTPARTUM CHANGES IN MAC OF ISOFLURANE

source (QA 0207, Bruel and Kjaer). All patients were allowed to breathe spontaneously. The fresh gas flow was adjusted and ventilation assisted manually to maintain the end-tidal carbon dioxide concentration between 4.5 and 5.5 vol%. All patients were monitored with electrocardiography, pulse oximetry, and noninvasive blood pressure measurement.

The investigator who determined all the MAC values in this study was unaware of the patient’s time of delivery. The MAC of each subject was determined by observing the motor responses to successive tetanic electric stimuli delivered to the ulnar nerve at varying concentrations of isoflurane as described in our earlier report. At each target end-tidal isoflurane concentration, we waited until the inspired-to-expired isoflurane concentration difference was 0.05 vol% or less and then allowed another 10 min for equilibration before the stimulus was repeated. The electric stimulus was a 10-s, 50-Hz, 80-mA transcutaneous tetanic stimulus delivered in 200-μs monophasic square-wave pulses by a constant current peripheral nerve stimulator (NS252, Fisher & Paykel Healthcare, Auckland, New Zealand). The volear surface of the forearm was cleaned with alcohol, one silver-silver chloride electrode (Medtronic, Haverhill, MA), the cathode, was placed over the ulnar nerve at the proximal skin crease of the wrist and the other electrode, anode, 5 cm proximally along the nerve. A positive motor response was recorded if there was any purposeful movement of the head, neck or limbs apart from the stimulated arm. Coughing, bucking, or swallowing were not considered positive responses.

The initial end-tidal isoflurane concentration for all patients was 1.0 vol%. If a positive response was observed with the tetanic stimulus, the end-tidal isoflurane concentration was increased by 0.2 vol% and then by 0.1 vol% in successive steps until the response disappeared. The end-tidal isoflurane concentration was then decreased by 0.05 vol% until the response returned and then increased by 0.05 vol% until the response disappeared again. A reverse bracketing procedure was undertaken if there was no response to the initial stimulus at 1.0 vol% isoflurane. The MAC for each patient was taken as the mean between the highest concentration just allowing and the lowest concentration just preventing a positive response.

A 10-ml venous blood sample was taken before induction of anesthesia for measurement of the plasma concentration of progesterone by solid-phase iodine 125 radioimmunoassay (Coat-A-Count, Diagnostic Products, Los Angeles, CA). The interassay coefficient of variation was 10% at 5.0 nm and 7.2% at 47 nm, and the limit of detection was 0.2 nm (where 1 nm = 3.18 ng·ml⁻¹).

All results are expressed as medians (with ranges in parentheses). MAC, plasma progesterone concentrations, and time after delivery were compared by Kendall’s rank correlation. P < 0.05 was considered significant.

Results

The age, weight, and height of the patients were 32 (28–41) yr, 66.3 (52–75) kg, and 162 (150–168) cm, respectively. The time after delivery, defined as the time from delivery to when MAC was determined, was 49.8 (28.0–126.5) h.

The expired gas waveform had an early plateau, and an inspired-to-expired isoflurane concentration difference of 0.05 vol% or less was obtained in all patients. There was consistency in patient response during the bracketing procedure. No patient responded at an end-tidal concentration at which they had not responded previously, and vice versa.

Kendall’s rank correlation between MAC and time after delivery was significant (P < 0.001). The MAC of isoflurane was 0.725 vol% (0.675–0.775; n = 5) during the early postpartum period (24–36 h). MAC increased gradually between 36 and 72 h postpartum (n = 9), but this increase was variable, with one patient having a MAC of 0.975 vol% at 50 h and one with a MAC of 0.775 vol% at 69 h. All six patients in the period more than 72 h postpartum had a MAC in the range 1.025–1.175 vol% (fig. 1).

Plasma progesterone concentration decreased progressively with time after delivery (P = 0.004) (fig. 2). Kendall’s rank correlation between MAC and plasma progesterone concentration was nearly statistically significant (P = 0.060) (fig. 3).

Nasopharyngeal temperature at the end of the study ranged from 36.2°C to 36.6°C. There were no anesthetic complications and no complaints from the patients on follow-up the next day.

Discussion

During the 1st 24–36 h postpartum, the MAC of isoflurane was decreased and was similar to the 0.775 vol% measured in pregnant patients of 8–12 weeks’
gestation.\(^1\) MAC increased during the next 36 h to reach normal values by 72 h postpartum. We were unable to recruit many patients more than 4 days postpartum because patients are usually discharged from our hospital before then. We also excluded patients less than 24 h postpartum because we believed that a slow inhalational induction may carry increased potential risk for acid aspiration. However, previous research in this institution has found normal gastric emptying\(^6\) and minimal gastric volumes\(^8\) in patients after the 1st 24 h postpartum, so that extra precautions against acid aspiration are not used routinely for all cases. Although different methods could be used to study patients within 24 h of delivery, logistic problems in our hospital prevented patients from being scheduled for elective tubal ligation surgery within 12 h of delivery. Given the ethical and practical difficulties of studying MAC during normal pregnancy, we are unable to predict the MAC of isoflurane at term pregnancy.

We assumed that 10 min of steady-state end tidal isoflurane concentration produced adequate equilibration for the determination of MAC.\(^8\) This is supported by the consistency in patient response during the bracketing procedure. Zbinden et al.\(^9\) measured arterial and end-tidal isoflurane concentrations in their study, in which they also used a 10-min equilibration period.

They found a constant arterial to end-tidal isoflurane ratio of approximately 0.90 at 5, 8, and 10 min, but they did not measure arterial concentrations before 5 min and equilibration may have occurred earlier. Theoretically, equilibration of isoflurane between arterial blood and alveoli would be within 10 min of an equilibration at the target concentration. A variably long equilibration period may be stabilized at the end of induction.

The use of individual MACs also assumes that isoflurane gas per se is not a uterotonic agent. The experimental data of Grunow et al.\(^7\) with the trachea-cannulated gravidovaginal study,\(^1\) with the uterine flush method,\(^1\) and the established MAC of 1.075 vol% for isoflurane gas in uterine muscle of sheep,\(^2\) as well as the study by Tanifuji et al.\(^1\) using the isolated uterus, demonstrate a significant decrease in uterine activity, which is slightly better correlated with the uterine model than with Tanifuji et al.\(^1\) uterine activity.\(^1\) The study of Tanifuji et al.\(^1\) has shown that the time-course of the uterine effect of isoflurane in the isolated rat uterus is similar to that found in women, with a delay of less than 10 min. They have also shown that pregnancy MAC of isoflurane is different between MACs measured in women and in pregnant women.

Experimental results indicate that progesterone and progesterone receptor levels decrease in a similar manner to that found in human pregnancy. The levels are lowest at term pregnancy in women.\(^9\) The MAC of isoflurane in pregnant rats is at least 30% lower than in nonpregnant rats.\(^9\)

**References**


terial blood and gray matter should be 95% complete within 10 min. As a practical point, although we specified an equilibration time of 10 min, the time spent at the target end-tidal isoflurane concentration was invariably longer because we did not start the equilibration period until the end-tidal concentration was stabilized at the target concentration.

The use of tetanic electric stimuli to determine individual MAC values enabled us to show that MAC of isoflurane gradually increased with time after delivery. The experimental design would have been impossible with the traditional skin incision method. Our previous study, 1 with identical methods and the same observer, established the MAC of isoflurane in normal women to be 1.07% vol. This value is very similar to the MAC of isoflurane (1.03% vol) determined by Zhiden et al. 6,7 by using transcutaneous tetanic electric stimuli but is slightly less than the MAC (1.16% vol) that they determined in the same patients by using skin incision. Tetanic stimuli are noninvasive and are repeatable in each subject, and give reproducible results. 10

The plasma progesterone concentrations postpartum are consistent with previous data showing a rapid decrease to normal nonpregnant values (0.3–89 nm) within 24 h of delivery. 11,12 We have shown that MAC increases after delivery so that an association between progesterone and MAC would be expected, and Kendall’s rank correlation was almost significant (P = 0.060). However, there cannot be a simple linear correlation between MAC and progesterone because the progesterone concentrations postpartum were similar to that found in normal nonpregnant women, and much less than the range (175–811 nm) measured at term pregnancy. Strout and Nahrwold 13 found no correlation between MAC and progesterone in pregnant rats.

Experiments with exogenously administered progesterone are required to demonstrate a causal relation between progesterone and MAC. Datta et al. 14 concluded that administration of progesterone in rabbits after ovarectomy decreased MAC of halothane by 12%, but the correlation was poor (r = 0.53), and they excluded four rats with high progesterone concentration and high MAC. However, Tanifuji et al. 4 showed that MAC of halothane was reduced by 15–20% in dogs given progesterone. If progesterone is responsible for a decrease in MAC, it is possible that a sustained threshold progesterone concentration is required, and on the evidence in this study, the effects of progesterone on MAC would have to persist after the plasma progesterone concentration has decreased. Other factors such as increased endorphin concentrations may also contribute to a reduced MAC. 4

In conclusion, MAC for isoflurane was decreased by approximately one third 24–36 h after delivery, and MAC gradually returned to nonpregnant values by 72 h postpartum. The underlying cause for these changes remains unclear.

References


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