Postpartum Changes in the Minimum Alveolar Concentration of Isoflurane

Matthew T. V. Chan, M.B., B.S.,* Tony Gin, M.D., B.Sc., F.R.C.A., F.A.N.Z.C.A.†

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 anaesthesia 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 not move–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 anaesthesia 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% (0.675–0.775 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: Anaesthesia, obstetric; postpartum; Anaesthetics, volatile; isoflurane. Hormones: progesterone. Potency, anaesthetic; minimum alveolar concentration.)

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.¹

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.³ 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 Anaesthesiologists physical status 1, 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. Anaesthesia 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 magnetooacoustic gas monitor (type 1304, Bruel and Kjaer, Naerum, Denmark).⁵ The monitor was calibrated with a commercially available reference gas source (QA1350) and was allowed to equilibrate for 2 min to maintain the error within 0.5 vol% with an electric stimulus and an invasive blood pressure line.

The investigator, who was not observing the patient, administered an electric stimulus of 0.5, 1, and 2 mA for 5 s, 50-Hz, 80-mA to each patient under constant conditions of anesthesia. Fisher & Freivogel™ electrode pads were used. The volley produced was any phasic contraction in the limbs associated with movement, twitching, or visible muscle responses.

The initial MAC was allowed to be observed with isoflurane concentration increased by 0.1 vol% until a response appeared, and then decreased by 0.1 vol% until a response disappeared. The procedure was repeated for each patient in the order of their concentration, and the patient was just perceptible.

A 10-min period was allowed for concentration to stabilize, with 125 rad.
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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 non-invasive 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 volar 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, buckling, 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 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 9.0% 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 (21–36 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. 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 and minimal gastric volumes 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. This is supported by the consistency in patient response during the bracing procedure. Zbinden et al. 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 inspired air may have occurred within 10 min. At the target concentration, establishment of concentration within the target concentration period of 5 min (72 h) was generally stabilized at the target concentration.

The use of individual MAC values for isoflurane greater than 0.7 MAC as a MAC for isoflurane greater than 0.7 was an advantage in this study, with the target concentration of 1.075 for the determination of isoflurane MAC by using 0.7 of its MAC by using the equation of Mac. This is slightly lower than the 0.76 equation determined in the previous study. Tetanic stimulus to the subject, and the measurement of MAC.

The plasma progesterone concentrations are consistent with the findings of other investigators. Progesterone increases by 24 h postpartum, and increases more rapidly as pregnancy progresses (Kendall's rank test, P = 0.060). However, there is no correlation between plasma progesterone concentrations and pregnancy, or between MAC and plasma progesterone. A correlation between plasma progesterone and pregnancy was found in a study of four rats with different MAC values. However, the results are not statistically significant.
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, with identical methods and the same observer, established the MAC of isoflurane in normal women to be 1.075 vol%. This value is very similar to the MAC of isoflurane (1.03 vol%) determined by Zbinden et al. 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, are repeatable in each subject, and give reproducible results.

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 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 Nahrwold1 found no correlation between MAC and progesterone in pregnant rats.

Experiments with exogenously administered progesterone were required to demonstrate a causal relation between progesterone and MAC. Datta et al.4 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.

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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