Isoflurane Minimum Alveolar Concentration Decreases during Anesthesia and Surgery

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Background: It generally is assumed that the potency of inhalational anesthetics remains unchanged during the course of the administration of an anesthetic. Only one study has indicated a decrease of minimum alveolar concentration with time. In this study, an effect of the duration of anesthesia administration and surgery on the potency of isoflurane was investigated by determining MAC_{retum} (the minimum alveolar concentration that prevents movement in response to electrical tetanic stimulation in 50% of patients) before and after surgery.

Methods: Ten patients who underwent removal of a herniated intervertebral disc were anesthetized with isoflurane only. Reaction to a standardized electrical stimulation applied to the forearm was observed and was graded as movement or no-movement. The isoflurane concentration was increased in steps of 0.10 vol% if the patient moved and decreased in steps of 0.10 vol% if no reaction was seen, until a “movement/no-movement/movement” or “no-movement/movement/no-movement” pattern, respectively, was achieved.

Results: MAC_{retum} decreased in all patients from 1.28 ± 0.22 vol% (mean ± SD) before surgery to 1.04 ± 0.22 vol% after surgery (P < 0.01). When the prestimulation arterial blood pressure or the maximal increase in blood pressure caused by stimulation at the individual MAC_{retum} before surgery were compared to the corresponding values at the individual MAC_{retum} after surgery, no significant difference could be found. The prestimulation heart rate and the maximal increase in heart rate were significantly lower after surgery, even though the end-tidal isoflurane concentration was 0.24 vol% lower at the individual MAC_{retum} after surgery.

Conclusion: The authors conclude that MAC_{retum} decreases during the administration of anesthesia and the performance of surgery. (Key words: Anesthetics, volatile: Isoflurane. Potency: MAC, time factors.)

MAC (the minimum alveolar concentration of an anesthetic that prevents movement in response to skin incision in 50% of patients) usually is determined in a population of patients and considered a standard measure of potency. Repeated MAC measurements in humans are difficult to obtain, as separate and repeated skin incisions are unusual. It has been assumed that the duration of anesthesia has no influence on MAC.1–3 An earlier study from this institution indicated that a decrease of MAC occurs during the administration of anesthesia (Zbinden et al., unpublished data, 1990–1992). Because muscle relaxants used during surgeries in that study might have influenced the response to tetanic stimulation, the present study was initiated. A new method was developed by which MAC measurements can be repeated in humans, allowing the determination of the individual MAC_{retum} value (the minimal alveolar concentration preventing movement in 50% of patients in response to electrical tetanic stimulation) for isoflurane before and after surgery.

Material and Methods

The study was approved by the ethics committee of the Faculty of Medicine, University of Berne. Ten patients (four women and six men) who had an American Society of Anesthesiologists physical status 1, were between 24 and 46 yr of age, and who underwent removal of a herniated intervertebral disc and who gave written informed consent were included in the study. Patients who had taken opioid analgesics within the 2 weeks before the operation, were on sedative and/or spasmytic drugs, or were either 15% over or under the ideal body weight of the general population4 were excluded from the study. The use of acetaminophen (paracetamol) was allowed.

The patients received no premedication, except for 300 mg of ranitidine orally, the evening before operation. Heart rate was monitored with an electrocardiogram, hemoglobin oxygen saturation (SaO2) was mon-
ntorized by pulse oximetry, body temperature was monitored with a rectal probe, and arterial blood pressure was monitored via a 20-G catheter introduced into the radial artery of the nondominant side. Inspired oxygen, end-tidal isoflurane, and carbon dioxide concentrations were monitored continuously with an infrared gas analyzer (Capnomac Ultima, Datex, Finland). Sampling was performed from a connector between the tracheal tube and the Y-piece or at the mask. The accuracy of the analyzer had been tested in an earlier study (Walder, unpublished data, 1992). It was calibrated before the administration of each anesthetic using the calibration gas provided by the manufacturer. All gas concentrations are given in volume percent (vol%). The arterial concentration of volatile anesthetics was determined at 37°C using a previously described head-space technique for gas chromatography. The arterial concentrations are expressed in volume percent, representing the concentration in volume percent of a gas phase in equilibrium with blood. No correction was made for an eventual change in solubility. The concentration values also were not corrected for barometric pressure. (Berne is approximately 500 m above sea level, so our values have to be divided by 1.065 to allow comparison with studies using values obtained at sea level.) Arterial blood pressure (measured in mmHg), heart rate, inspired and end-tidal isoflurane concentrations, and end-tidal CO₂ data were digitized and recorded on the hard disk of a personal computer. A sampling frequency of 50 Hz for blood pressure and 5 Hz for gas concentrations were used.

Induction was performed using the single breath induction method: the patient breathed 100% oxygen for 3 min. The patient then exhaled maximally, and then was asked to inhale maximally a mixture of 4 vol% isoflurane in pure oxygen from a 4 l bag via a mouthpiece and to maintain the inhalation as long as possible. A face mask then was applied, and the patient continued to breathe isoflurane in oxygen from a conventional semiclosed breathing circuit (Sulla, Drägerwerke Lübeck, Germany), with a total fresh gas flow of 6 l min⁻¹. The inspired concentration was adjusted to achieve an end-tidal isoflurane concentration of 2.20 vol% rapidly. After induction was complete, auditory stimulation was minimized with the application of sound-reducing headphones. This concentration was maintained for 15 min to achieve equilibration of partial pressures between blood and brain before the trachea was intubated without the use of muscle relaxants. Ventilation then was controlled, tidal volume was set at 8 ml·kg⁻¹ (measured by a volumeter), frequency was regulated to keep a constant end-tidal pCO₂ concentration of 5.0 vol%, and fresh-gas flow was reduced to 3 l·min⁻¹. In order to estimate the difference in arterial and brain isoflurane partial pressures, simulations of the uptake and elimination of isoflurane during the entire duration of anesthesia of two patients (numbers 8 and 9) were performed, using the recorded end-tidal and serially measured arterial isoflurane concentrations in a computer simulation (Gas Uptake Simulation [GUS], iMedEd, Phoenix, AZ). After an additional 5 min equilibration period at 2.20 vol%, isoflurane was discontinued, and the end-tidal isoflurane was allowed to decrease until it reached 0.7 vol%. Isoflurane then was reintroduced and regulated to keep a constant end-tidal value of 1.10 vol% (approximately 1 MACtermm) during a 10 min equilibration period. This procedure was used to minimize the brain tissue/arterial blood partial-pressure gradient.

The volar side of the dominant forearm was rubbed with ether. A line was drawn from the middle of the skin fold in the cubital fossa to the middle of the skin fold at the wrist. Marks were made 1 cm to the ulnar side of the line, and 5 and 13 cm below the skin fold in the cubital fossa. Electrocardiogram electrodes were placed at these marks, with the positive electrode placed proximally. A standardized 5 s, 60 mA, 50 Hz, 0.25 ms square-wave electrical impulse was applied as pain stimulus (Digitimer DS 7 constant current stimulator with a Digitimer DG2 trigger generator (Digitimer, Hertfordshire, England) and a timer device constructed in our laboratory). The stimulator had been bench-tested in our laboratory, and the current had been proven constant during the 5 s stimulation. Any movement was considered a positive reaction, except for a slight movement during the tetanic stimulus of the shoulder and/or arm on the stimulated side. A delayed movement of the shoulder or arm on the stimulated side within a minute after cessation of the tetanic stimulus was regarded as positive. Frowning, swallowing, and coughing were not considered positive reactions. If a positive reaction was observed, the end-tidal isoflurane concentration was increased by 0.10 vol%; if no reaction was observed, the concentration was decreased by 0.10 vol%. After each change of isoflurane concentration, 10 min of equilibration time was allowed before the stimulus was repeated. This procedure was continued until the bracketing procedure was completed (i.e., a pattern of movement/no-movement/movement/no-movement/no-movement)}
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was achieved). Arterial blood was sampled before the administration of each stimulus for analysis of isoflurane concentration. During the operation, the isoflurane concentration was kept sufficiently “high” to avoid movement. No muscle relaxants were given. Postoperatively, after stable hemodynamic conditions were reached, individual MAC_{tetanus} values were measured as described above, starting at an isoflurane concentration 0.10 vol% below the last concentration at which a positive response had been recorded. The pre- and postoperative MAC_{tetanus} values were calculated as the mean ± SD of all individual values. The individual MAC_{tetanus} values measured with the bracketing method (table 1, postoperative end-tidal value) were corrected according to Vitecz et al.⁸ (table 1, postoperative end-tidal value (temperature-corrected)). (In this study, the MAC of isoflurane in rats decreased 5.28% per 1 °C drop in temperature.)

When a bracketing method of evaluation is used, there must be steps at the beginning and end of the bracketing procedure in which the stimulus is applied at the same end-tidal isoflurane concentration. The increases in blood pressure and heart rate and the motor reaction at each of these steps were paired, so that each pair represents a stimulation administered at the beginning and at the end of a bracketing, both performed at the same isoflurane concentration.

Wilcoxon’s signed-rank test was used to test the statistical difference between the increases in heart rate and blood pressure taken at the beginning and the end of a bracketing. A chi-squared test was used to test the difference in motor reaction. Wilcoxon’s signed-rank test also was used to test the statistical difference between MAC_{tetanus} values taken before and after surgery, the prestimulation blood pressures and heart rates taken before and after surgery, the maximal increases in blood pressure and heart rate after stimulation before and after surgery, and the differences in end-tidal arterial concentrations before and after surgery. Values of $P < 0.05$ were regarded as significant.

Results

The individual MAC_{tetanus} values before and after surgery are shown in figure 1 and table 1. MAC_{tetanus} decreased from 1.28 ± 0.22 vol% (mean ± SD) before surgery to 1.04 ± 0.22 vol% after surgery ($P < 0.01$), or, expressed in median values, from 1.15 (range, 1.10–1.65) to 1.00 (range, 0.75–1.40). A decrease in individual MAC_{tetanus} was observed in all patients, but there was a large interindividual variation. Six subjects showed a change of 6.7% to 15.2%, and four subjects showed a change of 26.1% to 31.8%. No patient showed an increase in individual MAC_{tetanus}. Between the two MAC_{tetanus} measurements, a temperature decrease of 0.6 °C (mean value; range, 0.1–1.3) was noted. No correlation was found between the temperature decrease and the change in individual MAC_{tetanus}. The mean individual MAC_{tetanus} value after surgery, corrected for a decrease in temperature according to Vitecz et al.,⁸ would be 1.07 ± 0.22 vol% (mean ± SD), and still remain statistically significant ($P < 0.01$) compared to the value found before surgery.

Before surgery, MAC_{tetanus} was determined 77 min (range, 57–111 min) after induction (time from the single-breath induction until the middle of the bracketing procedure); after surgery, it was determined at 250 min (range, 187–301 min) after induction, giving an elapsed time of 173 min (range, 118–222 min) between the two MAC_{tetanus} determinations. The mean duration of surgery was 56 min (range, 35–90 min). A linear regression through all individual MAC values against time gives an intercept of 1.31 vol% isoflurane and a slope of $-0.000941$ vol%/min ($r = 0.35$).

The arterial isoflurane concentration (expressed as equivalent gas concentrations) decreased from 1.11 ± 0.21 vol% (mean ± SD) before surgery to 0.94 ± 0.17

Anesthesiology, V 79, No 5, Nov 1993
### Table 1. Individual Data for All Ten Patients

<table>
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<tr>
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<th>1</th>
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<th>9</th>
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<tr>
<td>End-tidal</td>
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<td>1.15</td>
<td>1.15</td>
<td>1.15</td>
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<td>0.99</td>
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<td>0.99</td>
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<td>1.48</td>
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<td>0.15</td>
<td>0.16</td>
<td>0.13</td>
<td>0.17</td>
<td>0.20</td>
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<td>0.22</td>
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<td><strong>MAC, postoperative (vol%)</strong></td>
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<td>0.06</td>
<td>0.15</td>
<td>0.096</td>
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<td>0.78</td>
<td>0.84</td>
<td>0.87</td>
<td>1.07</td>
<td>1.45</td>
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<td>1.41</td>
<td>1.11</td>
<td>1.02</td>
<td>1.065</td>
<td>1.04</td>
</tr>
</tbody>
</table>

Induction to MAC, preoperative (min)

| 76  | 69  | 66  | 73  | 61  | 111 | 57  | 89  | 105 | 60  | 77  |

Induction to MAC, postoperative (min)

| 277 | 187 | 236 | 295 | 224 | 248 | 252 | 252 | 301 | 228 | 250 |

Time between MAC determinations (min)

| 201 | 118 | 170 | 222 | 163 | 137 | 195 | 163 | 196 | 168 | 173 |

Duration of operation (min)

| 60  | 65  | 40  | 90  | 45  | 40  | 49  | 70  | 70  | 35  | 58  |

Temperature, preoperative (°C)

| 36.6| 36.4| 36.1| 36.5| 36.6| 36.5| 36.5| 36.4| 35.9| 36.7| 36.4 |

Temperature, postoperative (°C)

| 35.9| 35.6| 35.1| 36.0| 35.3| 35.8| 36.4| 36.2| 35.8| 36.4| 35.9 |

Temperature, difference (°C)

| 0.7 | 0.8 | 1.0 | 0.5 | 1.3 | 0.7 | 0.1 | 0.2 | 0.1 | 0.3 | 0.6 |

Isorurane concentrations are not corrected for barometric pressure.

* Arterial values represent equivalent gas concentrations in volume %.
† Correction according to Vitez et al.²

vol% after surgery (P < 0.01). These values were not corrected for an eventual change in solubility. The blood loss during the operation was minimal in all patients, and between the two MAC determinations, no patient had received more than 1,000 ml of lactated Ringer's solution.

![Graph](image)

**Fig. 2.** Computer simulation of the whole anesthesia of patient number 8, based on recorded end-tidal and serially measured arterial isoflurane concentrations. The vertical axis represents the concentration in vol% of a gas phase in equilibrium with the blood or brain compartment—simulated arterial isoflurane concentrations, ⋯⋯ simulated brain isoflurane concentrations, X measured arterial isoflurane concentrations (end-tidal curve omitted for sake of clarity).
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The end-tidal/arterial concentration difference decreased from a mean of 0.16 vol% (range, 0.04–0.35 vol%) at the MAC\textsubscript{mean} determination before surgery to 0.10 vol% (range, 0.00–0.28 vol%) after surgery (P < 0.01). The computer simulation of the whole anesthesia of patient number 8 is shown in figure 2. For patient number 8, the arterial-to-brain isoflurane concentration differences (expressed as equivalent gas concentrations) were 0.02 vol% (range, 0.01–0.02 vol%) during the bracketing period before surgery, and 0.01 vol% (range, 0.00–0.02 vol%) after surgery. For patient number 9, the arterial to brain isoflurane concentration differences before and after surgery were 0.03 vol% (range, 0.01–0.06 vol%) and 0.03 vol% (range, 0.01–0.06 vol%), respectively.

At the isoflurane concentrations used during the individual MAC\textsubscript{mean} bracketing (individual MAC\textsubscript{mean} ± 0.05 to 0.10 vol% isoflurane), mean arterial blood pressure and heart rate values before and after each tetanic stimulation were pooled into a preoperative and a postoperative group. The stimulation blood pressure at the individual MAC\textsubscript{mean} before surgery was 88.6 ± 9.4 mmHg (mean ± SD) versus 92.6 ± 14.8 mmHg after surgery (not significant), with a maximal increase after stimulation of 23.9 ± 16.1 mmHg (mean ± SD) before surgery versus 16.4 ± 9.5 mmHg after surgery (not significant). The premuscular heart rate at the individual MAC\textsubscript{mean} determination was 74 ± 6.9 min\textsuperscript{-1} (mean ± SD) before surgery versus 67 ± 5.9 min\textsuperscript{-1} after surgery (P < 0.01), with a maximal increase after stimulation of 21 ± 16.6 min\textsuperscript{-1} (mean ± SD) before surgery versus 12 ± 8.9 min\textsuperscript{-1} after surgery (P < 0.01). The four patients with the greatest decrease in MAC tended to have weaker hemodynamic reactions than the other six patients. (The rises in blood pressure and heart rate in these four patients were 60% and 50%, respectively, of the values for the other six patients.)

There were no differences in the increases in blood pressure or heart rate, or in the motor reaction to stimulation when stimulations at the beginning of a bracketing were compared to stimulations performed at the same isoflurane concentration at the end of the bracketing.

Discussion

Results from this study show a significant decrease of MAC\textsubscript{mean} during anesthesia and surgery, contradicting results from earlier studies.\textsuperscript{1–3} Eger \textit{et al.}\textsuperscript{1} found MAC in dogs constant for a duration of up to 500 min of anesthesia. However, the first MAC determination taken in that study was taken 1–2 h after the induction of anesthesia\textsuperscript{a}; therefore, the MAC already might have decreased and reached a steady concentration. In our investigation, the stimulations started much earlier (25 min after induction). Gregory \textit{et al.}\textsuperscript{3} and Eger,\textsuperscript{3} studying eight patients of less than 6 yr of age, found no difference in MAC for two separate herniorrhaphy incisions performed at different times during the same anesthesia, but the time between the two incisions was approximately 30 min,\textsuperscript{9} which may have been too little to show a decrease in MAC.

The decrease in MAC suggests a bimodal distribution, because six subjects showed a decrease in MAC of 6.7–15.2%, and four subjects showed a decrease of 26.1–31.8%. The subjects with the largest decreases in MAC were all men (the other group consisted of two men and four women). The mean operation time was slightly longer for those who showed the largest decrease in MAC (66 min compared to 48 min), but the time between the two measurements was similar in the two groups. The hemodynamic reactions to stimulation also were lesser in the group with the larger decreases in MAC. The number of patients in our study was too small to allow us to determine if this difference is statistically significant.

The effects of temperature on MAC in dogs and rats were studied by Eger \textit{et al.}\textsuperscript{10} and Vitez \textit{et al.}\textsuperscript{8} The decrease of 0.6°C in temperature in the present study might reduce the difference in MAC\textsubscript{mean} with 0.03 vol% isoflurane. Statistically, MAC\textsubscript{mean} still is significantly lower after than before surgery.

The end-tidal isoflurane concentration required to prevent motor reaction following electrical stimulation was almost 20% lower after than before surgery. Presuming a linear decrease, this would mean a decrease of approximately 0.05 vol%/h. The correlated decrease in MAC against time probably did not reach statistical significance for two reasons: (1) because of the relatively small number of patients studied, and (2) the MAC determinations were not spread evenly over time but grouped around one determination before surgery and one after surgery. Traditional MAC determinations in humans all have been performed at approximately the same time after induction,\textsuperscript{11} but time after induction may have to be incorporated into the definition of MAC.

The difference in the arterial concentrations required to achieve the same clinical effect was less than the difference in end-tidal concentrations. The arterial values were not corrected for an eventual decrease in solubility. Lerman \textit{et al.}\textsuperscript{12} found a decrease in solubility for isoflurane in blood parallel to a decrease in hema-
tocrit. Because blood loss was minimal and the amount of fluid infused between the two MAC determinations was small, the resulting change in hematocrit in our patients, and therefore the change in solubility, should be negligible. The end-tidal-to-arterial gradient decreased between the two MAC determinations, so the decrease in MAC could be considered a pharmacokinetic phenomenon, with a significant decrease in end-tidal isoflurane concentrations, a smaller decrease in arterial partial pressure, and possibly no decrease in partial pressures at the brain receptor or binding site at the two MAC determinations.

To achieve bracketing, the isoflurane concentration was changed in steps of 0.10 vol%. Smaller step changes might have increased the accuracy, but would have extended the duration of the study in each patient. A 10-min equilibration period might have been too short, but again, longer periods would extend the measurements. According to the computer simulation, 10 min was sufficient to achieve brain equilibration. Although the computer simulation also indicates that a decrease in the blood/brain-tissue gradient at the time of MAC_{tetanus} determination after surgery is not the explanation for the decrease in individual MAC_{tetanus}, it does not rule out a delayed diffusion into a brain receptor or binding site.

Electrical tetanic stimuli previously have been used to simulate the stimulus of a skin incision.\textsuperscript{15–16} Repeated electrical stimulation, however, may cause a progressive desensitization of the underlying skin. Laitinen and Eriksson\textsuperscript{17} found an increase in pain threshold following two short-spaced electrical stimulations. Further stimulation did not change the threshold. DeBroucker et al.,\textsuperscript{18} using randomized electrical stimulations of the sural nerve, showed a significant linear relationship without hysteresis between current intensity (0–40 mA) and pain perception. Brull et al.\textsuperscript{19} found that the facilitation of a train of four or a double burst stimulation after a 5 s, 50–100 Hz tetanic stimulus returned to baseline within 2 min. This also would indicate a return to baseline of nociception, because DeBroucker et al.\textsuperscript{18} also found a close link between nociception and motor response. We used a standardized, constant-current electrical tetanic stimulus, with only one stimulus given at each isoflurane concentration, and with at least 10 min between two stimulations to be sure that "stimulation fatigue" was avoided. If a desensitization of the underlying skin occurred, the nociception would be less at the end of a bracketing than at the beginning. No differences were found in the increase in blood pressure, increase in heart rate, or motor reaction to stimulation when stimulations at the beginning of a bracketing were compared to stimulations performed at the same isoflurane concentration at the end of the bracketing.

We found a preoperative MAC_{tetanus} value of 1.28 vol%, which is higher than the value found earlier by our group (end-tidal 1.10 vol%; Zbinden et al., unpublished data, 1990–1992) The latter MAC_{tetanus}, however, was determined during anesthesia administered \textit{via} a mask, and the electrical stimulation patterns used to determine each were slightly different. Corrected to sea level measurements, our MAC value would be 1.20 vol%, which is close to the traditional MAC_{skin incision} (the MAC that prevents movement response to skin incision in 50% of patients) value of 1.15 vol%, indicating that our electrical tetanic stimulation is comparable to a skin incision. Traditional MAC determinations are based on a logistic regression of data from a population, whereas we used a mean of individual MAC_{tetanus} values, which also might explain the small difference.

The prestimulation blood pressures taken at individual MAC_{tetanus} before surgery were similar to those taken after surgery, as were the blood pressure increases after stimulation. The equivalent values for heart rate, however, were significantly different. Therefore, some hemodynamic reactions after surgery were attenuated, even though the corresponding end-tidal isoflurane concentrations were lower (mean, 0.24 vol%) than those before surgery. This finding is in agreement with previous results from this laboratory (Zbinden et al., unpublished data, 1990–1992), indicating an increase in isoflurane potency during anesthesia and surgery.

In summary, a new method for individual MAC_{tetanus} measurements in humans was developed. By comparing the individual MAC_{tetanus} value determined before surgery with one determined after surgery in 10 patients, the authors found a decrease in MAC_{tetanus} of almost 20%, which may be clinically relevant. The decrease also affected some hemodynamic reactions. Further investigations will have to determine whether the decrease in MAC is due to altered isoflurane pharmacokinetics, an effect of anesthesia time, an effect of surgical time, or a combination of the three.

The authors thank the anesthesia research department for its technical assistance, especially M. Hutmacher, R.N., for clinical assistance, and G. M. Xie, M.D., for the analysis of isoflurane in the blood.
References