SUMMARY

End-tidal anaesthetic concentrations at first eye opening in response to a verbal command during recovery from anaesthesia (MAC-awake), were measured for isoflurane \( (n = 16) \), enfurane \( (n = 16) \) and halothane \( (n = 14) \). MAC-awake was measured during either slow or fast alveolar washout. Slow washout was obtained by decreasing anaesthetic concentrations in predetermined steps of 15 min, assuming equilibration between brain and alveolar partial pressures. Fast alveolar washout was obtained by discontinuation of the inhalation anaesthetic, which had been maintained at 1 MAC for at least 15 min. Mean MAC-awake obtained with slow alveolar washout was similar for isoflurane \( (0.25 \pm 0.03) \) MAC, and enfurane \( (0.27 \pm 0.04) \) MAC and significantly greater than values obtained by fast alveolar washout (isoflurane: \( 0.19 \pm 0.03 \) MAC; enfurane: \( 0.20 \pm 0.03 \) MAC). The MAC-awake of isoflurane and enfurane was significantly less than that of halothane, which was \( 0.59 \pm 0.10 \) MAC as evaluated by the slow and \( 0.50 \pm 0.05 \) MAC as evaluated by the fast alveolar washout method. Recovery time from anaesthesia with fast alveolar washout was 8.8 (4.0) min for halothane, which was not different from isoflurane (15 (2.5) min), but significantly shorter than for enfurane (22 (10) min), reflecting differences in the anaesthetic concentration gradient between MAC and MAC-awake values. These data do not support the hypothesis of a uniform ratio between MAC and MAC-awake values.

KEY WORDS
was inserted and routine monitoring commenced consisting of ECG, non-invasive automatic arterial pressure and pulse oximetry. Anaesthesia was induced with propofol 2.5 mg kg⁻¹ i.v. After loss of the eyelid reflex, the patients' lungs were ventilated by face mask with the group-specific inhalation anaesthetic in an air–oxygen mixture. Before tracheal intubation, vecuronium 0.1 mg kg⁻¹ i.v. was given and topical anaesthesia of the larynx and upper trachea was performed with 4% lignocaine 3 ml. The patients' lungs were ventilated spontaneously with 1 MAC and \( E_{\text{CO}_2} \) values maintained within the normal range (\( E_{\text{CO}_2} \): 4.5–5.5%). Inspired and end-expiratory concentrations of oxygen, carbon dioxide and isoflurane, enflurane or halothane were measured continuously by a multiple gas analyser (Capnomac, Datex) by aspiration from the end of the tracheal tube (200 ml min⁻¹). 

Volatile anaesthetic concentrations were detected by infra-red photometry with a rapid measurement rise time of < 770 ms. Calibration was performed before each case with a standard gas mixture (Quick Cal, Datex).

Anaesthesia was maintained with isoflurane, enflurane or halothane in an air–oxygen mixture throughout surgery and no other anaesthetic drugs were given. At the end of surgery and before the start of the alveolar washout period, all patients in group I and group III underwent mechanical ventilation of the lungs for 15 min with 1 MAC of isoflurane (1.2 vol %) or halothane (0.8 vol %), respectively, in 100% oxygen [3, 4]. Correspondingly, patients in group II, subjected to fast alveolar washout, underwent ventilation for 15 min with 1 MAC of enflurane (1.7 vol %) [5], while patients for slow alveolar washout received 1.0 vol % of enflurane before the beginning of the washout period. This initial 15-min equilibration period should have produced equilibration between brain and alveolar partial pressures, at a comparable anaesthetic concentration (1 MAC) before alveolar washout of the different inhalation anaesthetics. Patients for slow alveolar washout of enflurane were treated differently. In this group, we deliberately chose a sub-MAC concentration for the initial equilibration period, in order to keep the wake-up time within acceptable limits, as the concentration gradient between MAC and MAC-aware was especially great for enflurane (see below). 

Alveolar washout was conducted in all patients by maintaining normoventilation with 100% oxygen 10 litre min⁻¹. Slow alveolar washout was performed by decreasing the inspiratory anaesthetic concentration in predetermined steps every 15 min, to achieve equilibration between inspiratory and expiratory concentrations and cerebral partial pressure. These steps were 0.1–0.2 vol % for halothane, 0.2–0.3 vol % for enflurane and 0.2–0.4 vol % for isoflurane. Fast alveolar washout was conducted by discontinuing the anaesthetic, flushing of the circle breathing system with 100% oxygen and maintenance of normoventilation with 100% oxygen.

From the beginning of the alveolar washout period until the end of the study, all patients received a standardized verbal command to open their eyes, played from a tape every 20 s via occlusive head-phones. No other stimulus was used during the entire wake-up period. At first eye opening to command, the end-tidal concentration of the inhalation anaesthetic was recorded as MAC-aware value, and the elapsed time from the start of the alveolar washout was recorded. At this point the study was terminated, and the trachea was extubated.

MAC-aware values were divided by the age-adjusted MAC values. For enflurane, similar factors were assumed as had been established for halothane and isoflurane [5, 6]: the 1 MAC value of enflurane (1.7%) was multiplied by the factor 1.1 for age 19–30 yr and by the factor of 1.2 for age less than 19 yr. Duration of anaesthesia was calculated as the time from induction of anaesthesia until the start of the alveolar washout period. Wake-up time was considered the period from the beginning of the alveolar washout to first eye opening. Comparison for age and duration of anaesthesia was conducted between all groups by one-way analysis of variance (ANOVA). Comparison of wake-up times between groups was performed for fast alveolar washout by one-way ANOVA, followed by the Fisher's PLSD test. Comparison of wake-up times with slow alveolar washout was not performed, as the equilibration steps were chosen arbitrarily. MAC-aware values, expressed as vol % of the anaesthetic, were compared within each group for slow vs fast alveolar washout by unpaired t test. MAC-aware values expressed as ratio of MAC were compared between groups for slow and fast alveolar washout by one-way ANOVA, followed by the Fisher's PLSD test. \( P < 0.05 \) was considered significant in all tests. Statistical analyses were performed on a Macintosh SE computer using the Statview 512 program (Brain Power, Inc.; Calabasas, California 91302).

**Results**

There was no difference in patients' age and duration of anaesthesia between the groups. Mean wake-up times with fast alveolar washout were significantly shorter for halothane (8.8 (SD 4.0) min) than for enflurane (22 (10) min), while wake-up times for isoflurane (15 (2.5) min) did not differ from those for halothane or enflurane (table I). For each of the inhalation anaesthetics, MAC-aware values obtained by slow alveolar washout were significantly greater than those obtained by fast alveolar washout. Using slow alveolar washout, end-tidal anaesthetic concentrations at eye opening generally corresponded to inspiratory concentrations, indicating brain–alveolar equilibration. However, two patients anaesthetized with isoflurane and three patients each, anaesthetized with enflurane or halothane, had 0.1 vol % lesser inspiratory than end-tidal anaesthetic concentrations at eye opening, indicating that equilibration was not achieved completely (table I).

There was no difference between the MAC-aware values of isoflurane and enflurane, when MAC-aware was expressed as ratio of MAC. With slow alveolar washout the MAC-aware of isoflurane was 0.25 (0.03) MAC and that of enflurane 0.27 (0.04) MAC; with fast alveolar washout, values were 0.19 (0.03) MAC and 0.20 (0.03) MAC, respectively. The MAC-aware of halothane was significantly greater.
Table 1. Patient characteristics and study data (mean (SD) [range]). Comparison was conducted for age and duration of anaesthesia between all groups, for wake-up times between groups with fast alveolar washout, for MAC-awake (%) between slow and fast alveolar washout within each anaesthetic group, and for MAC-awake (% × MAC* (%) between different anaesthetic groups with slow or fast alveolar washout. P < 0.05: * between slow and fast alveolar washout within each anaesthetic group; † between anaesthetic groups for fast or slow alveolar washout; ‡ halothane different from isoflurane and enflurane; € halothane different from enflurane.

<table>
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<tr>
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<th>Isoflurane washout</th>
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<td>Slow</td>
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<td>Age (yr)</td>
<td>32 (18-49)</td>
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<td>Duration of anaesthesia (min)</td>
<td>101 (33)</td>
<td>101 (23)</td>
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<tr>
<td>Wake-up time (min)</td>
<td>46 (13)</td>
<td>15 (2.5)</td>
<td>32 (10)</td>
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<tr>
<td>MAC-awake (%)</td>
<td>0.31 (0.04)*</td>
<td>0.23 (0.05)</td>
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<td>MAC-awake (%) × MAC* (%)</td>
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<td>0.03-0.31</td>
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<td>0.021-0.32</td>
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The present study has shown clearly that there was a difference between MAC-awake values of isoflurane and enflurane compared with halothane. Therefore, the hypothesis of a uniform MAC-awake value, representing a fixed ratio of MAC [1], cannot be supported.

The slow alveolar washout method we used corresponded to that described initially by Stoelting, Longnecker and Eger [1]; this assumed brain–alveolar equilibration of the anaesthetic after maintaining alveolar concentrations constant for 15 min. As indicated above, this was achieved in the majority of our patients. However, because of the predetermined steps of decreased inspiratory anaesthetic concentrations, some inaccuracy in determining MAC-awake may have occurred in some patients, as a result of incomplete brain–alveolar equilibration. However, we believe that this error was small, as differences in inspiratory to end-tidal anaesthetic concentrations at eye opening, which occurred in some patients, did not exceed 0.1 vol%. Furthermore, based on the degree of decreased inspiratory concentrations, isoflurane should have exhibited the greatest variability. However, it had the smallest difference between MAC-awake values of isoflurane and enflurane; ‡ halothane different from isoflurane and enflurane.

Pain on recovery from anaesthesia may modify awakening by causing additional stimulation and lead to an increase in the measured MAC-awake value. Although this aspect was not studied specifically, most of our patients experienced pain during the early postoperative period, necessitating administration of opioids or anti-inflammatory drugs. This may be an important difference from the study by Stoelting’s group, in which patients were reported to be pain free after surgery, and may partially explain the greater MAC-awake values we observed. The great difference between the two studies with regard to MAC-awake obtained by fast alveolar washout may result from differences in several factors which modify anaesthetic elimination and equilibration of brain and alveolar partial pressures, such as duration of anaesthesia, anaesthetic gas concentration, anaesthetic concentration at which alveolar washout was started, mode of ventilation and patient’s body weight [6-8].

Permitting eye opening to a non-standardized verbal command and the value just preventing this response. In our study, more accuracy was provided by continuous measurement of inspiratory and end-expiratory anaesthetic concentrations, and standardization of the verbal command. Patients in Stoelting’s study did not receive any i.v. induction agent, while our patients received propofol i.v. and topical laryngeal anaesthesia on induction. These drugs may have decreased the MAC-awake value, by providing some postoperative sedation and by attenuating the cough reflex, induced by the tracheal tube. However, as the MAC-awake values of halothane were greater in our study than in that of Stoelting, Longnecker and Eger, these effects may be of minor importance.

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clinically important differences in hypnotic potencies of volatile anaesthetics, with isoflurane and enflurane being approximately twice as potent as halothane, ether, methoxyflurane or fluoroxyene [1]. It was shown also that subanaesthetic doses of isoflurane produced more mental and physical sedation than equi-anaesthetic doses of nitrous oxide [10]. These data therefore permit selection of volatile anaesthetics for the desired degree of sedation during anaesthesia or in the intensive care unit [11]. Furthermore, differences in hypnotic potencies of volatile anaesthetics are important in view of the fact that, even under surgical anaesthesia, there is some subconscious processing of information, which may modify post-operative psychological behaviour [12]. The MAC-awake of isoflurane (0.19 MAC) and enflurane (0.20 MAC), obtained by fast alveolar washout, were comparable. For isoflurane, the value was slightly greater than that reported by Gross and Alexander (0.15 MAC) [2], which is probably a result of differences in the study design. In our study, normoventilation was used, while in Gross and Alexander’s study fast alveolar washout was conducted with hyperventilation. Hyperventilation may have increased the brain to alveolar isoflurane partial pressure gradient as a result of cerebral vaso-constriction, and thus decreased the MAC-awake value. Further, thiopentone, used as an induction agent by Gross and Alexander, has more pronounced sedative effects during recovery from anaesthesia than propofol, which was used in the present study [13].

Wake-up times of the different volatile anaesthetics obtained in the present study depended on the number of equilibration steps in the case of slow alveolar washout. In the case of fast alveolar washout, wake-up times mainly reflected differences in the concentration of the anaesthetics at the beginning of the washout period (which corresponded to 1 MAC) and in MAC-awake values. Thus shortest wake-up times (8.8 min) were observed with halothane, as the concentration gradient for halothane between MAC and MAC-awake was small (0.4 vol %). Longer wake-up times occurred with enflurane (22 min), reflecting a greater anaesthetic concentration gradient between MAC and MAC-awake (1.3 vol %). Wake-up times for isoflurane (15 min) were intermediate between those of halothane and enflurane and corresponded to a MAC to MAC-awake concentration gradient of 0.9 vol %. The low MAC-awake value of isoflurane explains the longer wake-up times after isoflurane compared with halothane anaesthesia, which were studied previously in children and were in apparent contrast with predictions based on the physical properties of these anaesthetics [14].

REFERENCES
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