Minimum Alveolar Concentrations in Man on Awakening from Methoxyflurane, Halothane, Ether and Fluoxetine Anesthesia:

MAC Awake

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Alveolar anesthetic concentrations at the first response to command and those concentrations just preventing the response were determined in man during recovery from methoxyflurane, halothane, ether and fluoxetine anesthesia. The authors assumed equilibration of cerebral anesthetic concentration with alveolar concentration after alveolar concentration had been kept constant for at least 15 minutes. The anesthetic concentration midway between the value permitting the response and that just preventing the response was defined as “MAC awake.” MAC awake values were 0.081 ± 0.021 (SD) per cent methoxyflurane, 0.41 ± 0.05 per cent halothane, 1.41 ± 0.22 per cent ether, and 2.20 ± 0.49 per cent fluoxetine. MAC awake-to-MAC ratios were fairly close for the four agents, being 0.52, 0.52, 0.67, and 0.60 for methoxyflurane, halothane, ether, and fluoxetine, respectively. When the alveolar concentrations were allowed to fall spontaneously, falsely low MAC awake values were obtained for halothane and fluoxetine, while MAC awake for methoxyflurane was unchanged from that found at constant alveolar concentration. (Key words: MAC; MAC awake; Methoxyflurane; Halothane; Ether; Fluoxetine.)

MINIMUM ALVEOLAR CONCENTRATIONS OF INHALATIONAL ANESTHETICS NECESSARY TO PREVENT RESPONSE TO A PAINFUL STIMULUS IN 50 PER CENT OF PATIENTS HAVE BEEN DESCRIBED.1 THE ALVEOLAR CONCENTRATIONS AT WHICH AWAKENING FROM INHALATIONAL ANESTHESIA OCCURS HAVE NOT BEEN DETERMINED, HOWEVER. WE MEASURED THE ALVEOLAR ANESTHETIC CONCENTRATIONS PRESENT WHEN PATIENTS FIRST OPENED THEIR EYES ON REQUEST AND THOSE CONCENTRATIONS JUST PREVENTING THE RESPONSES DURING RECOVERY FROM METHOXYFLURANE (PENTHANE), HALOTHANE (FLUOTHANE), ETHER, AND FLUOROXENE (FLUOROMAR) ANESTHESIA. THE ALVEOLAR CONCENTRATION MIDWAY BETWEEN THE VALUE PERMITTING AND THAT PREVENTING THE RESPONSE WAS DEFINED AS THE MINIMUM ALVEOLAR CONCENTRATION OF ANESTHETIC ON AWAKENING ("MAC AWAKE") AND COMPARED WITH PREVIOUSLY REPORTED MAC VALUES IN ANESTHETIZED SUBJECTS.1

METHODS

Data were gathered from two groups of subjects. Ether data and those in six of the fluoxetine studies were obtained from volunteers undergoing studies of the circulatory effects of these anesthetics. No surgical operation was performed on the volunteers. The remaining subjects underwent general anesthesia for elective operations. Volunteers were unpremedicated and received only the anesthesia under study (ether or fluoxetine). Patients undergoing operation received atropine for premedication. Anesthesia was induced and maintained with the anesthetic under study plus muscle relaxants. Respiration was controlled via endotracheal tube during all observations. Following the circulatory studies or surgical operation, the alveolar anesthetic concentration was decreased to a pre-
TABLE 1. Data Obtained When the Alveolar Concentration Was Held Constant (Part A). and When It Was Allowed to Decrease Spontaneously (Part B)

<table>
<thead>
<tr>
<th>Anesthetic</th>
<th>A Alveolar Concentration Constant</th>
<th>B Spontaneous Decrease in Alveolar Concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Methoxyflurane</td>
<td>Halothane</td>
</tr>
<tr>
<td>Number of subjects*</td>
<td>8</td>
<td>10</td>
</tr>
<tr>
<td>Age (years)</td>
<td>Mean</td>
<td>51</td>
</tr>
<tr>
<td></td>
<td>SD</td>
<td>14</td>
</tr>
<tr>
<td>Duration of anesthesia (min)</td>
<td>Mean</td>
<td>200</td>
</tr>
<tr>
<td></td>
<td>SD</td>
<td>81</td>
</tr>
<tr>
<td>Nasopharyngeal temperature (°C)</td>
<td>Mean</td>
<td>33.8</td>
</tr>
<tr>
<td></td>
<td>SD</td>
<td>0.5</td>
</tr>
<tr>
<td>Alveolar concentration on response†</td>
<td>Mean</td>
<td>0.070</td>
</tr>
<tr>
<td></td>
<td>SD</td>
<td>0.017</td>
</tr>
<tr>
<td>Alveolar concentration when no response†</td>
<td>Mean</td>
<td>0.002</td>
</tr>
<tr>
<td></td>
<td>SD</td>
<td>0.024</td>
</tr>
<tr>
<td>MAC awake†</td>
<td>Mean</td>
<td>0.081</td>
</tr>
<tr>
<td></td>
<td>SD</td>
<td>0.021</td>
</tr>
<tr>
<td>MAC awake /MAC‡</td>
<td>Mean</td>
<td>0.32</td>
</tr>
</tbody>
</table>

* All ether and six fluoroxene subjects were volunteers who did not undergo surgical operations.
† Methoxyflurane values represent arterial blood tensions converted to equivalent alveolar concentrations.
‡ MAC corrected for age using the data of Gregory et al.²

determined level and held constant for at least 15 minutes to insure equilibration with cerebral partial pressure. During this time the patient was asked at frequent intervals to open his eyes. If he failed to open his eyes the alveolar concentration was lowered and again held constant for 15 minutes. The process was repeated until an alveolar concentration at which the patient responded to command was reached. The concentration midway between the value permitting the response (open eyes on request) and that just preventing the response was defined as the minimum alveolar concentration of anesthetic on awakening, or MAC awake.

In addition, MAC awake was determined for methoxyflurane, halothane and fluoroxene when patients were disconnected from the anesthesia machine and breathed ambient air spontaneously through an endotracheal tube. In these patients the inspired anesthetic concentrations were zero and no attempt was made to hold the alveolar concentrations constant. Alveolar gas samples were obtained every three to five minutes and MAC awake calculated as that value midway between the alveolar concentration at the initial response and the anesthetic concentration of the last sample obtained prior to response.

MAC awake/MAC ratios were calculated for each agent after correction of MAC for patient age. Gregory et al. found halothane MAC to be 0.92 per cent in subjects 12–18 years of age and 0.84 per cent in the 19–30-year range, compared with 0.76 per cent for those 31–55 years old.² Assuming similar changes in MAC with other agents, we corrected for patient age by multiplying MAC values for 31–55-year-olds by 1.21 (i.e., 0.92 /0.76) for those 12–18 years of age and by 1.1 (i.e., 0.84/0.76) for the 19–30-year age group. For example, we calculated MAC in
the 19-30-year group as 0.18 per cent methoxyfluurane (i.e., 0.16 times 1.1), 2.1 per cent ether (i.e., 1.92 times 1.1) and 3.6 per cent fluroxene (i.e., 3.4 times 1.1).

End-tidal (alveolar) gas samples were collected in glycerinized glass syringes via a nylon catheter inserted through the endotracheal tube to a level near the carina. Halothane and fluroxene concentrations were determined with a Beckman GC-2A gas chromatograph using a flame ionization detector. Alveolar samples from volunteers undergoing ether and fluroxene anesthesia were measured by infrared analysis. Methoxyfluorane was extracted from arterial blood with tetrachloroethylene and analyzed by gas chromatography. Blood methoxyfluorane concentrations in mg/100 ml were converted to equivalent alveolar concentrations in volumes per cent.

Results

Table 1, part A shows results for the four agents studied at constant alveolar concentrations. MAC awake values were 0.081 ± 0.021 (SD) per cent methoxyfluorane, 0.41 ± 0.05 per cent halothane, 1.41 ± 0.22 per cent ether, and 2.20 ± 0.49 per cent fluroxene. Part B gives data obtained when alveolar concentrations were allowed to decrease spontaneously. Awake values were 0.082 ± 0.017 per cent methoxyfluorane, 0.27 ± 0.03 per cent halothane, and 1.16 ± 0.23 per cent fluroxene. Ratios of MAC awake to MAC when the alveolar concentration was held constant were 0.52 for methoxyfluorane, 0.52 for halothane, 0.67 for ether, and 0.60 for fluroxene. On spontaneous recovery ratios were 0.50 for methoxyfluorane, 0.33 for halothane, and 0.34 for fluroxene.

Figures 1 to 4 illustrate the data summarized in table 1.

Discussion

We defined consciousness as present when an individual could make an appropriate response to a verbal request. For this reason we chose opening eyes on command as the criterion for awakening from inhalational anesthesia.

It is essential that alveolar and cerebral partial pressures be identical for the data to be meaningful. We assumed that 15 minutes at constant alveolar concentration assured equilibration between the alveolar and cerebral partial pressures. When the alveolar concentrations were allowed to fall spontaneously
MAC awake values for halothane and fluoroxyne were much lower than when the alveolar concentrations were held constant. Values for methoxyflurane were similar in the two groups. These findings suggest that the alveolar concentrations of the less soluble anesthetics in our study (halothane and fluroxene) fell so rapidly that the measured alveolar concentrations on spontaneous recovery did not represent true cerebral partial pressures. Cerebral and alveolar tensions decreased at the same rate with methoxyflurane, and MAC awake on spontaneous recovery was identical to that found when alveolar concentration was held constant.

Alveolar gas from unperfused but ventilated alveoli could contaminate end-tidal gas samples. In the group studied at a constant alveolar concentration an inspired concentration greater than the alveolar concentration could falsely elevate the true alveolar concentration. For this reason we determined inspired halothane and fluroxene concentrations to confirm the presence of an inspired-to-alveolar gradient of less than 10 per cent. Inspired either concentrations were not measured, but prolonged administration (444 ± 45 min) prior to determination of MAC awake should have reduced the inspired-to-alveolar concentration gradient. It was not possible to eliminate the gradient for methoxyflurane, so blood methoxyflurane concentrations of all patients were determined.

On spontaneous recovery, when the inspired concentration was zero, gas coming from unperfused alveoli could falsely lower measured end-tidal gas concentrations. To assure that contamination was not the cause of lower values for halothane and fluroxene on spontaneous recovery we determined the blood concentrations of several patients. Differences between blood and alveolar concentrations were small and could not account for the low values on recovery from halothane and fluroxene.

Effects of age, body temperature, type of operation and $P_{aCO_2}$ on MAC awake cannot be appreciated from our data. Anesthetized MAC varies inversely with age, and directly with body temperature, and is not altered by hypocapnia. MAC awake for fluroxene in six patients (average age 35 years, nasopharyngeal temperature 35.8°C, operation and hypocapnia secondary to controlled hyperventilation) was $2.24 \pm 0.58$ per cent. Six volunteers (average age 24 years, nasopharyngeal temperature 36.7°C and alveolar $P_{aCO_2}$ maintained about 35 torr) had an average fluroxene MAC awake of $2.15 \pm 0.37$ per cent. Differences between the two awake values were not
significant. A study of individual data with regard to MAC awake vs. age did not confirm a higher awake value for younger patients or a lower value for older subjects with any of the anesthetics. However, the younger age group may be partly responsible for the higher MAC awake/MAC ratios seen with awakening from ether and fluroxene (table 1, part A). Pain resulting from operation appeared not to be an important stimulus in the immediate awakening period; no patient stated he had pain when questioned and those who had surgical operations had fluroxene MAC awake values similar to those who did not. Unperceived discomfort may still act as a stimulus to arousal, however. Thus, MAC awake in volunteers without operation may underestimate true awake values on recovery after operation.

The relative consistency of the ratio of MAC awake to anesthetized MAC (average 0.58) allows predictions of MAC awake for other inhalation anesthetics. For example, MAC for cyclopropane is reported as 9.2 per cent.\textsuperscript{1} We would predict MAC awake cyclopropane to be about 5.3 per cent (MAC awake equals anesthetized MAC times 0.58). Nitrous oxide MAC awake calculated is 59 per cent (101 times 0.58).\textsuperscript{1} The consistency of the ratios also suggests that any difference between anesthetics in time required for awakening must result only from differences in the rates of elimination. This agrees with the clinical impression of slow recovery with highly soluble anesthetics and more rapid recovery with poorly soluble agents.

The fluroxene for the volunteer studies was provided by Ohio Medical Products Company.

References


Erratum

An error appeared in the article, “Nonspecific Stimulation of Drug Metabolism in Rats by Methoxyflurane,” by M. Lawrence Berman and Julius F. Boechtlin (Anesthesiology 32: 506, 1970). The fourth sentence in the last paragraph on page 506 should be corrected to read: “Converting this dose to a kilogram body weight basis, it would be 200 to 250 mg administered twice a day at the beginning of the experiment and 111 mg twice a day at the end.”