Laboratory Note

Halothane and Methoxyflurane Concentrations in End-tidal Gas, Arterial Blood, and Lumbar Cerebrospinal Fluid

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Simultaneous inspired, end-tidal, arterial-blood, and lumbar cerebrospinal fluid (CSF) concentrations of halothane or methoxyflurane were measured during anesthesia in man. End-tidal and arterial-blood halothane approached the constant inspired concentration (0.44 ± 0.06 per cent) at nearly the same rate. After 120 minutes these concentrations were 82 per cent of the inspired concentration. The concentration in CSF was less than that in arterial blood (P < 0.05) during this time; after 270 ± 25 minutes of anesthesia it was 81 per cent of that in arterial blood (P > 0.05). After discontinuation of halothane it was 60–90 minutes before the concentration in CSF decreased 50 per cent. The concentration in CSF was greater than that in arterial blood (P < 0.05) during this time.

After 210 ± 18 minutes of constant inspired methoxyflurane (0.50 ± 0.08 per cent) the arterial-blood concentration was 38 per cent of the inspired concentration and the concentration in CSF was 63 per cent of the arterial-blood concentration. End-tidal methoxyflurane concentration did not accurately reflect the concentration in arterial blood. The concentration in CSF decreased slowly and exceeded that in arterial blood (P > 0.05) during the 120 minutes after discontinuation of methoxyflurane. Sixty to 90 minutes passed before the CSF methoxyflurane concentration decreased 50 per cent. (Key words: Halothane; Methoxyflurane; Concentration end-tidal gas; Arterial blood and cerebrospinal fluid.)

Lumbar spinal fluid drainage for elective operations provided a unique opportunity to measure anesthetic concentrations in cerebrospinal fluid (CSF). Since CSF/gas partition coefficients are known, it was possible to convert the values obtained to equivalent concentrations in volumes per cent. This study reports concentrations of halothane (Fluothane) and methoxyflurane (Penthrane, MOF) in lumbar CSF during anesthesia and operation in man. These values are compared with simultaneous concentrations of the anesthetics in the end-tidal gas and arterial blood while the inspired concentration was maintained constant.

Methods

Adult patients undergoing elective hypophysectomies for which spinal fluid drainage was utilized were studied. Anesthesia was induced with thiopental, followed by succinylcholine to facilitate tracheal intubation. Anesthesia was maintained with nitrous oxide–halothane (four patients) or MOF–oxygen (five patients), using a nonrebreathing anesthetic system. d-Tubocurarine (0.4 mg/kg) was administered and respiration was controlled with a Bird ventilator. A Teflon catheter was placed in the lumbar subarachnoid space. Intravascular blood pressure and nasopharyngeal temperature were monitored.

Halothane was added to the delivered gases only after the placement of all catheters. The inspired concentration was held constant (Copper Kettle vaporizer, 125–150 ml oxygen flow diluted in nitrous oxide, 8 l, and oxygen 5 l) for the next 120 minutes. Simultaneous inspired, end-tidal, arterial-blood, and CSF samples were obtained 1, 3, 5, 10, 20, 30, 45, 60, and 120 minutes after adding halothane. After the patient had breathed halothane for 270 ± 25 minutes (mean ± SE) all samples were again obtained and halothane then discon-
continued. Measurements were repeated 1, 5, 10, 20, 30, 60, and 90 minutes later.

MOF concentrations were measured after 210 ± 18 minutes of administration and then 10, 20, 30, 45, 60, 90, and 120 minutes after discontinuing the drug. After discontinuation of halothane or MOF, anesthesia was maintained with 60 per cent nitrous oxide and incremental doses of Innovar and d-tubocurarine.

The inspired and end-tidal gas samples were collected into glycerinized glass syringes and analyzed for halothane or MOF by gas chromatography. Two-milliliter samples of blood and CSF were collected into heparinized glass syringes; the anesthetics were then extracted anaerobically into tetrachloroethylene and the concentrations (mg/100 ml) measured by gas chromatography. These concentrations were converted to equivalent concentrations in volumes per cent using previously determined blood/gas and CSF/gas partition coefficients appropriate for the patient’s temperature.1

Data were analyzed with Student’s t test. P < 0.05 was considered significant.

Results

End-tidal and arterial-blood halothane approached the constant inspired concentration (0.44 ± 0.06 per cent) at nearly the same rate and had reached 82 per cent of the inspired concentration (0.34 ± 0.04 per cent) after 120 minutes (fig. 1). Halothane was not detectable in CSF for 5 minutes after administration began; then the concentration gradually increased to 0.14 ± 0.01 and 0.23 ± 0.03 per cent after 60 and 120 minutes of administration. End-tidal and arterial-blood halothane concentrations were less than the inspired concentration (P < 0.05), and CSF concentration was less than the corresponding arterial-blood concentration (P < 0.05) at all times measurements were made.

After 270 ± 25 minutes of halothane administration, the concentration in CSF was 81 per cent of that in the blood (0.30 ± 0.03 vs. 0.37 ± 0.06 per cent); no value was significantly less than the inspired concentration (fig. 2). Arterial-blood and end-tidal concentrations decreased rapidly when halothane was discontinued, but CSF halothane decreased slowly and was greater (P < 0.05) than arterial-blood halothane at all times. Sixty minutes after discontinuation of halothane the concentration in CSF was 0.17 ± 0.05 per cent.

After the patient had breathed 0.5 ± 0.08 per cent MOF for 210 ± 18 minutes the arterial-blood concentration was 0.19 ± 0.04 per cent (P < 0.03) and CSF MOF was significantly less than that in arterial blood (0.12 ± 0.01 per cent) (fig. 3). CSF MOF decreased more slowly than the concentration in blood but, unlike halothane, was not significantly greater than the concentration in blood at any time. Sixty minutes after discontinuation of MOF, the concentration in CSF was 0.07 ± 0.02 per cent, compared with 0.05 ± 0.01 per cent arterial-blood MOF.

Discussion

End-tidal and arterial-blood halothane concentrations approached the constant inspired concentration at nearly the same rate. After 120 minutes the end-tidal-to-inspired ratio was 0.82, compared with 0.79 reported by Sechzer et al.2 CSF halothane approached the inspired concentration slowly and was significantly less than the end-tidal and arterial-blood concentrations even after 120 minutes. The rate at which CSF equilibrates with the inspired concentration will depend largely on the blood flow exposed to CSF and anesthetic solubility in CSF. Since halothane is poorly soluble in CSF (CSF/gas partition coefficient 0.77 at 37 C1), rapid equilibration with arterial blood would be predicted. Therefore, the slow increase of halothane in CSF probably reflected a small proportion of blood flow in contact with CSF.

Discontinuing halothane after 270 ± 25 minutes resulted in rapid decreases in the end-tidal and arterial-blood concentrations. CSF halothane decreased slowly and was significantly greater than the arterial-blood concentration between 5 and 90 minutes. Twenty minutes after discontinuation of halothane the arterial-blood concentration had decreased 73 per cent (0.37 to 0.10 per cent). Analog alveolar recovery curves would predict about a 70 per cent decrease 20 minutes after four hours of halothane anesthesia if alveolar ventilation were 4 l/min.4 We again speculated
that low exposure of CSF to blood flow provided the best explanation for the slow decrease in CSF halothane concentration after the anesthetic was discontinued.

Halothane represented an anesthetic of intermediate solubility, while MOFillustrated a very soluble anesthetic. Large-volume MOF uptake slowed the increase in anesthetic concentration such that after $210 \pm 18$ minutes the arterial-blood concentration was only 38 per cent of the constant inspired value. End-tidal MOF was significantly greater than the arterial-blood concentration. This falsely high end-tidal value probably represented contamination of alveolar samples with deadspace gas. This is the reason such samples are not valid

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**Fig. 1.** Halothane was added to the delivered gases at zero time and simultaneous inspired, end-tidal, arterial-blood, and CSF concentrations were measured at intervals for the following 120 minutes (mean values, four patients).

**Fig. 2.** All measurements were repeated after $270 \pm 25$ minutes (0 time) of halothane administration. Halothane was then discontinued and concentrations measured during the next 90 minutes (mean values, four patients).
Fig. 3. Values at zero time represent concentrations after 210 ± 18 minutes of methoxyflurane administration. Methoxyflurane was discontinued and recovery followed for 120 minutes (mean values, five patients).

Reflections of the arterial-blood concentrations of very soluble anesthetics when uptake remains great. In contrast, end-tidal halothane values accurately reflected arterial-blood concentrations because the effect of contamination by gas in the deadspace was decreased by the small volume of uptake and the subsequent smaller inspired-to-end-tidal concentration difference. Some discrepancy between the alveolar and arterial concentrations may always exist, owing to varying degrees of intrapulmonary shunt.7

After 275 ± 25 minutes, end-tidal, arterial-blood, and CSF concentrations of halothane were nearly identical. In contrast, CSF MOF was less than the arterial-blood concentration \( P < 0.05 \) after 210 ± 18 minutes. Presumably blood flows were not greatly different, so the slower increase in MOF CSF concentration was probably the result of the greater solubility (five to six times) of MOF in CSF compared with halothane.1

Twenty minutes after discontinuation of MOF, the arterial concentration had decreased 58 per cent. Computer curves predict a 30 per cent decrease after four hours of MOF anesthesia with 4 l/min alveolar ventilation.4 Ventilation greater than 4 l/min and administration for less than four hours may account for the more rapid decreases in our patients. Like halothane, MOF in CSF exceeded the arterial-blood concentration, but unlike halothane, the values were not significantly greater. As with halothane, 60–90 minutes of recovery were necessary before the concentration in CSF was reduced 50 per cent. Unlike the fast decrease of halothane, the slow decrease in arterial-blood MOF may have acted to slow the loss of MOF from spinal fluid further by decreasing the gradient between CSF and blood.

Anesthetic concentrations in lumbar CSF may not accurately reflect ventricular CSF levels. CSF \( P_{O_2} \) is highest in the ventricles and decreases along a ventriculo-lumbar axis.8 This is felt to be due to oxygen transfer between blood and spinal fluid, which takes place mainly at the ventricular level through the choroid plexus.8 Assuming this is true for anesthetics, the lumbar concentrations might underestimate ventricular concentrations during anesthesia. During recovery, ventricular anesthetic concentrations might decrease more rapidly if blood flow is greater than that to the lumbar CSF.

It seems possible that anesthetics in CSF might depress respiratory chemoreceptors on the medullary surface and contribute to intra-
operative and postoperative hypoventilation. However, ventilation measurements to confirm this speculation are not available.

References

Obstetrics
OXYTOCIN AND REGIONAL ANESTHESIA Epidural or caudal anesthesia provides excellent pain relief during labor and delivery. Judicial use of oxytocin in association with regional anesthesia can lead to increased convenience and shorter labor. However, indiscriminate use of this combination may be hazardous to both mother and fetus. By the use of continuous monitoring of fetal heart rate, the author has studied the effects of oxytocin stimulation and epidural anesthesia on the fetus.

Three hundred and sixty fetuses were observed for cardiac deceleration occurring late in the uterine contraction cycle, during labor, in four treatment groups. The 119 mothers of Group A received neither epidural anesthesia nor oxytocin stimulation; Group B (41 patients) received oxytocin stimulation with several other forms of anesthesia; Group C (135 patients) received epidural anesthesia without oxytocin; Group D (65 patients) received a combination of epidural anesthesia and oxytocin stimulation. The incidence of uteroplacental insufficiency patterns in Group A was 16.8 per cent; Group B, 26.8 per cent; Group C, 24.4 per cent; Group D, 40 per cent.

A fall in maternal systolic blood pressure greater than 20 mm Hg during epidural anesthesia caused 72 per cent of fetuses to develop uteroplacental insufficiency patterns. When uterine hypertonus developed during oxytocin infusion, 50 per cent of fetuses developed late deceleration. Control of oxytocin infusion, correction of hypotension by maternal hydration, and avoidance of the supine position were usually accompanied by improvement in these ominous fetal heart-rate patterns. There was no difference in neonatal outcome among the various treatment groups. (Schiilrin, B. S.: Fetal Heart Rate Patterns Following Epidural Anesthesia and Oxytocin Infusion during Labor, J. Obs. Gynecol. Br. Commonwealth 79: 332-339, 1972.)