

Effects of Methoxyflurane on Canine Cerebral Metabolism and Blood Flow

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The rate of cerebral oxygen consumption (CMR_{O_2}) and the cerebral blood flow (CBF) were determined in eight dogs at three end-expired concentrations of methoxyflurane (means <0.1, 0.25, and 0.44 per cent). With each increase in concentration above <0.1 per cent, a significant decrease in CMR_{O_2} was observed (approximately 10 and 25 per cent less than the <0.1 per cent value, respectively). The cerebrovascular effects of methoxyflurane were less striking. At 0.25 per cent, a small but significant increase in CBF and a decrease in (cerebral vascular resistance) CVR were observed, compared with the <0.1 per cent values. No further significant change was observed at higher concentrations. The cerebrovascular responses to changes in P_{aCO_2} were tested at 0.25 per cent end-expired methoxyflurane. Over a range of P_{aCO_2} of approximately 20 mm Hg (30 to 50 mm Hg), the expected responses of CBF and CVR were observed. The authors conclude that methoxyflurane resembles halothane in its overall cerebral metabolic effects but, unlike halothane, produces only modest changes in CVR and CBF. (Key words: Methoxyflurane; Cerebral metabolism; Cerebral blood flow.)

THE CEREBRAL metabolic and vascular effects of methoxyflurane have not been thoroughly investigated. Yet it is generally assumed that this anesthetic resembles halothane in its effects on cerebral metabolism and blood flow. In a recent report, Gray and associates¹ described an effect of methoxyflurane in the dog opposite to that observed with halothane, namely, decreases in cerebral blood flow (CBF) with increasing concentrations. They concluded that methoxyflurane might be particu-

larly suitable for neurosurgical anesthesia. Fitch and associates,² on the other hand, found that methoxyflurane, like halothane, may increase CSF pressures in patients with intracranial mass lesions, although the increases may be smaller. This effect of the halogenated anesthetics on CSF pressure has been assumed to be secondary to an increase in CBF. It was the purpose of the present study to determine the cerebral metabolic effects of methoxyflurane and to resolve the discrepancies concerning the cerebrovascular effects.

Material and Methods

Eight unmedicated mongrel dogs (weights 12 to 16 kg) were studied in the prone position. Anesthesia was induced with methoxyflurane (0.8 to 1.2 per cent inspired) in oxygen (30 per cent) and nitrogen and maintained with an inspired concentration of 0.3 to 0.4 per cent. Succinylcholine (20 mg) was given to facilitate intubation of the trachea and thereafter at a rate of 150 mg/hour to maintain muscle paralysis. Ventilation was controlled with a Harvard pump. Catheters were inserted into a femoral artery for pressure measurement and blood sampling and a femoral vein for the administration of drugs, fluids, and blood. Body and brain temperatures were maintained with heat lamps and electric blankets.

Cerebral blood flow was measured by a direct venous outflow method as previously described³ and modified.⁴ This requires surgical isolation, cannulation, and posterior occlusion of the sagittal sinus. The sagittal sinus blood flow is automatically measured by timed collection in a reservoir, maintained at the level of the sinus, and then returned to the dog by a pump. In our initial studies,³ the sagittal sinus cannula was placed approximately 1.5 cm anterior to the torcular; in a series of 15 dogs, after postmortem injection of vinylacetate into the sinus and subsequent dissection,

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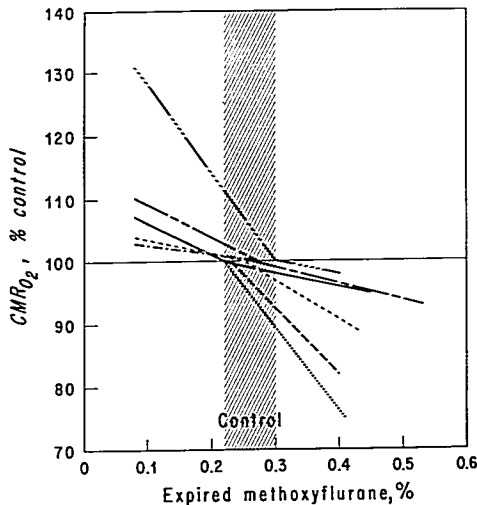


FIG. 1. Effects of methoxyflurane on CMR_{O_2} in eight dogs. Initial observations were made at an expired concentration of approximately 0.25 per cent ($CMR_{O_2} = 100$ per cent); at increasing concentrations, CMR_{O_2} 's decreased significantly (six dogs); with reduction of expired concentrations to <0.1 per cent, the increase in mean CMR_{O_2} was significant (five dogs).

the weight of the brain drained by the cannula averaged 43 per cent of the total brain weight. In recent studies,⁴ because of improvement in surgical technique, it has been possible to place the cannula more posteriorly and thus to collect flow from a larger portion of the cerebral hemispheres. In a series of 20 dogs, the more posterior placement increased the average weight of brain drained to 54 per cent of the total brain weight. This percentage is used to convert units of flow (from ml/min to ml/100 g/min).

The oxygen contents of arterial and sagittal sinus blood were calculated from measurements of oxyhemoglobin concentration (IL 182 CO-Oximeter) and oxygen tension (IL electrodes, 37 C).⁵ The glucose contents of arterial and sagittal sinus blood were measured by an enzymatic method.⁶ Additional measurements included those of arterial blood pH and P_{CO_2} (electrodes), arterial blood pressure (strain gauge), parietal epidural temperature (thermistor), and inspired and end-expired methoxyflurane concentrations (Mayo Vapor Analyzer). The rates of cerebral oxygen consumption (CMR_{O_2}) and cerebral glucose con-

sumption ($CMR_{glucose}$) were calculated as the products of CBF and the arterial-sagittal sinus blood content differences ($C_{(a-v)}$). Cerebral vascular resistance (CVR) was calculated as the ratio of mean arterial pressure (MAP) and CBF (MAP equals perfusion pressure when the venous reservoir is maintained at the level of the sagittal sinus). The oxygen-glucose index (OGI) was calculated in the manner described by Cohen and associates.⁷

Control determinations were initiated 1½ to 2 hours after induction of anesthesia, when the following conditions (mean \pm SD) had been established: inspired methoxyflurane concentration, 0.33 ± 0.04 per cent; end-expired methoxyflurane concentration, 0.25 ± 0.03 per cent; Pa_{CO_2} , 40 ± 2 mm Hg; Pa_{O_2} , 140 ± 15 mm Hg; buffer base, 47 ± 1 mEq/l; brain temperature, 37.0 ± 0.1 C; MAP, >70 mm Hg; hemoglobin concentration, >11 g/100 ml. Values for CBF and CMR_{O_2} were determined from 8 to 12 sequential measurements at 2-3-min intervals of $C_{(a-v)O_2}$ and CBF. Values for $CMR_{glucose}$ were based upon three measurements of $C_{(a-v)glucose}$ and CBF, with blood sampling limited to periods of steady CBF.

TABLE 1. Effects of Methoxyflurane on Cerebral Metabolism and Hemodynamics (Mean \pm SE)

End-expired Methoxyflurane (Per Cent)	CMR_{O_2} (ml/100 g/min)	$CMR_{glucose}$ (mg/100 g/min)	Oxygen-Glucose Index (Per Cent)	Cerebral Blood Flow (ml/100 g/min)	Cerebral Vascular Resistance (mm Hg/ml/100 g/min)	MAP (mm Hg)	P_{aCO_2} (mm Hg)
<0.10 (five dogs)	5.67 \pm 0.24	8.9 \pm 0.6	85 \pm 5	45 \pm 4	3.0 \pm 0.2	137 \pm 8	35 \pm 2
0.25 (eight dogs)	5.11 \pm 0.22*	8.1 \pm 1.0	84 \pm 11	61 \pm 4*	2.1 \pm 0.2*	130 \pm 6	42 \pm 1*
0.44 (six dogs)	4.37 \pm 0.26†	7.7 \pm 0.9	75 \pm 5	52 \pm 7	2.1 \pm 0.3*	108 \pm 9†	43 \pm 2*

* Significantly different from the 0.1 per cent values ($P < 0.05$).
 † Significantly different from the 0.1 per cent and 0.25 per cent values ($P < 0.05$).

$CMR_{glucose}$ calculations were discarded whenever an abrupt change in arterial glucose concentration occurred.

Following control determinations, methoxyflurane was discontinued in four dogs, and when the expired concentration was less than 0.1 per cent (usually after one hour) all measurements were repeated. Methoxyflurane was then reintroduced in high concentrations (1.0 to 1.5 per cent) until the expired concentration was approximately twice the initial control concentration (after 60 to 90 minutes); the inspired concentration was then decreased to approximately the expired concentration and the measurements were repeated. Two dogs did not maintain adequate MAP's during this final step and the studies were terminated.

In the other four dogs, the sequence of change in methoxyflurane concentrations was reversed. In three of these, no expired concentration less than 0.1 per cent was achieved even after methoxyflurane had been discontinued for 90 minutes and, because of progressive deterioration of the preparations, the studies were terminated.

In four dogs, the responses of CBF to changes in P_{aCO_2} were determined before the control methoxyflurane concentration (0.25 per cent) was altered. This was accomplished by introducing CO_2 to or removing CO_2 from the inspired gases while the dog was being hyper-ventilated at a constant rate and tidal volume; in each dog the effects of three P_{aCO_2} 's (approximately 30, 40, and 50 mm Hg) were examined in random sequence.

In three additional dogs, end-expired concentrations of 0.25 per cent methoxyflurane were established, as were the other control conditions. These conditions were maintained

and measurements were repeated at 10-minute intervals during a three-hour period in order to examine the effect of time on the preparation.

The significances of the differences between mean values were determined by Student's *t* test for paired data ($P < 0.05$ being considered significant). The linear regression equation for response of CBF to change in P_{aCO_2} was calculated by the method of least squares.

Results

CHANGES IN CMR_{O_2}

An increase in the mean expired methoxyflurane concentration from 0.25 (control) to 0.44 per cent caused a significant decrease in CMR_{O_2} to 86 per cent of the mean control value (fig. 1, table 1). A decrease in expired concentration to less than 0.1 per cent (five dogs, fig. 1) caused a significant increase (11 per cent) in CMR_{O_2} . Changes in $CMR_{glucose}$, although not significant, paralleled changes in CMR_{O_2} .

CHANGES IN CBF

Decreasing the methoxyflurane concentration from control levels to less than 0.1 per cent decreased CBF significantly, to 74 per cent of the mean control value (table 1). This difference was entirely accounted for by an increase in CVR, since MAP increased during this time. Increasing the methoxyflurane concentration to above control concentrations caused no further decrease in CVR, and the insignificant decrease in CBF which occurred was accompanied by a significant reduction in MAP. At control concentrations of methoxyflurane, a virtually linear response of CBF to

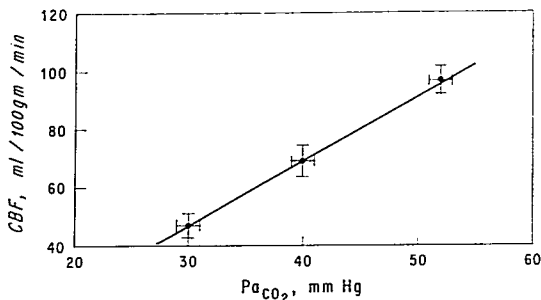


FIG. 2. Effect of P_{aCO_2} on CBF during methoxyflurane anesthesia (0.25 per cent expired concentration) in four dogs. Values are means \pm SE (vertical and horizontal bars) $CBF = 2.2 \times P_{aCO_2} - 19$.

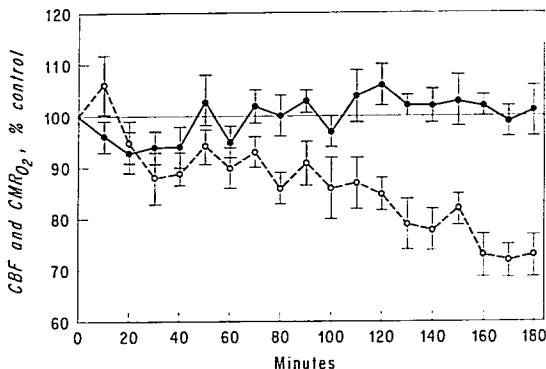


FIG. 3. Effects of time on CMR_{O_2} and CBF during methoxyflurane anesthesia (0.25 per cent expired) in three dogs. CMR_{O_2} varied insignificantly during a three-hour period, whereas a significant progressive decrease in CBF was observed. ● — ● = CMR_{O_2} ; ○ - - ○ = CBF; values are means \pm SE (vertical bars).

changes in P_{aCO_2} was observed (fig. 2). An increase in P_{aCO_2} of 12 mm Hg caused an increase in the CBF (mean) of 41 per cent, while a decrease in P_{aCO_2} of 10 mm Hg caused a reduction in CBF of 32 per cent.

EFFECTS OF TIME

In the three dogs observed for three hours without change in control conditions, mean CMR_{O_2} did not change significantly (fig. 3). However, a progressive decrease in CBF and a progressive increase in CVR occurred with time. The decrease in CBF averaged approximately 10 per cent per hour and became significant after the first hour.

Discussion

The canine cerebral metabolic and vascular effects of methoxyflurane qualitatively resemble those of halothane. Quantitatively, the effects differ. Methoxyflurane caused dose-related reductions in CMR_{O_2} such that at concentrations approximating MAC the mean decrease (compared with CMR_{O_2} at <0.1 per cent) was 10 per cent and at concentrations of approximately twice MAC a 23 per cent decrease was observed. This differs from the effects of halothane in that with halothane the maximum decrease in CMR_{O_2} occurs at concentrations approximating MAC and little further reduction occurs with increasing concen-

trations.⁸ The effects of either anesthetic at concentrations greater than twice MAC have not been examined.

Methoxyflurane appears to have only a modest effect, not clearly dose-related, on the cerebral vasculature. Halothane, on the other hand, significantly decreases CVR, and this effect is dose-related. This difference is consistent with observations in man in that halothane is apparently capable of producing larger increases in CSF pressure than methoxyflurane, presumably a flow-related phenomenon.²

Contrary to our observations, Gray and associates¹ reported that methoxyflurane decreases CBF in the dog and that this effect is dose-related. Such divergent results must be related to differences in methodology. As previously reported by Raichle and associates⁹ and as demonstrated by us in a previous study,⁴ and again in the present study, CBF in an immobile, paralyzed, ventilated dog tends to decrease progressively with time. This might be explained by gradual vasoconstriction following a vasodilatory response to the initial surgical manipulation. If allowance for this effect is not made either by a correction factor or by varying the sequence of events studied, a systematic error will be introduced. In the study by Gray and associates, methoxyflurane was always the second agent studied, and presumably the observed decrease in CBF was magnified by the effect of time. In addition, body temperatures decreased in most of their dogs following introduction of methoxyflurane. When corrections for both of these factors are applied to their data, an effect of methoxyflurane on CBF is not apparent. In our study, 0.25 per cent expired methoxyflurane was the control circumstance and concentrations thereafter were either increased or decreased. Regardless of the sequence, the CBF following control always decreased. When these observations are

corrected for the effect of time, it is apparent that increasing concentrations did not, *per se*, alter CBF, whereas decreasing concentrations did appear to cause small decreases in CBF. However, if accurate correction for the effect of time were possible, the differences probably would not be significant. Thus, when all of these factors are considered, the evidence from both this study and that by Gray and associates supports the conclusion that methoxyflurane has little effect on the cerebral vasculature of the dog. Finally, methoxyflurane, like halothane, does not alter the responses of the cerebral vasculature to changes in PaCO₂.

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