DEPRESSION OF HYPOXIC VENTILATORY RESPONSE BY HALOTHANE, ENFLURANE AND ISOFLURANE IN DOGS

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SUMMARY

The ventilatory responses to isocapnic hypoxia and hypercapnia were studied in six dogs each with a tracheostomy, awake and during anaesthesia with halothane, enflurane and isoflurane (1–2.5 MAC). Isocapnic hypoxic ventilatory response (HVR) was expressed as the parameter $A$, such that the greater the value of $A$, the greater the hypoxic response. In the anaesthetized dogs HVR ($A$) was reduced significantly from the awake value of $2010 \pm 172$ (mean + SEM) to $630 \pm 173$ by 1 MAC halothane, $495 \pm 105$ by 1 MAC enflurane and $952 \pm 157$ by 1 MAC isoflurane ($P < 0.05$). All three anaesthetic agents produced significant depression of HVR at 1 MAC, but enflurane was more depressant than isoflurane. At 1.5 MAC all three anaesthetics produced equal and significant depression of HVR at equianalgesic concentrations. Further increases in anaesthetic concentration caused no increase in depression. Hypercapnic drive, as measured by the slope of the $Ve/Paco_2$ response curve, was reduced significantly from $9.75 \text{ litre min}^{-1} \text{ kPa}^{-1} \pm 2.4$ in awake dogs to $0.83 \pm 0.56$ after 1 MAC halothane, $0.68 \pm 0.53$ after 1 MAC enflurane and $1.58 \pm 0.75$ after 1 MAC isoflurane. In addition, hypercapnia-induced augmentation of the hypoxic drive was abolished by 1 MAC halothane or enflurane and diminished markedly by 1 MAC isoflurane.

It may be clinically significant that hypoxia and hypercapnia during anaesthesia with these agents did not produce optimal stimulation of ventilation.

The ventilatory response to carbon dioxide is depressed during anaesthesia in both man and dog (Dunbar, Ovassapian and Smith, 1966; Munson et al., 1966; Larson et al., 1969; Muallem, Larson and Eger, 1969; Fourcade et al., 1971). The ventilatory response to hypoxia has been thought to be unaffected by anaesthetic drugs (Wylie and Churchill-Davidson, 1972), although evidence to the contrary is accumulating (Weiskopf, Raymond and Severinghaus, 1974; Hirshman et al., 1975). Weiskopf and others showed that 1.1% halothane was a potent depressant of the ventilatory response to hypoxia in three dogs, and we have shown previously that pentobarbitone and thiopentone anaesthesia depress the hypoxic ventilatory response while ketamine does not. It is not known whether enflurane and isoflurane also depress the ventilatory response to hypoxia, whether the depression by halothane is dose-dependent, and what the relative degree of respiratory depression is produced by equianalgesic concentrations of halothane, enflurane and isoflurane. Accordingly, we studied the effect of 1–2.5 MAC halothane, enflurane and isoflurane on hypoxic and hypercapnic ventilatory responses (HVR and HCVR) in six dogs. In addition, the hypoxic drive was measured at several levels of hypocapnia and hypercapnia to assess the interaction of carbon dioxide and hypoxia.

METHODS

Six mongrel dogs (four male and two female) weighing in the range 20–25 kg were prepared with a chronic tracheostomy and trained to lie quietly without panting during the awake studies. The dogs breathed through a cuffed tracheostomy tube attached to a non-rebreathing Rudolph valve (Collins). Details of the technique used for measurement of hypoxic ventilatory response (Weil et al., 1970; Hirshman et al., 1975) have been published elsewhere, but a brief description of the technique is given here. The dogs breathed 40% oxygen to which nitrogen was added gradually, such that $P_{A_o_2}$ was decreased gradually to 5.3 kPa over 20 min. The end-tidal gases (oxygen, carbon dioxide and anaesthetic concentration) were measured with a mass spectrometer (Finnigan, model 100). Ventilation was monitored continuously by a pneumotachograph (Fleisch). Hypocapnia was maintained by the addition of carbon dioxide to the inspired air. End-tidal gas tensions were assumed to equal alveolar gas tensions. The
output from the analysers, with information from the pneumotachograph, were fed into an on-line Nova 1200 computer. The data emerged as continuous real-time oscilloscopic plots of end-tidal oxygen tension, carbon dioxide tension and minute ventilation.

The plots of ventilation in relation to $P_{ACO_2}$ are hyperbolic. To compare curves the following equation relating ventilation and alveolar $P_{O_2}$ was used (Weil et al., 1970; Hirshman et al., 1975):

$$V_E = V_O + \frac{A}{P_{O_2} - 3.5}$$

where $V_E$ is minute ventilation (litre min$^{-1}$), $V_O$ is the value for ventilation extrapolated to an infinitely great $P_{O_2}$ ($x$ asymptote); 26 is the $y$ asymptote. The parameter $A$ describes the shape of the curve such that the greater the value for $A$ the greater the ventilatory response to hypoxia. The curve-fitting procedure and evaluation of parameters are computed by a least-squares regression plot of $V_E$ against $1/(P_{O_2} - 3.5)$.

The ventilatory response to carbon dioxide was measured by a rebreathing method similar to that of Read (1966). While the end-tidal carbon dioxide and oxygen tensions, anaesthetic concentration and minute ventilation were monitored continuously, the dog breathed 40% oxygen in a closed system over 10-15 min, resulting in a gradual increase in $P_{ACO_2}$ of 10-15 kPa. Over the first few minutes, no data were recorded while rebreathing caused the inspired carbon dioxide concentration to increase to approximately 4%, at which time changes in tidal volume had little effect on $P_{ACO_2}$ ("closed-loop conditions"). The relationship between $P_{ACO_2}$ and minute ventilation was linear and the data were analysed by a least-squares regression. The equation used to relate ventilation and $P_{ACO_2}$ is $V_E = S (P_{ACO_2} - B)$ where $B$ is the extrapolated intercept on the abscissa ($P_{ACO_2}$ axis) and $S$ is the slope of the line expressed as change in ventilation per unit change in $P_{ACO_2}$.

Resting ventilation ($V_E$) was measured directly at $P_{O_2}$ 13.3 kPa at normocarbia.

Halothane, enflurane and isoflurane were administered in air via the tracheostomy tube. An inhalation induction of anaesthesia was carried out and the dogs breathed spontaneously for 2 h before the study to allow for equilibration of the partial pressure of the anaesthetic in the brain and in the arterial blood. End-tidal anaesthetic concentrations were monitored continuously with a mass spectrometer. Studies were performed at 1, 1.5, 2 and, in some cases, 2.5 MAC anaesthetic concentration (Eger, 1974) in random order with respect to concentration and drug.

In awake dogs and at 1 MAC and 1.5 MAC anaesthetic concentrations, hypoxic response studies were performed at hypocapnia and hypercapnia and at isocapnia also, to evaluate the interaction of oxygen and carbon dioxide. Only one agent was studied in any dog on any one day. At least 2 weeks elapsed between successive studies on any one animal. No premedication was used. The MAC value of halothane used was 0.87% (Eger et al., 1965), enflurane 2.2% (Eger et al., 1969) and isoflurane 1.6% (E. I. Eger, personal communication).

In the anaesthetized dogs, e.g. e.g. and rectal temperature were monitored continuously. Temperature was maintained at 37–38 °C.

| TABLE I. Effect of three agents on hyperoxic minute ventilation, $V_E$ and $P_{ACO_2}$ (there is no difference in $V_E$ or in $P_{ACO_2}$ awake or during anaesthesia with the three agents) |
|----------------|----------------|----------------|----------------|----------------|
|               | Awake          | Halothane      | Enflurane      | Isoflurane     |
|               | $V_E$ (litre min$^{-1}$) | $P_{ACO_2}$ (kPa) | $V_E$ (litre min$^{-1}$) | $P_{ACO_2}$ (kPa) | $V_E$ (litre min$^{-1}$) | $P_{ACO_2}$ (kPa) | $V_E$ (litre min$^{-1}$) | $P_{ACO_2}$ (kPa) |
| Dog           |                |                |                |                |                |                |                |
| 1             | 2.18           | 5              | 2.12           | 4.3            | 5.35           | 6.3            | 3.95           | 6.1            |
| 2             | 2.57           | 5.6            | 2.52           | 5.9            | 2.14           | 6.0            | 2.13           | 6.0            |
| 3             | 3.69           | 4.5            | 4.78           | 5.2            | 4.46           | 5.2            | 4.58           | 6.0            |
| 4             | 5.83           | 5              | 1.49           | 5              | 2.51           | 5.7            | 3.14           | 4.4            |
| 5             | 1.81           | 5              | 3.30           | 5.5            | 2.13           | 5.7            | 2.79           | 4.3            |
| 6             | 2.23           | 4.5            |                |                | 2.28           | 5.5            | 4.46           | 4.3            |
| Mean          | 3.08           | 4.9            | 2.84           | 5.2            | 3.35           | 6.0            | 3.51           | 5.2            |
| SEM           | ±0.62          | ±0.13          | ±0.57          | ±0.13          | ±0.65          | ±0.13          | ±0.40          | ±0.13          |
The effects of the three anaesthetic agents on the hypoxic response, hypercapnic response, $P_{A\text{CO}_2}$ and hyperoxic minute ventilation were compared with the awake control values and with each other by a two-way analysis of variance (Dixon and Massey, 1969) and the Scheffe test for multiple comparisons (Scheffe, 1969). For the plots of $A$ versus $P_{A\text{CO}_2}$ lines were drawn through the data points using the reduced major axis method of Kermack and Haldane (1950). The level of statistical significance used was 0.05 throughout.

**RESULTS**

Minute ventilation and end-tidal carbon dioxide were not significantly affected by 1 MAC halothane, enflurane and isoflurane (table I). At 2 MAC all three anaesthetics resulted in significant increases in $P_{A\text{CO}_2}$. $P_{A\text{CO}_2}$ was increased from an awake value of 5.0±0.13 kPa to 6.0±0.27 kPa by halothane, 7.0±0.4 kPa by enflurane and 6.0±0.4 kPa by isoflurane.

The effects of the three anaesthetic agents on the hypoxic response, hypercapnic response, $P_{A\text{CO}_2}$ and hyperoxic minute ventilation were compared with the awake control values and with each other by a two-way analysis of variance (Dixon and Massey, 1969) and the Scheffe test for multiple comparisons (Scheffe, 1969). For the plots of $A$ versus $P_{A\text{CO}_2}$ lines were drawn through the data points using the reduced major axis method of Kermack and Haldane (1950). The level of statistical significance used was 0.05 throughout.

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Results of the studies on the ventilatory response to hypoxia as measured by the shape parameter $A$ are presented in table II and figure 1. Relative to the awake state ($A = 2010 ± 172$) (mean± SEM), all three anaesthetic agents produced significant depression of the hypoxic ventilatory drive at 1 MAC. Enflurane produced the greatest depression ($A = 495 ± 105$), halothane less depression ($A = 630 ± 172$) and isoflurane least depression ($A = 952 ± 157$).

Dose–response curves of anaesthetic concentration versus hypoxic ventilatory response are shown in figure 2. During halothane and enflurane anaesthesia increases in anaesthetic concentrations above 1 MAC resulted in no further depression. During isoflurane anaesthesia maximal depression of HVR occurred at 1.5 MAC. At 1.5 MAC all three anaesthetic agents produced equal depression of the ventilatory response to hypoxia.

The ventilatory response to carbon dioxide in one dog is presented in figure 3. At 1 MAC all three drugs produced significant depression of the ventilatory response to carbon dioxide as measured by $S$, the slope of the $\dot{V}E/P_{A\text{CO}_2}$ response curve. In awake dogs $S$ was $9.8 ± 2.4$ litre min$^{-1}$ kPa$^{-1}$ and was decreased to $0.83 ± 0.56$ litre min$^{-1}$ kPa$^{-1}$ by 1 MAC halothane, $0.68 ± 0.23$ litre min$^{-1}$ kPa$^{-1}$ by 1 MAC enflurane and $1.58 ± 0.75$ litre min$^{-1}$ kPa$^{-1}$ by 1 MAC isoflurane.
Fig. 2. Comparison of dose-response curves for enflurane, halothane and isoflurane. Increasing concentrations of halothane and enflurane above 1 MAC and isoflurane above 1.5 MAC result in no further depression of HVR.

Fig. 3. Depression of the ventilatory response to carbon dioxide by isoflurane, halothane and enflurane in a dog.

In the awake dog, increasing the value of $P_{\text{ACO}_2}$ at which HVR is measured increased markedly the ventilatory response to hypoxia. Conversely, decreasing the $P_{\text{ACO}_2}$ depressed the hypoxic response. In figure 4, this oxygen/carbon dioxide interaction is depicted by plotting the hypoxic response ($A$) against the carbon dioxide tension at which the study was performed. The interaction was depressed by isoflurane (1 MAC) and abolished by 1 MAC halothane and enfurane. Isoflurane (1.5 MAC) also abolished the oxygen/carbon dioxide interaction.

Fig. 4. Depression of oxygen/carbon dioxide interaction by 1 MAC halothane, enfurane and isoflurane.

Enflurane produced seizures in dog no. 6 preventing measurement of HVR. Dog no. 7 developed ventricular arrhythmia during halothane anaesthesia which was abolished by atropine; because atropine increases deadspace and because its effect on HVR is not known, the study was discontinued.

DISCUSSION

End-tidal gas concentrations were measured throughout the study. The end-tidal anaesthetic partial pressure has been shown to be a reasonable estimate of the arterial anaesthetic partial pressure when the inspired-to-alveolar anaesthetic difference is small (Eger and Bahlman, 1971).
HYPOXIC VENTILATORY RESPONSE

End-tidal, not arterial, oxygen and carbon dioxide tensions were measured because it has previously been shown by us (Hirshman et al., 1975) that $A$ values resulting from plotting $\dot{V}_E, P_{A\text{O}_2}$ and $P_{A\text{CO}_2}$ were not significantly different during anaesthesia. Moreover, our HVR curves for halothane are similar to those of Weiskopf, Raymond and Severinghaus (1974) who plotted arterial oxygen tensions against ventilation.

Resting ventilation during anaesthesia with 2 MAC halothane, enflurane and isoflurane was depressed as shown by the increase in $P_{A\text{CO}_2}$. This is in agreement with the studies of others in man (Munson et al., 1966; Fourcade et al., 1971).

The ventilatory response to hypoxia is depressed markedly by enflurane, isoflurane and halothane in concentrations used clinically. The data obtained for halothane are in agreement with that of Weiskopf, Raymond and Severinghaus (1974), although they studied only one concentration. Cullen and Eger (1970) examined the ventilatory response to hypoxia during halothane anaesthesia in dogs; however, the dogs were not studied awake, nor was carbon dioxide maintained constant during hypoxia. To our knowledge no studies of hypoxic ventilatory response during enflurane and isoflurane anaesthesia have been reported. Isoflurane 1 MAC is significantly less depressant to HVR than enflurane 1 MAC. We have no explanation for this difference; nor can we explain why anaesthetic concentrations greater than 1 MAC halothane and enflurane and 1.5 MAC isoflurane resulted in no further depression. It is possible that the MAC value of isoflurane is incorrect and all three anaesthetic agents behaved similarly. On the other hand, if Eger's data on the isoflurane MAC are indeed correct, there is a real difference between anaesthetic drugs with respect to hypoxic ventilatory response.

All general anaesthetic agents studied depress the ventilatory response to carbon dioxide as measured by the slope of $\dot{V}_E v. P_{A\text{CO}_2}$ (Dunbar, Ovassapian and Smith, 1966; Munson et al., 1966; Larson et al., 1969; Muallem, Larson and Eger, 1969; Fourcade et al., 1971; Weiskopf, Raymond and Severinghaus, 1974; Hirshman et al., 1975). Our data confirm this for halothane and isoflurane and add enflurane to the list.

Hypoxia and hypercapnia interact in driving respiration (Hornbein, Griffe and Roos, 1961). The slope of the line obtained by plotting the hypoxic response, as measured by $A$, against the value of $P_{A\text{CO}_2}$ at which the study was performed is very steep in the awake state. This augmentation of the hypoxic response by carbon dioxide was blunted markedly by 1 MAC isoflurane and abolished by 1 MAC halothane and isoflurane, as shown by the negative slope of the plot of $A v. P_{A\text{CO}_2}$. Moreover, 1.5 MAC isoflurane abolished this interaction.

The ventilatory response to hypoxia is depressed at least as much as the ventilatory response to carbon dioxide by clinical concentrations of halothane, enflurane and isoflurane. In addition, these anaesthetic agents substantially eliminate augmentation of the hypoxic response by carbon dioxide. These studies in the dog may not apply to man, but in the absence of contrary evidence one may assume that hypoxia during anaesthesia may not stimulate ventilation, and moreover hypoxia during anaesthesia in the presence of increased carbon dioxide values may actually depress ventilation.

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REFERENCES


Les réactions ventilatoires à l'hypoxie isocapnique et à l'hypercapnie ont été étudiées sur six chiens ayant subi une trachéotomie chronique, élevées et sous anesthésie par l'halothane, l'enflurane et l'isoflurane (concentration alvéolaire minimale (MAC) 1-2,5). La réaction ventilatoire hypoxique isocapnique (HVR) a été exprimée sous la forme de paramètre A, de telle manière que plus la valeur de A est forte, plus la réaction hypoxique est grande. Sur les chiens anesthésiés, la HVR (A) a été réduite d'une manière significative par rapport aux valeurs des chiens élevés de 2010 ± 172 (moyenne ± moyenne des erreurs types) à 630 ± 173 par 1 MAC d'halothane, à 495 ± 105 par 1 MAC d'enflurane et à 952 ± 157 par 1 MAC d'isoflurane; (P < 0,05). Ces trois agents anesthésiants ont produit une dépression significative de la HVR à 1 MAC, mais l'enflurane a été plus déprimante que l'isoflurane. A 1,5 MAC, ces trois agents anesthésiants ont produit une dépression égale et significative de la HVR à des concentrations équivalant à la concentration alvéolaire minimale (MAC) 1-2,5. Les autres augmentations de la concentration anesthésique n'ont provoqué aucune augmentation de la dépression. La pulson hypercapnique, tel qu'on l'a mesurée par la pente de la courbe de la réaction VE/Paco₂, a été réduite de manière significative de 9,75 1/min-kPa⁻¹ ± 2,4 par les chiens éveillés, à 0,83 ± 0,56 après 1 MAC d'halothane, à 0,68 ± 0,53 après 1 MAC d'enflurane et à 1,58 ± 0,75 après 1 MAC d'isoflurane. En outre, l'augmentation de la pulsion hypoxique provoquée par l'hypercapnie a été abolie par 1 MAC soit d'halothane soit d'enflurane et a diminué d'une manière sensible sous l'effet de 1 MAC d'isoflurane. Il peut être important du point de vue clinique de voir que l'hypoxie et l'hypercapnie pendant l'anesthésie par ces agents n'a pas produit de stimulation optimale de la ventilation.
significativa de la RVH a 1 CAM, pero el enfurano resultó más depresivo que isoflurano. A 1,5 CAM las tres anestesias produjeron una depresión igual y significativa de RVH en concentraciones equianalgésicas. Al aumentar las concentraciones de anestesia no se produjo un aumento en la depresión. El impulso hipercapnico, medido por la inclinación de la curva de respuesta de $\dot{V}E/\dot{P}A_{CO_2}$, fue reducido significativamente desde 9,75 l/min.kPa$^{-1}$ ± 2,4 en perros despiertos a 0,83 ± 0,56 después de 1 CAM halotano, 0,68 ± 0,53 después de 1 CAM enfurano y 1,58 ± 0,75 después de 1 CAM isoflurano. Además, un aumento de impulso hipoxico hipercapnicamente inducido fue eliminado tanto por 1 CAM de halotano como por uno de enfurano y disminuido considerablemente por 1 CAM de isoflurano. Podría ser clínicamente significativo que hipoxia e hipercapnia durante anestesia con estos agentes no produjo un estímulo óptimo de ventilación.