Comparison of the Ventilatory Effects of Etomidate and Methohexital

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Using a dual-isohypercapnic technique, the authors determined the effect of equipotent doses of methohexital (1.5 mg/kg) and etomidate (0.3 mg/kg) on the ventilatory response to CO₂ (V₆CO₂) in six healthy volunteers. Speed of induction and duration of hypnosis did not differ significantly between the two drugs. Within 2 min after injection, the slope of V₆CO₂ decreased significantly after both methohexital (from 2.52 to a minimum of 0.15 l·min⁻¹·mmHg⁻¹, P < 0.05) and etomidate (from 2.56 to a minimum of 0.62 l·min⁻¹·mmHg⁻¹, P < 0.05); the magnitude of this depression did not differ significantly between the drugs. Methohexital also caused a significant decrease in minute ventilation at end-tidal P₆CO₂ of 46 mmHg (V₆ 46) from 14.6 to 4.3 l·min⁻¹ within 60 s after injection (P < 0.05). In contrast, after etomidate V₆ 46 gradually increased from 17.9 l·min⁻¹ to a maximum of 31.6 l·min⁻¹ at 3.5 min after injection (P < 0.05); respiratory rate increased significantly, while changes in tidal volume were not significant. Effects of etomidate and methohexital on V₆ 46 differed significantly (P < 0.001). These data indicate that, while etomidate and methohexital similarly depress the medullary centers that modify ventilatory drive in response to changing CO₂ tensions, ventilation at any given CO₂ tension is greater after etomidate than after methohexital. This indicates that etomidate may cause a CO₂-independent stimulation of ventilation, suggesting its use for induction of anesthesia in cases where maintenance of spontaneous ventilation is desirable. (Key words: Anesthetics, intravenous: etomidate; methohexital. Carbon dioxide: ventilation response. Ventilation: carbon dioxide response.)

ETOMIDATE, an imidazole-derived hypnotic agent, is an alternative to the ultrashort-acting barbiturates for induction of general anesthesia. Although etomidate has been available in Europe for a number of years, it only recently has been released for clinical use in the United States. Advantages of etomidate include rapid induction of anesthesia, cardiovascular stability,¹,² and short duration of action.³ Previous studies suggest that etomidate may cause less ventilatory depression than other commonly used induction agents. However, these results are difficult to interpret for a variety of reasons. Before most of the studies, subjects received sedative or narcotic premedication; furthermore, ventilatory depression was assessed only by changes in respiratory rate or the occurrence of apnea.⁴⁻⁷ Colvin et al. found that P₆CO₂ increased after etomidate induction, despite an increase in respiratory rate; however, they did not measure minute ventilation, and their subjects had received narcotic premedication.⁸ Kay showed that small doses of etomidate (0.067 mg/kg) depressed mouth occlusion pressures less than equivalent doses of methohexital (0.5 mg/kg); however, his subjects were anesthetized with enflurane at the time of drug injection, and CO₂ tensions varied during the measurements.⁹

In this study, we used the previously described dual-isohypercapnic technique¹⁰ to determine the time course of the ventilatory response to CO₂ (V₆CO₂) after an induction dose of etomidate. For comparison, we also studied the time course of V₆CO₂ after methohexital induction.

Methods

Six healthy male volunteers, ranging in age from 27 to 33 yr and in weight from 66 to 97 kg, consented to participate in this study, which was approved by our Institutional Review Board. Subjects abstained from alcohol and caffeine for 24 h and took nothing by mouth for at least 8 h prior to the beginning of the study. After inserting an 18-G catheter into an antecubital vein, we started an infusion of 0.9% NaCl, affixed ECG and blood pressure (oscillogonometer) monitors, and administered glycopyrrolate 0.2 mg iv to each subject. Throughout the study, subjects listened to symphonic music through occlusive headphones to minimize external stimuli.

The supine subjects breathed mixtures of CO₂ in O₂ through an anesthesia mask incorporated in the circuit shown in figure 1; the resistance of this system is 0.02 cmH₂O·l⁻¹·min⁻¹ at a flow of 100 l·min⁻¹. An Instrumentation Laboratory End-tidill 200° CO₂ analyzer, calibrated with three reference mixtures of CO₂ in O₂ (previously standardized by microcholander analysis) measured P₆CO₂. Ventilation was measured by an

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Electro/med® #780 dry spirometer calibrated with a 2-L calibrating syringe; a Yellow Springs® 400 series thermistor monitored the temperature of the bag-in-box assembly. A multichannel analog-to-digital converter (Connecticut Microcomputer® AIM-16) served to interface the CO₂ and volume signals to a CBM 8032® computer.

After allowing 8 min for CO₂ tension to equilibrate at either 46 or 58 mmHg for alternate subjects, we administered either methohexital 1.5 mg/kg or etomidate 0.3 mg/kg iv (determined by a randomization table) over 15 s. For the next 15 min, we performed breath-by-breath measurement of \( V_E \) and \( P_{ET}CO_2 \) while adjusting the flow of the gas through the CO₂ absorber to maintain \( P_{ET}CO_2 \) within 2.0 mmHg of the desired value, despite variations in subjects' ventilation. Small volumes of O₂ were added to the circuit to replace subjects' oxygen consumption and keep the gas volume of the circuit constant.

A minimum of 3 h later, when blood levels of the agents had declined to less than 5% of their peak values, the study sequence was repeated with the same induction agent and dose; this time, however, \( P_{ET}CO_2 \) was maintained at 58 or 46 mmHg, the value not studied earlier. Three or more days after his first study, each subject returned to be tested with the drug (etomidate or methohexital) that was not administered on the first study day. At the end of each study session, subjects were transferred to the recovery room and observed until fully awake.

After injection of each study drug, we assessed subjects' level of consciousness at frequent intervals to determine the time to loss of responsiveness to verbal stimuli and the duration of unconsciousness. We also noted the incidence of pain or burning on injection, myoclonic movements, and hiccoughs associated with each induction agent.

Using standard formulas, we adjusted ventilatory volumes to BTPS and corrected gas tensions for ambient barometric pressure. We then computed five-breath averages of \( V_E \), \( P_{ET}CO_2 \), respiratory rate (RR), and tidal volume (Vₜ) at 30-s intervals after each drug injection. From these data, we constructed hyperoxic CO₂ ventilatory response curves (\( V_ERCO_2 \)) at 30-s intervals for the first 5 min and at longer intervals for an additional 10 min. Representative curves appear in figure 2. The slope of \( V_ERCO_2 \) at each time after injection is given by the difference between \( V_E \) at high (≈58 mmHg) and low (≈46 mmHg) CO₂ tensions, divided by the difference between the measured \( P_{ET}CO_2 \) (≈12 mmHg). From the equation of each \( V_ERCO_2 \) line, we calculated \( V_E \) at a \( P_{ET}CO_2 \) of 46 mmHg (\( V_E \) 46), which served as an index of displacement of \( V_ERCO_2 \).

We used two-way analysis of variance and the protected least significant difference test to determine the significance of changes of slope, \( V_E \) 46, RR, and \( V_T \) after injection of each drug. To compare the effect of the two drugs on slope, \( V_E \) 46, RR (at \( P_{ET}CO_2 \) ≈ 46 mmHg), and \( V_T \) (at \( P_{ET}CO_2 \) ≈ 46 mmHg), we used...
three-way analysis of variance. Three-way analysis of variance also compared etomidate and methohexital for speed of induction and duration of anesthesia at low and high CO₂ tensions. Fisher’s exact test compared the incidence of side effects accompanying etomidate and methohexital induction.⁴ Throughout the analysis, values of $P < 0.05$ indicated statistical significance.

**Results**

The mean duration of unconsciousness after etomidate, (281 ± 20 s, $\bar{x}$ ± SEM) did not differ significantly from that after methohexital (247 ± 30 s). At low P₄CO₂ ($\approx 46$ mmHg) the mean duration of unconsciousness was $285 \pm 28$ s, which did not differ significantly from the $244 \pm 23$ s observed at high P₄CO₂ ($\approx 58$ mmHg). Induction time, measured from the beginning of drug injection to loss of consciousness, also did not differ significantly between etomidate (31 ± 3 s) and methohexital (31 ± 1 s). However, analysis of variance showed that mean induction time for both drugs was significantly shorter at high P₄CO₂ (29 ± 2 s) than at low P₄CO₂ (33 ± 2 s, $P < 0.005$).

Before injection of methohexital, the slope of $\dot{V}_E$RCO₂ was $2.52 \pm 0.26 \text{ l min}^{-1} \text{ mmHg}^{-1}$; it decreased significantly to a minimum of $0.15 \pm 0.50 \text{ l min}^{-1} \text{ mmHg}^{-1}$ 30 s after methohexital administration ($P < 0.05$) and returned to $1.68 \pm 0.32 \text{ l min}^{-1} \text{ mmHg}^{-1}$ within 5 min after injection (fig. 3). Fifteen minutes after methohexital, the slope was essentially the same as before induction ($2.45 \pm 0.33 \text{ l min}^{-1} \text{ mmHg}^{-1}$). Prior to etomidate administration, mean slope of the $\dot{V}_E$RCO₂ was $2.56 \pm 0.36 \text{ l min}^{-1} \text{ mmHg}^{-1}$; it decreased to a minimum of $0.62 \pm 0.58 \text{ l min}^{-1} \text{ mmHg}^{-1}$ 2 min after injection ($P < 0.05$). Slope returned to $1.64 \pm 0.56 \text{ l min}^{-1} \text{ mmHg}^{-1}$ 5 min after injection; by 15 min, slope was $2.47 \pm 0.36 \text{ l min}^{-1} \text{ mmHg}^{-1}$. The slope of $\dot{V}_E$RCO₂ decreased significantly after administration of both etomidate and methohexital; the effect of the two drugs on the slope of the $\dot{V}_E$RCO₂ did not differ significantly.

Before injection of methohexital, computed $\dot{V}_E$ at a CO₂ tension of 46 mmHg ($\dot{V}_E$ 46) was $14.6 \pm 3.3 \text{ l min}^{-1}$; it decreased significantly to a minimum of $4.3 \pm 9.0 \text{ l min}^{-1}$ 60 s after methohexital ($P < 0.05$) and returned to $10.7 \pm 5.8 \text{ l min}^{-1}$ 5 min after injection (fig. 4). At 15 min, $\dot{V}_E$ 46 was $9.9 \pm 2.4 \text{ l min}^{-1}$, which did not differ significantly from the preinduction value. Prior to etomidate administration, $\dot{V}_E$ 46 was $17.9 \pm 2.6 \text{ l min}^{-1}$; 3.5 min after injection, it had increased to a maximum of $31.6 \pm 6.8 \text{ l min}^{-1}$ ($P < 0.05$). Fifteen minutes after etomidate, $\dot{V}_E$ 46 had returned to $16.1 \pm 3.8 \text{ l min}^{-1}$, again similar to the preinjection value.

It is apparent from figure 4 that $\dot{V}_E$ 46 increased significantly after etomidate, while it decreased significantly after methohexital. The difference between the effect of the two drugs on $\dot{V}_E$ 46 was highly significant ($P < 0.001$). As shown in figure 5, respiratory rates (RR) were significantly greater after etomidate than after methohexital ($P < 0.005$). This increase in RR resulted in an increase in $\dot{V}_E$ 46, since tidal volumes ($V_T$) did not change significantly after etomidate (fig. 6). In contrast, methohexital caused a significant decrease in $V_T$, accounting for the decrease in $\dot{V}_E$ 46 observed after this agent.

The incidence of hiccoughs was significantly greater after methohexital (42% of injections) than after etomidate (0%, $P < 0.05$). Myoclonic movements, however, occurred more frequently after etomidate (58% of injections) than after methohexital (8%, $P < 0.01$). Incidence of pain on injection did not differ significantly between etomidate (33% of injections) and methohexital (8%).

![Graph showing CO₂ ventilatory response curves during the 15 min after injection of etomidate or methohexital. For purposes of clarity, the values shown in this and subsequent figures are means ± representative SEM (N = 6).](http://anesthesiology.pubs.asahq.org/pdfaccess.ashx?url=/data/journals/jasa/931412/ on 11/13/2018)
Discussion

Induction of anesthesia with either etomidate or methohexital decreases the slope of the ventilatory response to carbon dioxide ($V_{E}R_{CO_2}$); the magnitude of this depression does not differ significantly between the drugs. This indicates that the two agents have similar effects on the medullary centers, which modify ventilatory drive in response to changing CO$_2$ tensions.

In contrast, the effects of etomidate and methohexital on the displacement of the $V_{E}R_{CO_2}$ (expressed as the $V_{E}$ at 46 mmHg) differ significantly. While methohexital induction causes a downward shift of the $V_{E}R_{CO_2}$, etomidate induction is associated with a significant upward shift of this curve at physiologic CO$_2$ tensions (an alternative interpretation is "rotation" of the $V_{E}R_{CO_2}$ curve about a point in the first Cartesian quadrant). This implies that in addition to depressing the medullary responsiveness to added CO$_2$, etomidate directly stimulates ventilation in a manner that is independent of CO$_2$ tension. Of the intravenous induction agents that have been studied with the dual-isohypercapnic technique, etomidate is the only one that causes this upward shift in the $V_{E}R_{CO_2}$; methohexital, diazepam, midazolam, and thiopental all cause downward shifts.

Our results are consistent with those of previous investigators: after induction of anesthesia with etomidate, normocarbic ventilation is better maintained than after induction with a barbiturate. The present study indicates, however, that etomidate depresses medullary CO$_2$ responsiveness as much as does methohexital. Thus, etomidate appears to stimulate ventilation by an alternate, CO$_2$-independent mechanism.

The CO$_2$-independent ventilatory stimulation caused by etomidate is strikingly similar to that observed during anesthesia with diethyl ether. Larson et al. demonstrated that although 5.4% diethyl ether causes a 68% decrease in the slope of the $V_{E}R_{CO_2}$, ventilation at low CO$_2$...
tensions is maintained. This finding contrasts with the downward displacement of the $\dot{V}_E$CO$_2$, which they observed during methoxyflurane anesthesia. In a companion study, the same investigators demonstrated that diethyl ether's stimulation of ventilation at low CO$_2$ tensions was not mediated by the vagus nerves, carotid bodies, pharyngeal or chest wall receptors, or cerebrospinal fluid pH changes. They therefore concluded that, in addition to depressing those medullary centers responsible for the ventilatory response to CO$_2$, ether directly stimulates those centers responsible for maintenance of basal ventilation. The exact site of this action, however, remains unknown.

Our conclusion that the ventilatory effects of methohexital and etomidate differ significantly assumes that we administered equivalent doses of the two drugs. We attempted to validate this by analyzing the time to induction of anesthesia and duration of anesthesia after injection of each agent; had the dose of one of the drugs been significantly "more hypnotic" than the dose of the other, we would have expected a more rapid onset or longer duration of anesthesia with that agent. Since neither of these variables differed significantly between the two drugs, it seems that our doses of methohexital and etomidate were approximately equivalent.

The dual isohypercapnic technique assumes that the time course of drug effect on the central nervous system is independent of inhaled CO$_2$ tension. This hypothesis recently has been questioned by Roy, who suggested that the augmented cerebral blood flow accompanying elevated CO$_2$ tensions increases the rate of delivery and removal of anesthetics from the central nervous system. This would cause the dual-isohypercapnic technique to overestimate slightly the degree of slope depression during the induction phase while underestimating the degree of slope depression during the recovery phase.

In fact, induction of anesthesia with both agents was slightly but significantly more rapid when $P_{ET}$CO$_2$ was elevated. The magnitude of this difference, however, was only 4 s; because our calculations were based on five-breath averages of $\dot{V}_E$ and $P_{ET}$CO$_2$, it is unlikely that this difference significantly affected our results. The absence of a significant difference in duration of anesthesia at the two CO$_2$ tensions indicates that our measurements accurately reflect ventilatory depression during emergence from anesthesia.

Because normocarbic ventilation is better maintained after etomidate than after barbiturates, etomidate is a logical choice for induction of anesthesia in cases where spontaneous ventilation is desired. However, the anesthesiologist must be aware of the fact that CO$_2$ sensitivity is no better preserved after etomidate than after other induction agents.

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References