Title: CO_2-INDEPENDENT VENTILATORY STIMULATION FOLLOWING ETOMIDATE INDUCTION

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Introduction: Previous studies suggest that etomidate, an imidazole-derived hypnotic agent, causes less ventilatory depression than the barbiturates (1). These results are difficult to interpret because subjects were premedicated with narcotics, end-tidal CO_2 tensions were not controlled, and ventilation was assessed only in terms of respiratory rate. In this study, we used the dual-isohypercapnic technique (2) to assess the ventilatory response to CO_2 after etomidate and methohexital in unpremedicated volunteers.

Methods: Six healthy males, ranging in age from 27 to 33 yr, consented to participate in this institutionally-approved study. Supine subjects breathed mixtures of CO_2 in O_2 from a spirometer circuit with variable CO_2 absorption. After 8 min of equilibriation at $P_{ET}CO_2 \approx 46$ or 58 mmHg for alternate subjects, we administered etomidate 0.3 mg/kg or methohexital 1.5 mg/kg i.v. We then performed breath-by-breath measurements of $\dot{V}_E$ and $P_{ET}CO_2$ while adjusting CO_2 absorption to maintain a constant $P_{ET}CO_2$. After a 3 h recovery period, the study was repeated with the same drug at the other $P_{ET}CO_2$ (58 or 46 mmHg). Subjects' level of consciousness was assessed continuously after each induction. Three or more days later, subjects returned to be tested with the other drug. After adjusting ventilatory volumes to BTPS, we constructed each subject's hyperoxic CO_2 ventilatory response curve ($\dot{V}_ERCO_2$) at 30-s intervals after each drug. From these curves, we computed the slope and $\dot{V}_E$ at $P_{ET}CO_2 = 46$ mmHg ($\dot{V}_E46$). Two-way analysis of variance and the PSD test assessed the significance of observed changes in slope and $\dot{V}_E46$ after each drug; three-way analysis of variance compared the effects of etomidate and methohexital on slope, $\dot{V}_E46$, induction time, and duration of anesthesia. $P<0.05$ indicated statistical significance.

Results: Induction time and duration of unconsciousness did not differ significantly between etomidate and methohexital. After methohexital, the slope of $\dot{V}_ERCO_2$ fell from 2.52 to a minimum of 0.15 $l \cdot min^{-1} \cdot mmHg^{-1}$ ($P<0.05$) within 30 s, and returned to 1.68 $l \cdot min^{-1} \cdot mmHg^{-1}$ 5 min after injection (Figure 1). After etomidate, the slope fell from 2.56 to a minimum of 0.62 $l \cdot min^{-1} \cdot mmHg^{-1}$ ($P<0.05$) within 2 min, returning to 1.64 $l \cdot min^{-1} \cdot mmHg^{-1}$ 5 min after injection. Slope depression did not differ significantly between the drugs. After methohexital, $\dot{V}_E46$ decreased from 14.6 to 4.3 $l \cdot min^{-1}$ within 60 s ($P<0.05$), returning to 10.7 $l \cdot min^{-1}$ 15 min after injection (Figure 2). In contrast, after etomidate, $\dot{V}_E46$ increased from 17.9 to a maximum of 31.6 $l \cdot min^{-1}$ ($P<0.05$) 3.5 min after injection, returning to 16.1 $l \cdot min^{-1}$ 15 min after injection. The effects of etomidate and methohexital on $\dot{V}_E46$ differed significantly ($P<0.001$).

Discussion: The absence of significant differences in induction time and duration of hypnosis between etomidate and methohexital verifies that doses of the drugs we studied were equivalent. The significant but similar depression of the slope of $\dot{V}_ERCO_2$ after etomidate and methohexital indicates that the two agents may have similar effects on the medullary centers which modify ventilatory drive in response to changing CO_2 tensions. However, the increase in $\dot{V}_E46$ observed after etomidate indicates that, in contrast to methohexital, etomidate causes a CO_2-independent stimulation of ventilation. This stimulation is strikingly similar to that observed during anesthesia with diethyl ether (3): although 5.4% ether causes a 68% depression of the slope of $\dot{V}_ERCO_2$, ventilation at normal CO_2 tensions is maintained or increased. The exact site of this action is not known. Because normocarbic ventilation is better maintained after etomidate than after methohexital, etomidate is a better induction agent for cases where spontaneous ventilation is desirable. However, CO_2 sensitivity is no better preserved after etomidate than after methohexital.

References:

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3. Larson CP. Eger EI, et al: The effects of diethyl ether and methoxyflurane on ventilation. Anesthesiology 30:174-184, 1969

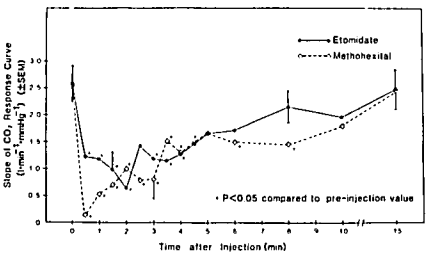

Figure 1: Slope of $\dot{V}_ERCO_2$ after etomidate and methohexital

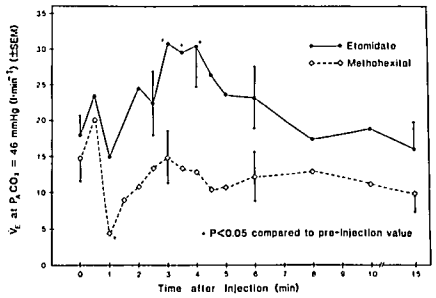

Figure 2: $\dot{V}_E46$ after etomidate and methohexital