Time Course of Ventilatory Depression Following Induction Doses of Propofol and Thiopental

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To improve our understanding of the respiratory pharmacology of intravenous induction agents, the authors compared the acute effects of intravenous (iv) propofol 2.5 mg·kg^{-1} and iv thiopental 4.0 mg·kg^{-1} on the ventilatory response to CO_2 ($\dot{V}ER_{CO_2}$) of eight healthy volunteers. The slope of $\dot{V}ER_{CO_2}$ decreased from 1.75 ± 0.23 to a minimum of 0.77 ± 0.14 l·min^{-1}·mmHg^{-1} (mean ± standard error) 90 s after propofol; similarly, the slope of $\dot{V}ER_{CO_2}$ decreased from 1.79 ± 0.22 to a minimum of 0.78 ± 0.23 l·min^{-1}·mmHg^{-1} 30 s after thiopental. For both drugs, the slope was less than control in the 0.5–5-min period after injection ($P < 0.05$). The slope returned to baseline within 6 min after thiopental; in contrast, after propofol, the slope remained less than control for the entire 20-min follow-up period ($P < 0.05$ at 6–10, 11–15, and 16–20 min after injection). Also, from 6–10, 11–15, and 16–20 min after injection, the slope was less after propofol than at corresponding times after thiopental ($P < 0.05$). Recovery of consciousness was approximately 4 min slower after propofol than after thiopental; nonetheless, awareness scores returned to baseline within 14 min after both drugs. The authors conclude that propofol 2.5 mg·kg^{-1} iv produces longer-lasting depression of $\dot{V}ER_{CO_2}$ than a 4.0 mg·kg^{-1} iv dose of thiopental; after propofol, ventilatory depression may persist despite apparently complete recovery of consciousness. (Key words: Anesthetics, intravenous: propofol; thiopental. Carbon dioxide: ventilatory response; hypercarbia. Lungs, ventilation: hypercapnic drive.)

PROPOFOL (2,6 di-isopropyl phenol), a rapidly acting intravenous hypnotic, is an alternative to the ultrashort-acting barbiturates for induction of general anesthesia. Induction of anesthesia with propofol (2.0–2.5 mg·kg^{-1}) frequently causes apnea that may last 60 s or more.[1]§ Taylor et al.,[2] and Grounds et al.[3] found that minute ventilation ($\dot{V}E$) decreases for 2–4 min after injection of propofol 2.5 mg·kg^{-1}; this effect is similar to that of thiopental 4 mg·kg^{-1}. However, these studies did not determine the effect of induction of anesthesia with propofol on the ventilatory response to CO_2 ($\dot{V}ER_{CO_2}$). Previous studies of the effect of propofol on hypercapnic ventilatory drive have been performed during propofol infusion because of methodologic limitations; these studies have been

inconclusive, showing either a decrease[4] or no change[5] in the slope of the $\dot{V}ER_{CO_2}$ curve in unpremedicated individuals. In the present study, we used the previously described dual-isohypercapnic technique[6] to determine the time course of $\dot{V}ER_{CO_2}$ after induction doses of propofol and to compare the acute ventilatory effects of propofol with those of thiopental.

Materials and Methods

Nine healthy male volunteers, 19–30 yr of age and weighing 67–90 kg, consented to participate in this study, which was approved by our Institutional Review Board. In preparation for the study, subjects abstained from alcohol and caffeine for 24 h and took nothing by mouth for at least 8 h prior to each of two study days. After inserting a 22-G catheter in a hand vein, we started an infusion of lactated Ringer's solution and affixed electrocardiographic, pulse oximeter, and noninvasive blood pressure monitors; subjects received glycopyrrolate 0.2 mg intravenously to reduce oral secretions. To minimize external auditory stimulation, subjects listened to soft orchestral music through headphones during the ventilatory measurements.

The supine subjects breathed a mixture of CO_2 in O_2 through an anesthesia mask incorporated in a rebreathing circuit with variable CO_2 absorption[7]; the resistance of this system is 0.03 cmH$_2$O·l^{-1}·min at a flow of 100 l·min^{-1}. An Instrumentation Laboratory End-tidIL 200® CO_2 analyzer, calibrated with three reference mixtures of CO_2 in O_2 (Linde® primary standard grade ± 0.01%), measured end-tidal CO_2 tension (PET$_{CO_2}$). Ventilation was measured by a Hans Rudolf® 3700 heated pneumotachograph, a Validyne® DP45 differential pressure transducer, and an electronic integrator; we performed a three-point volume calibration and linearity check before each set of measurements with a Collins® 3200 3-1 Supersyringe. A multichannel analog-to-digital converter (Connecticut Microcomputer® AIM-16) interfaced the CO_2 and volume signals to a Commodore Business Machines 8032® computer.

After allowing 8 min for PET$_{CO_2}$ to equilibrate at either 46 or 58 mmHg (chosen to lie on the linear portion of the $\dot{V}ER_{CO_2}$ curve[6]) for alternate subjects, we administered either sodium thiopental 4 mg·kg^{-1} or propofol 2.5 mg·kg^{-1} intravenously (determined by a randomization table) over 10 s. For the next 20 min, we performed breath-by-breath measurement of $\dot{V}E$ and PET$_{CO_2}$ while adjusting the flow of the gas through the CO_2 absorber

to maintain PET_{CO_2} within $\pm$ 1 mmHg of the desired value, despite variations in subjects' ventilation. Small volumes of O_2 ($\approx$ 300 ml·min^{-1}) were added to the circuit to replace subjects' O_2 consumption and to keep the gas volume of the circuit constant. After injection of each study drug, we assessed subjects' level of consciousness (table 1), at 1-min intervals for the first 10 min and at 2-min intervals thereafter.

A minimum of 4 h later, when blood levels of the agents had declined to less than 5% of their peak values,[8,9] the study sequence was repeated with the same induction agent and dose; this time, however, PET_{CO_2} was maintained at 58 or 46 mmHg, the value not studied earlier. Four or more days after his first study, each subject returned to be tested with the drug (propofol or thiopental) that was not administered on the first study day. At the end of each study session, subjects were observed until fully awake.

From the breath-by-breath data stored in the computer, we computed five-breath averages of $\dot{V}E$, PET_{CO_2}, respiratory rate and tidal volume at 30-s intervals after each drug injection. We used these data to construct $\dot{V}ER_{CO_2}$ curves at 30-s intervals for the first 5 min and at 1-min intervals for an additional 15 min. The slope of the $\dot{V}ER_{CO_2}$ at each time after injection is given by the difference between $\dot{V}E$ at high ($\approx$ 58 mmHg) and low ($\approx$ 46 mmHg) CO_2 tensions, divided by the difference between the measured values of PET_{CO_2} ($\approx$ 12 mmHg). Because it approximates normal mixed venous CO_2 tension, we used $\dot{V}E$ at PET_{CO_2} $\approx$ 46 mmHg ($\dot{V}E46$) as an index of the displacement of the ventilatory response curve, and we used tidal volume (V_T) and respiratory rate at PET_{CO_2} $\approx$ 46 mmHg to indicate changes in ventilatory pattern.

We analyzed data in five time periods: control (0 and 0.5 min prior to injection) and four 5-min time periods after injection (0.5–5, 6–10, 11–15, and 16–20 min). This enabled us to use repeated-measures analysis of variance followed by single degree-of-freedom contrasts to perform within-drug comparisons with corresponding control values, and to make between-drug comparisons within each period.[10] To analyze awareness scores, we used Bonferroni-corrected Kruskal-Wallis analysis of variance to detect differences between propofol and thiopental; Bonferroni-corrected Wilcoxon rank sums tests compared awareness scores after each drug with their predrug con-

TABLE 1. Definition of Awareness Scores

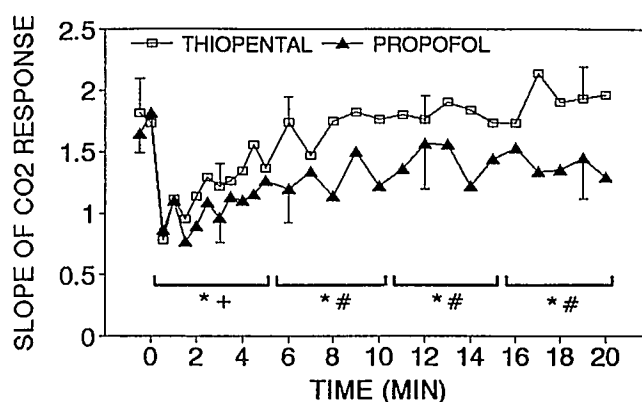| |
|---|
| 4 = Awake and alert |
| 3 = Drowsy with ptosis of eyelids |
| 2 = Asleep but awakens with verbal stimulation |
| 1 = Responds to tactile stimulation (tap on shoulder) |
| 0 = Unresponsive to verbal or tactile stimulation |

FIG. 1. Slope of ventilatory response to carbon dioxide (liters per minute per mmHg) following propofol and thiopental. Values are means $\pm$ representative SEM. *$P < 0.05$ versus preinjection value for propofol. †$P < 0.05$ versus preinjection value for thiopental. #$P < 0.05$ for propofol versus thiopental during the same time period.

trol values. Parametric results are expressed as means $\pm$ standard error, and awareness scores are expressed as medians; $P < 0.05$ indicates statistical significance.

Results

Eight of the nine volunteers completed the study protocol. One subject experienced uncontrollable agitation upon emergence from propofol anesthesia, with PET_{CO_2} $\approx$ 58 mmHg. Although this resolved promptly when the mask was removed, he was excluded from further study. The other eight subjects recovered uneventfully, and none of the subjects suffered any sequelae. Because of the preexisting hypercarbia subjects never became apneic after propofol or thiopental.

After the injection of thiopental, the slope of the $\dot{V}ER_{CO_2}$ decreased from 1.79 $\pm$ 0.22 to 0.78 $\pm$ 0.23 l·min^{-1}·mmHg^{-1} within 30 s (fig. 1, mean $\pm$ SEM). Similarly, after propofol, the slope of $\dot{V}ER_{CO_2}$ decreased from a baseline of 1.75 $\pm$ 0.23 to a minimum of 0.77 $\pm$ 0.14 l·min^{-1}·mmHg^{-1} at 90 s. After propofol, the slope of the $\dot{V}ER_{CO_2}$ remained significantly depressed ($P < 0.05$) during the four subsequent 5-min time periods. In contrast, the slope of the $\dot{V}ER_{CO_2}$ was significantly less than control only during the first 5-min period after thiopental injection. From 6–20 min after injection, the slope was significantly less after propofol than after thiopental.

Before administration of thiopental, the $\dot{V}E46$ was 16.7 $\pm$ 2.0 l·min^{-1}. It decreased to 7.1 $\pm$ 1.2 l·min^{-1} 60 s after injection and remained significantly depressed during the subsequent 15 min; $\dot{V}E46$ did not differ significantly from control in the 16–20 min time period (fig. 2). Thirty seconds after propofol, $\dot{V}E46$ increased from 16.6 $\pm$ 2.0 to 24.5 $\pm$ 2.5 l·min^{-1}, after which it decreased to a minimum of 7.3 $\pm$ 1.1 l·min^{-1} within 90 s; despite the
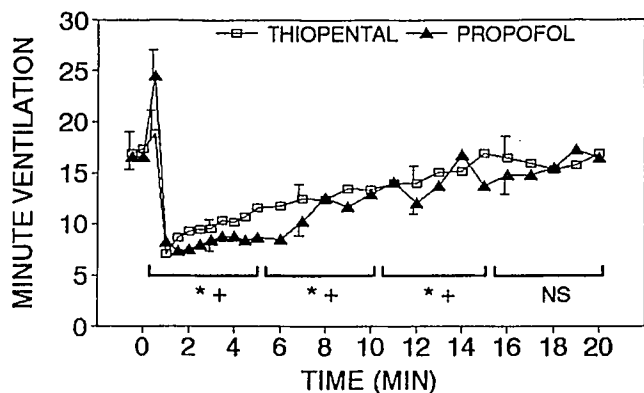
FIG. 2. Minute ventilation (liters per minute) at $P_{ET_{CO_2}} \approx 46$ mmHg following propofol and thiopental. Values are means ± representative SEM. $*P < 0.05$ *versus* preinjection value for propofol. $\dagger P < 0.05$ *versus* preinjection value for thiopental. NS = no significant difference for this time period.

FIG. 4. Respiratory rate (breaths per minute) at $P_{ET_{CO_2}} \approx 46$ mmHg following propofol and thiopental. Values are means ± representative SEM. $*P < 0.05$ *versus* preinjection value for propofol. $\dagger P < 0.05$ *versus* preinjection value for thiopental. $\#P < 0.05$ for propofol *versus* thiopental during the same time period. NS = no significant difference in this time period.

initial increase, $\dot{V}_{E}46$ was significantly less than control during the 0.5–5 min time period. $\dot{V}_{E}46$ remained significantly depressed for 15 min after injection but did not differ from control during the final 5-min time period. $\dot{V}_{E}46$ did not differ significantly between thiopental and propofol during any of the 5-min time periods.

The changes in $\dot{V}_{E}46$ resulted from changes in V_T at $P_{ET_{CO_2}} \approx 46$ mmHg (V_T46). Thirty seconds after propofol, V_T46 increased from 1026 ± 52 to 1363 ± 144 ml, before decreasing to 370 ± 58 ml 1 min after injection (fig. 3). V_T46 remained significantly less than control for the first 15 min after propofol and for 20 min after thiopental. However, V_T46 never differed between drugs.

Within 1 min after propofol, respiratory rate increased from 16 ± 2 to 22 ± 2 breaths per min; respiratory rate was significantly greater than control during the first 15 min after propofol injection. Although respiratory rate increased significantly after thiopental as well, the increase
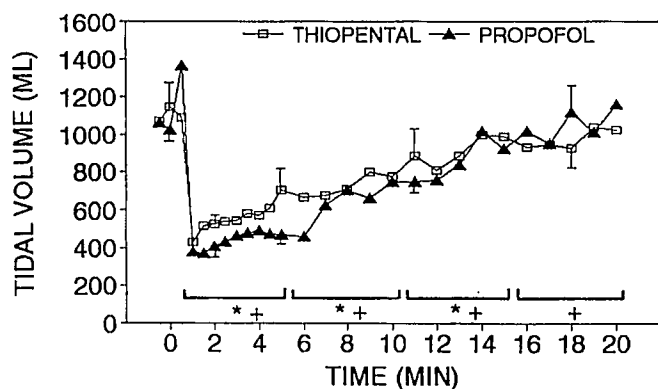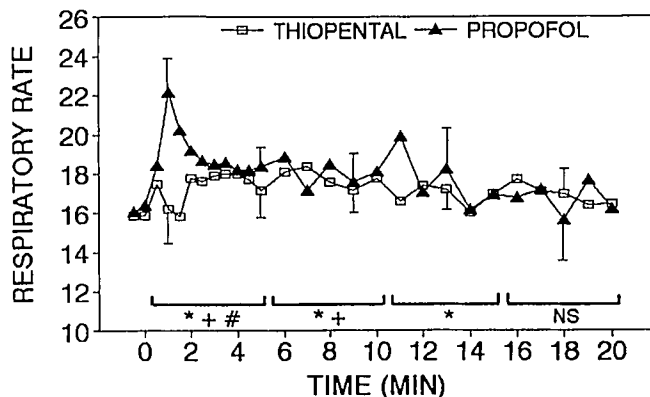
was significant only during the first 10 min after injection. From 0.5–5 min after injection, respiratory rates were significantly greater after propofol than after thiopental (fig. 4).

After both propofol and thiopental, awareness scores (table 1) decreased from 4 to 0 (*i.e.*, subjects became unresponsive to both verbal and tactile stimuli) within 60 s ($P < 0.05$ *vs.* predrug control). From figure 5, it is apparent that consciousness returned more quickly after thiopental than after propofol: awareness scores were significantly less during the first three 5-min periods after propofol than at corresponding times after thiopental ($P < 0.05$; fig. 5). However, by 14 min after injection, awareness scores had returned to baseline values in both groups.

Discussion

Previous investigations have yielded conflicting results regarding the effect of propofol on ventilatory control. Many of these conflicts can be explained by differences in experimental design. For instance, Streisand *et al.*§ reported no change in the $\dot{V}_{E_{R_{CO_2}}}$ after induction of anesthesia with propofol 2.5 mg·kg^{-1}; however, their postdrug measurements were made a minimum of 1 h after propofol was given. Similarly, Allsop *et al.*[5] reported no change in the slope of $\dot{V}_{E_{R_{CO_2}}}$ during infusion of propofol at rates ranging from 100 to 333 μg·kg^{-1}·min^{-1}; however, bolus injections of drugs may affect ventilation differently than steady-state infusions.[11] In contrast, Goodman *et al.*[4] reported a 58% decrease in the slope of the $\dot{V}_{E_{R_{CO_2}}}$ during infusion of propofol at a rate of 200 μg·kg^{-1}·min^{-1}; unfortunately, their patients received an unspecified number of supplemental propofol doses, and control data were obtained days after the experiment,

FIG. 3. Tidal volume (milliliters) at $P_{ET_{CO_2}} \approx 46$ mmHg following propofol and thiopental. Values are means ± representative SEM. $*P < 0.05$ *versus* preinjection value for propofol. $\dagger P < 0.05$ *versus* preinjection value for thiopental.
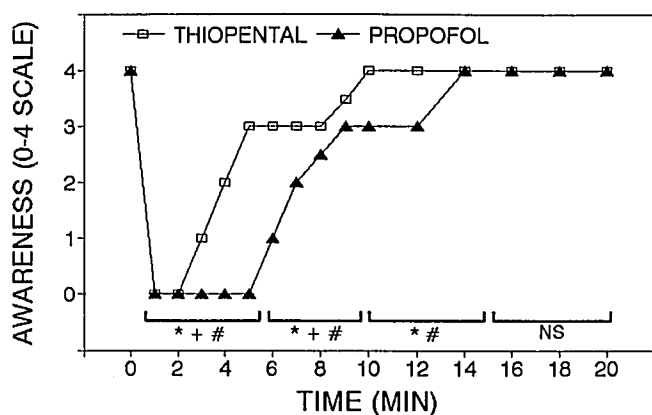
FIG. 5. Median awareness scores (0–4 scale, table 1) following propofol and thiopental. *$P < 0.05$ versus preinjection value for propofol. †$P < 0.05$ versus preinjection value for thiopental. #$P < 0.05$ for propofol versus thiopental during the same time period. NS = no significant difference in this time period.

decreasing their validity. Because these investigators all used modifications of the Read rebreathing technique,[12] which takes 5–10 min to perform, it was necessary for subjects to have stable propofol levels during the measurements. This precluded determination of the acute changes in ventilatory drive after induction of anesthesia with a single dose of propofol.

In contrast, by using the dual-isohypercapnic technique[6] we were able to determine minute-by-minute changes in the $\dot{V}E_{R_{CO_2}}$ after induction of anesthesia with a single dose of propofol or thiopental. While both propofol and thiopental decreased the slope of the $\dot{V}E_{R_{CO_2}}$ by more than 50% within 2 min after injection, recovery was more rapid after thiopental than after propofol. In fact, from 6–20 min after injection, the slope of $\dot{V}E_{R_{CO_2}}$ was significantly less after propofol than after thiopental. One possible explanation for this difference is that our 2.5-mg · kg^{-1} propofol dose was too large relative to the 4 mg · kg^{-1} thiopental dose. However, Grounds et al. used probit analysis of induction dose–response data (based on loss of response to verbal stimulation) to establish that propofol is 1.6 times more potent than thiopental[13]; this suggests that the doses used in the present study, thiopental 4 mg · kg^{-1} and propofol 2.5 mg · kg^{-1}, were equivalent with regard to their acute effects on level of consciousness. Furthermore, during the 0.5–5-min time period, the effects of thiopental and propofol on the slope of $\dot{V}E_{R_{CO_2}}$ did not differ significantly; this suggests that the doses used in the present study were equipotent with regard to their *initial* depression of ventilatory drive.

Our findings that both propofol and thiopental cause significant downward displacement of $\dot{V}E_{R_{CO_2}}$, as reflected by $\dot{V}E46$, complement those of previous investigators. For instance, Grounds et al.[3] found a significant

decrease in $\dot{V}E$ after both propofol and thiopental; however, in this study, both groups received opioid premedication. Taylor et al.[2] observed a significant decrease in $\dot{V}E$ after propofol administration but found no significant change in minute volume after thiopental. In neither of these studies, however, was PET_{CO_2} controlled during $\dot{V}E$ determination; drug-induced changes in PET_{CO_2} may have affected the measured values of $\dot{V}E$. Our observation that the initial effect of propofol was to increase $\dot{V}E46$ significantly has not been described previously. One possible explanation for this increase is that pain or discomfort on injection may have stimulated ventilation. All of our subjects recalled a painful, burning sensation when propofol was injected, whereas none reported discomfort after thiopental. After awakening from propofol, one subject volunteered, "My arm was on fire."

Figure 5 shows that recovery of awareness was 3–4 min slower after propofol than after thiopental. Subjects were fully awake within 10 min after thiopental; after propofol, subjects did not recover fully until 14 min after injection. The pharmacokinetics of propofol have been described in terms of a three-phase elimination; after injection, a rapid distribution phase is followed by a slower redistribution phase of 45–55 min, which is followed by a prolonged terminal elimination phase.[14,15] It is possible that in our subjects the increase in cardiac output accompanying recovery caused increased perfusion of tissue stores and mobilization of propofol back to the central compartment, where its depressant effects continued.[9] Similarly, remobilization of propofol into the central compartment may help to explain the relatively long duration of propofol-induced depression of ventilatory drive.

The dual-isohypercapnic technique offers the advantage of providing minute-to-minute measurements of ventilatory drive. We have previously shown that the two-point curves obtained by this technique have the same slopes as conventional, four-point steady-state $\dot{V}E_{R_{CO_2}}$ curves obtained at the same study session[6]; this is most likely related to the fact that we chose points on the linear portion of the $\dot{V}E_{R_{CO_2}}$ curve. The stability of ventilatory data obtained by this method is suggested by the observation that ventilatory variables return to their baseline values within 20 min of injection of numerous short-acting anesthetics, including methohexital,[16] etomidate,[16] lidocaine,[11] and thiopental.[6] It is certainly conceivable that residual propofol or thiopental may have affected the second trial on each study day. To minimize this effect, we allowed a minimum of 4 h between trials; by this time, drug levels would be expected to drop to less than 5% of their peak values.[17,18] In addition, to reduce the likelihood that residual drug levels would affect our results, we alternated the sequence of determinations at 46 and 58 mmHg. Because of the significant day-to-day variations in ventilatory drive,[19] it would have been inappropriate

to perform the two measurements for a given drug on different days.

In conclusion, propofol 2.5 $mg \cdot kg^{-1}$ and thiopental 4.0 $mg \cdot kg^{-1}$ caused similar, significant decreases in the slope of the $\dot{V}ER_{CO_2}$; they also caused similar downward displacements, as indicated by $\dot{V}E46$. However, the slope recovered more slowly after propofol; even though subjects were fully awake, the slope was significantly lower 16–20 min after propofol than during the corresponding period after thiopental. These data suggest that patients may be at risk for ventilatory depression during recovery from propofol anesthesia; apparently complete recovery of consciousness may not ensure return of ventilatory drive to prepropofol levels.

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