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# *Diphenhydramine Enhances the Interaction of Hypercapnic and Hypoxic Ventilatory Drive*

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***Background:*** **Although diphenhydramine is frequently used to treat pruritus and nausea in patients who have received neuraxial opioids, there are no data regarding its effect on ventilatory control. We conducted the current study to evaluate the effects of diphenhydramine on hypercapnic and hypoxic ventilatory control in healthy volunteers.**

***Methods:*** **First, we measured the steady-state ventilatory response to carbon dioxide during hyperoxia with an end-tidal carbon dioxide tension of 46 or 54 mmHg (alternate subjects) in eight healthy volunteers. We then determined the hypoxic ventilatory response during isocapnic rebreathing at the same carbon dioxide tension. After a 10-min recovery period, we repeated the steady-state and hypoxic ventilatory response measurements at the other carbon dioxide tension (54 or 46 mmHg). Ten minutes after subjects received diphenhydramine 0.7 mg · kg$^{-1}$ intravenously, we repeated this sequence of ventilatory measurements.**

***Results:*** **Under hyperoxic conditions (inspired oxygen fraction > 0.5) diphenhydramine did not affect the ventilatory response to hypercapnia. Similarly, at an end-tidal carbon dioxide tension of 46 mmHg, neither the slope nor the position of the hypoxic ventilatory response curve changed significantly after diphenhydramine. However, at an end-tidal carbon dioxide tension of 54 mmHg, the slope of the hypoxic ventilatory response increased from 1.28 ± 0.33 to 2.13 ± 0.61 l · min$^{-1}$ · %$Sp_{O_2}^{-1}$ (mean ± standard error), and $\dot{V}_E$ at an arterial hemoglobin oxygen saturation of 90% increased from 31.2 ± 3.1 to 43.1 ± 5.4 l · min$^{-1}$).**

***Conclusions:*** **We conclude that although it did not affect the ventilatory response to carbon dioxide during hyperoxia or the ventilatory response to hypoxia at an end-tidal carbon dioxide tension of 46 mmHg diphenhydramine augmented the hypoxic response under conditions of hypercapnia in our young healthy volunteers. Although these findings may help to explain the apparent safety of diphenhydramine, they may not be applicable to debilitated patients or those who have received systemic or neuraxial ventilatory depressants. (Key words: Antihistamines: diphenhydramine. Oxygen: hypoxia; ventilatory response. Carbon dioxide: hypercapnia; ventilatory response.)**

DESPITE the widespread use of diphenhydramine as a sedative, antiemetic, and antipruritic agent, there are no data available regarding its effect on ventilatory control. This may be of particular concern because diphenhydramine is frequently used to treat side effects associated with known respiratory depressants such as systemic and neuraxial opioids.[1] Therefore, we designed the current study to evaluate the effects of diphenhydramine on hypercapnic and hypoxic ventilatory responses.

## Materials and Methods

After approval by our institutional review board, we obtained written informed consent from eight healthy volunteers (six men and two women) weighing 55–85 kg and aged 23–33 yr. Subjects abstained from beverages containing alcohol and caffeine for 24 h and had nothing by mouth for at least 8 h before the start of the study session; all had normal hematocrits. The subjects were nonsmokers and denied current upper respiratory infection. For each subject, we inserted a 20 g catheter in a hand vein and infused lactated Ringer's solution at 50 ml · h$^{-1}$. A Propaq 104 monitor (Beaverton, OR) continuously displayed the electrocardiogram and determined the blood pressure noninvasively at 2-min intervals. An Ohmeda 3700 (Boulder, CO) pulse oximeter, operating in the fast (3-s averaging mode) continuously measured arterial oxygen *via* an ear probe; we have previously shown that this oximeter configu-

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ration reliably measures hemoglobin oxygen saturation ($Sp_{O_2}$) during rapid desaturation.[2] To minimize the effect of auditory stimulation during ventilatory testing, subjects listened to quiet continuous music through headphones.

The supine subjects breathed mixtures of oxygen, nitrogen, and carbon dioxide through a face mask incorporated in a closed, to-and-fro circuit with variable carbon dioxide absorption. The resistance of the circuit is approximately 0.03 $cmH_2O \cdot l^{-1} \cdot min$ at a flow rate of 100 $l \cdot min^{-1}$, and its internal volume is approximately 5.5 l. An Instrumentation Laboratories IL200 $CO_2$ analyzer, calibrated with three reference mixtures of carbon dioxide in oxygen, continuously measured carbon dioxide tension at the mask. By varying the flow through the carbon dioxide absorber, we kept the $P_{ET_{CO_2}}$ constant within ± 1 mmHg despite changes in ventilation. A Hans-Rudolph 3700 heated pneumotachograph, with a Validyne DP45 differential pressure transducer and electronic integrator, determined ventilatory volumes at body temperature and pressure, saturated. Before each set of measurements, we performed a three-point volume calibration and linearity check with a Collins 3200 (Braintree, MA) super syringe. A computer recorded breath-by-breath values for $Sp_{O_2}$, $P_{ET_{CO_2}}$, tidal volume ($V_T$), and minute ventilation ($\dot{V}_E$) *via* an analog-to-digital converter.

To determine the steady-state ventilatory response to carbon dioxide, subjects breathed hyperoxic (inspired oxygen fraction > 0.5) mixtures of oxygen in nitrogen with $P_{ET_{CO_2}}$ held constant at 46 or 54 mmHg for alternate subjects. After a 6-min equilibration period, we obtained the mean of four consecutive, five-breath average values of $\dot{V}_E$, $V_T$ and $P_{ET_{CO_2}}$. We then measured the ventilatory response to hypoxia at the same carbon dioxide tension (46 or 54 mmHg) using the isocapnic rebreathing method.[3] After rapidly (30 s) decreasing the inspired oxygen fraction within the breathing circuit to 0.21 while maintaining a constant $P_{ET_{CO_2}}$, we discontinued oxygen inflow to the circuit. As metabolic oxygen consumption progressively decreased the inspired oxygen fraction, we continuously recorded $\dot{V}_E$, $V_T$, $P_{ET_{CO_2}}$, and $Sp_{O_2}$. We adjusted the nitrogen inflow to maintain constant rebreathing bag volume and varied the carbon dioxide absorber flow to maintain constant $P_{ET_{CO_2}}$ despite changes in ventilation. When $Sp_{O_2}$ reached 70%, usually 5–6 min after discontinuation of oxygen inflow, we terminated data collection, removed the face mask, and allowed subjects to breathe room air for 10 min. We then repeated the steady-state and hypoxic ventilatory measurements at the alternate carbon dioxide tension (54 or 46 mmHg, whichever was not used previously).

After the baseline ventilatory measurements were complete, subjects received diphenhydramine 0.7 $mg \cdot kg^{-1}$ intravenously over 30 s. Ten minutes later we repeated the determination of steady-state and hypoxic ventilatory responses at $P_{ET_{CO_2}}$ = 46 and 54 mmHg, using the same sequence of carbon dioxide tensions that had been used for the prediphenhydramine measurements. Each subject was thus studied at both carbon dioxide tensions, before and after diphenhydramine.

*Data Analysis*

For each hypoxic response determination, the computer calculated five-breath averages[4] of $\dot{V}_E$, $V_T$, and $Sp_{O_2}$. Using least-squares linear regression, we calculated the slopes of $\dot{V}_E$ and $V_T$ *versus* $Sp_{O_2}$ of 95–70% at each $P_{ET_{CO_2}}$, to quantitate the hypoxic ventilatory control response before and after diphenhydramine at each carbon dioxide tension. Because ventilation increases as arterial saturation decreases, these slopes have negative signs; to allow larger values to indicate greater hypoxic drive, we multiplied each slope by −1 before analysis. From the regression of $\dot{V}_E$ *versus* $Sp_{O_2}$ we determined the $\dot{V}_E$ at an $Sp_{O_2}$ of 90% ($\dot{V}_{90}$), as an index of the displacement of the $\dot{V}_E$ *versus* $Sp_{O_2}$ regression line. The regression of $V_T$ *versus* $Sp_{O_2}$ enabled us to determine $V_T$ at $Sp_{O_2}$ = 90% ($V_{T90}$) during each measurement of hypoxic ventilatory response.

For each subject, we determined the ventilatory response to carbon dioxide before and after diphenhydramine, by computing two-point steady-state carbon dioxide response lines from the $\dot{V}_E$ measurements made at $P_{ET_{CO_2}}$ = 46 and 54 mmHg during hyperoxia. The slope and $\dot{V}_E$ at $P_{ET_{CO_2}}$ = 46 mmHg ($\dot{V}_{46}$) served as indices of the sensitivity and "setpoint" of the carbon dioxide response, respectively.

Paired *t* tests compared pre- and postdiphenhydramine ventilatory variables: slope and $\dot{V}_{46}$ of the steady-state hypercapnic response and slope, $\dot{V}_{90}$, and $V_{T90}$ of the hypoxic ventilatory response. Data are presented as means ± standard error, with significance accepted at $P < 0.05$.

## Results

All of the subjects completed the protocol and none suffered any sequelae as a result of participation in the

**Table 1. Hypoxic Ventilatory Response before and after Diphenhydramine 0.7 mg/kg iv**

| | Prediphenhydramine | | Postdiphenhydramine | |
|---|---|---|---|---|
| | Low $CO_2$ | High $CO_2$ | Low $CO_2$ | High $CO_2$ |
| $P_{ET}CO_2$ (mmHg) | 46.0 ± 0.1 | 54.0 ± 0.2 | 46.1 ± 0.1 | 54.1 ± 0.1 |
| Slope ($l \cdot min^{-1} \cdot \%Sp_{O_2}{}^{-1}$) | 0.88 ± 0.28 | 1.28 ± 0.33 | 0.87 ± 0.21 | 2.13 ± 0.61* |
| $\dot{V}_{90}$ (l/min) | 15.3 ± 1.9 | 31.2 ± 3.1 | 17.5 ± 2.6 | 43.1 ± 5.4* |
| $V_T90$ (l) | 1.07 ± 0.10 | 1.98 ± 0.16 | 0.96 ± 0.12 | 2.08 ± 0.17 |

Values are mean ± SE.

* $P < 0.05$ *versus* corresponding prediphenhydramine value.

study. After diphenhydramine, subjects were mildly sedated but remained fully responsive. $P_{ET}CO_2$ readings were stable within ± 1 mmHg of their target values and did not differ between pre- and postdiphenhydramine studies.

Pre- and postdiphenhydramine values for $\dot{V}_{90}$, $V_{T90}$, and the slope of the hypoxic ventilatory response appear in table 1. At $P_{ET}CO_2$ = 46 mmHg, diphenhydramine did not affect any of these variables (fig. 1). In contrast, at $P_{ET}CO_2$ = 54 mmHg, diphenhydramine caused the slope of the hypoxic ventilatory response to increase from 1.28 ± 0.33 to 2.13 ± 0.61 $l \cdot min^{-1} \cdot \%Sp_{O_2}{}^{-1}$ ($P < 0.05$, fig. 2), while $\dot{V}_{90}$ increased from 31.2 ± 3.1 to 43.1 ± 5.4 $l \cdot min^{-1}$ ($P < 0.05$); $V_{T90}$ was not affected.

Before diphenhydramine, the slope of the steady-state ventilatory response to carbon dioxide was 1.35 ± 0.39 $l \cdot min^{-1} \cdot mmHg^{-1}$; after the drug it was 1.80 ± 0.24 $l \cdot min^{-1} \cdot mmHg^{-1}$ (fig. 3). The fact that this change in slope did not achieve statistical significance may be

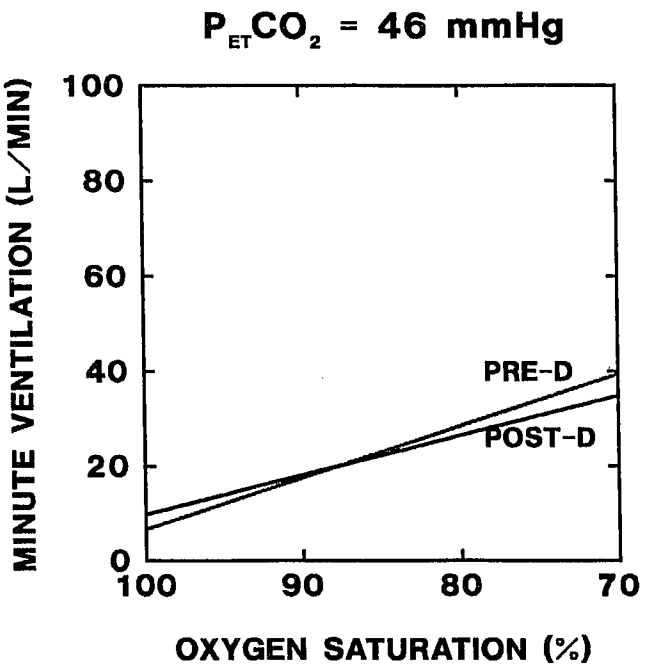


**Fig. 1. Hypoxic ventilatory response curves determined with end-tidal carbon dioxide tension of ≈ 46 mmHg. Before and after intravenous administration of diphenhydramine 0.7 $mg \cdot kg^{-1}$ (PRE-D and POST-D, respectively), responses did not differ significantly.**

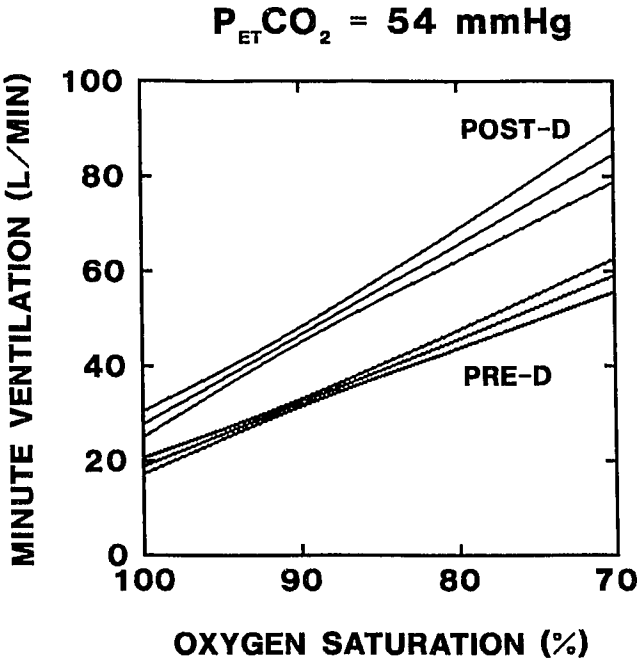


**Fig. 2. Hypoxic ventilatory response curves and 95% confidence limits determined with end-tidal carbon dioxide tension of ≈ 54 mmHg. After diphenhydramine administration (POST-D), both the slope and minute ventilation at an $Sp_{O_2}$ of 90% were significantly ($P < 0.05$) greater than in the control state, before diphenhydramine (PRE-D).**

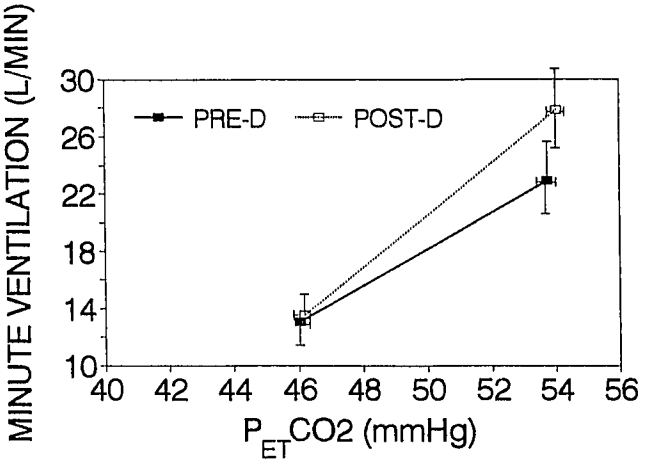


**Fig. 3. Two-point steady-state carbon dioxide response curves determined during hyperoxia. Pre- and postdiphenhydramine curves do not differ significantly in slope or displacement. Values shown are means ± standard error.**

related, in part, to the large degree of variability of the data along with the relatively small size of our sample. Power analysis indicates that if diphenhydramine actually causes the slope to increase by 50%, there would be a 30% chance ($\beta = 0.3$) that we would have failed to detect significance at the 0.05 level ($\alpha = 0.05$). A sample of 28 subjects would have been necessary to reduce $\beta$ to 0.2.[5]

## Discussion

Diphenhydramine, an $H_1$-histamine–receptor antagonist, has a long record of safe use. Despite its tendency to cause significant sedation,[6] respiratory depression has not been reported to be a side effect of diphenhydramine. However, it is commonly prescribed postoperatively to treat the pruritus that affects up to 80% of patients who receive epidural or subarachnoid opioids.[7] Because ventilatory depression is a frequent side effect of both neuraxial and systemic opioids, diphenhydramine might potentiate this effect *via* its sedative properties. Although the current findings suggest that diphenhydramine may actually stimulate the interaction between central and peripheral ventilatory control mechanisms, it is conceivable that diphenhydramine might have a different effect in the presence of opioid-induced respiratory depression.

All histamine antagonists currently in use, with the exception of newer agents such as terfenadine, bind to central nervous system $H_1$ receptors, where they result in central nervous system depression or excitation, depending on the dose.[8] Central depression is the result of therapeutic doses of $H_1$ antagonists, especially the ethanolamine group to which diphenhydramine belongs. This tendency to produce sedation, diminished alertness, and slowed reaction times[9] has led to the use of diphenhydramine as a hypnotic. In addition it is a common ingredient of proprietary, nonprescription remedies for insomnia.[10]

However, several differences exist when hypnotics such as barbiturates or benzodiazepines are compared to diphenhydramine. Sleep studies indicate that diphenhydramine, in contrast to the benzodiazepines, decreases sleep latency but does not maintain the sleep state (subjects fall asleep but do not tend to remain asleep).[11] Most hypnotics induce anesthesia after a large oral or systemic dose but this is not the case with diphenhydramine. Studies evaluating this drug as a nocturnal hypnotic have shown clinical activity different from placebo but not an increasing effect with increasing dose.[10,12] This limited effect is consistent with the observation that excitement is occasionally seen when diphenhydramine is used for sedation and that diphenhydramine actually increases motor activity during sleep.[11]

Central nervous system excitatory effects pose the greatest threat after an overdose of diphenhydramine, which may cause tremors, hyperactivity, hyperpyrexia, and tonic clonic seizures.[13] Although impaired consciousness is the most common finding after overdose, the clinical picture may include a catatonic stupor combined with anxiety and hallucinations. Respiratory failure has been reported only as a preterminal event resulting from cardiovascular collapse.[14]

We were unable to demonstrate a significant effect of diphenhydramine on the ventilatory response to carbon dioxide or the response to hypoxemia at $P_{ET}CO_2$ = 46 mmHg. However, diphenhydramine increased the hypoxic ventilatory response at a $P_{ET}CO_2$ = 54 mmHg. It has been well established that concurrent hypoxia and hypercapnia produce a greater than additive effect on afferent carotid body chemoreceptor activity[15] and ventilation.[16,17] Therefore, diphenhydramine's augmentation of this response strongly suggests an action on the peripheral chemoreceptors or their immediate central connections.

Because diphenhydramine has not been shown to affect the peripheral chemoreceptors in the carotid body, the mechanism of this effect is unknown. The literature

suggests that there are several drugs that do affect the carotid body. Dopamine, for example, is an important neurotransmitter that modulates carotid chemoreceptor sensitivity.[18] Dopamine infusion has been found to decrease hypoxic ventilatory response in humans[19] and in laboratory animals,[20] whereas droperidol, a dopamine antagonist, augments the ventilatory response to hypoxia.[21] Prochlorperazine, another dopamine antagonist, augments the ventilatory response to hypoxia without altering the responsiveness to hypercapnia.[22] Furthermore, it has no effect on morphine-induced ventilatory depression when hypercapnia, alone, is the stimulus, but reverses morphine-induced depression when hypercapnia is augmented by hypoxia.[23] Therefore, the results we observed could be explained by an antidopaminergic effect of diphenhydramine at the carotid body. However, experimental and clinical data do not support this hypothesis. Diphenhydramine's therapeutic effect in Parkinson's disease makes it unlikely that diphenhydramine has significant antidopaminergic activity. In addition, diphenhydramine inhibits the uptake of dopamine into synaptosomes in rodent brain, thereby potentiating rather than antagonizing the synaptic action of dopamine.[24]

Our results can, however, be explained by an anticholinergic effect of diphenhydramine. This drug is well known to inhibit responses to acetylcholine that are mediated by muscarinic receptors, leading to both tachycardia and xerostomia. Anticholinergic effects also explain diphenhydramine's salutary effect both in patients with motion sickness and in those with rhinorrhea associated with the common cold. Central anticholinergic activity explains diphenhydramine's ability to reverse the extrapyramidal side effects of phenothiazines and some of its value in Parkinson's disease.[25]

The chemoreceptor cells of the carotid body have both nicotinic and muscarinic cholinergic receptor sites.[26] Dinger *et al.* have localized muscarinic receptors to the type I parenchymal cells in the rabbit carotid body and found that these receptors inhibit the nicotine evoked release of catecholamines.[27] Earlier studies by Monti-Bloch and Eyzaguirre[28] and by Docherty and McQueen[29] showed that muscarinic drugs such as acetylcholine and pilocarpine inhibit chemosensory units of the carotid sinus nerve. In addition, bethanechol, a muscarinic cholinergic agonist, can inhibit the increase in catecholamine release and carotid sinus nerve discharge evoked by hypoxic stimulation in rabbit carotid body.[27] By blocking the effects of acetylcholine, diphenhydramine could enhance the activity of the carotid body under appropriate circumstances.

However, there is no previous experimental evidence to suggest that anticholinergic drugs affect ventilatory control. Steinberg *et al.* found that atropine had no significant stimulating or depressant effect on ventilation when the stimulus was hypercapnia.[30] Severinghaus and Stupfel showed that although ventilation may appear to increase after atropine administration, this could be explained by a 30% increase in pulmonary dead space.[31] On the other hand, physostigmine, an anticholinesterase resulting in increased concentrations of acetylcholine, does penetrate the central nervous system and significantly depresses ventilatory drive in both cats and humans.[32,33] Although we do not understand the mechanism of this finding, it is consistent with the hypothesis that diphenhydramine increases ventilatory response through some, possibly a central, anticholinergic mechanism.

There is little experimental data regarding the effect of other antihistamines on ventilatory drive. Hydroxyzine is a piperazine derivative with $H_1$-blocking capability that is used both as a premedication and to augment postoperative analgesia. Steen reported that the displacement of carbon dioxide response curves determined 20 min and 1 h after intramuscular administration of hydroxyzine 1.0 $mg \cdot kg^{-1}$ suggested respiratory stimulation,[34] whereas Gasser and Bellville found the drug to be a mild respiratory depressant after intravenous administration of 75 or 150 mg.[35] Benzquinamide (Emete-con, Roerig) is a mild sedative used principally as an antiemetic; animal studies have demonstrated anticholinergic and antihistaminic effects of this compound.[36] Benzquinamide is a ventilatory stimulant in human studies; Mull and Smith[37] and Steen and Yates[38] demonstrated a shift to the left of the ventilatory response to hypercapnia, as well as attenuation of meperidine associated depression of hypercapnic drive.

We found that the hypoxia–hypercapnia interaction was more sensitive to the effects of diphenhydramine than was the ventilatory response to hyperoxic hypercapnia or the hypoxic response at $P_{ET_{CO_2}} = 46$ mmHg. Other investigators have shown that this interactive effect is more sensitive to the depressant effects of anesthetic drugs as well. Weiskopf *et al.* found that halothane anesthesia in dogs produced a greater depressive effect on the ventilatory response to the interaction between hypoxia and hypercapnia than on the response to either stimulus alone.[39] Knill and Clement determined that sedation with halothane (0.1 MAC) de-

pressed the response to hypoxemia and acidemia more than the response to either condition alone.[40] The recent report by Temp *et al.* suggests than isoflurane sedation similarly depresses the sustained ventilatory response to hypoxemia and hypercapnia more than to either stimulus alone.[41] Our data confirm that assessment of ventilatory effects on the hypoxia–hypercapnia interaction may be the most sensitive test of a drug effect on ventilatory drive.

The results of hypoxic and hypercapnic response determinations depend upon the carbon dioxide tension or oxygen tension, respectively, at which they are measured. Whereas the effect of hypoxic stimulation can be eliminated during carbon dioxide response determination by maintaining hyperoxia, the converse is not true: it is not possible to eliminate the effects of carbon dioxide when determining hypoxic ventilatory drive, because the carbon dioxide tension cannot be reduced sufficiently to abolish hypercapnic drive while maintaining spontaneous ventilation. Because one cannot entirely eliminate the effect of carbon dioxide, a reasonable alternative has been to measure drug effects on hypoxic response in an isocapnic milieu.[42] In the current study, we have gone one step further, measuring hypoxic ventilatory response at two different $P_{ET_{CO_2}}$ levels. We chose 46 mmHg because it lies at the beginning of the linear portion of the carbon dioxide response curve, and a $P_{ET_{CO_2}}$ of 54 mmHg allowed us to determine the hypoxia–hypercapnia interaction. Measurement of hypoxic drive at these carbon dioxide concentrations revealed an interactive effect of diphenhydramine on ventilatory drive that would not have been apparent had we performed measurements only during eucapnia. However, this method may not accurately predict the effects of diphenhydramine on ventilatory drive at $P_{ET_{CO_2}} = 40$ mmHg.

In the current study, as in many previous studies of drug effects on ventilatory drive,[19,21,43] we did not use a placebo group to exclude a time-related effect on ventilatory response determinations. Although their methods were not identical to ours, Sahn *et al.*[44] demonstrated that there is no time-related variability of hypoxic or hypercapnic ventilatory drive with repeated determinations. Furthermore, we minimized the likelihood that a time effect would systematically affect our results by reversing the sequence of carbon dioxide tensions for alternate subjects. Therefore, it is unlikely that such effects are responsible for the significant changes we observed after diphenhydramine.

Our studies were performed in awake volunteers. Although they were slightly drowsy after diphenhydramine, they did not fall asleep. Because ventilatory responses are attenuated by sleep, it is possible that diphenhydramine could depress ventilatory response if its sedative effects caused patients who were otherwise awake to fall asleep.

In summary, we have found that in healthy volunteers, diphenhydramine augmented the interaction between hypoxic and hypercapnic ventilatory drive. Although the current findings may explain the apparent safety of diphenhydramine when administered alone, they may not be applicable to patients who are debilitated or who have received other ventilatory depressant medications, either systemically or *via* the neuraxis.

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