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·%SpO₂⁻¹ (mean ± standard error), and Vₐ 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.† 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-
ration reliably measures hemoglobin oxygen saturation \( (S_{pO_2}) \) 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\(_2\)O · l\(^{-1}\) · min\(^{-1}\), and its internal volume is approximately 5.5 l. An Instrumentation Laboratories II.200 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 PET\(_{CO_2}\) 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 \(SP_{O_2}\), PET\(_{CO_2}\), tidal volume (\(V_T\)), and minute ventilation (\(V_E\)) 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 PET\(_{CO_2}\) 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 \(V_E\), \(V_T\), and PET\(_{CO_2}\). 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 (50 s) decreasing the inspired oxygen fraction within the breathing circuit to 0.21 while maintaining a constant PET\(_{CO_2}\), we discontinued oxygen inflow to the circuit. As metabolic oxygen consumption progressively decreased the inspired oxygen fraction, we continuously recorded \(V_E\), \(V_T\), PET\(_{CO_2}\), 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 PET\(_{CO_2}\) 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 · kg\(^{-1}\) intravenously over 30 s. Ten minutes later we repeated the determination of steady-state and hypoxic ventilatory responses at PET\(_{CO_2} = 46\) 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 \(V_E\), \(V_T\), and \(SP_{O_2}\). Using least-squares linear regression, we calculated the slopes of \(V_E\) and \(V_T\) versus \(SP_{O_2}\), of 95–70% at each PET\(_{CO_2}\), 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 \(V_E\) versus \(SP_{O_2}\), we determined the \(V_E\) at an \(SP_{O_2}\) of 90% (\(V_{90}\)), as an index of the displacement of the \(V_E\) versus \(SP_{O_2}\) regression line. The regression of \(V_T\) versus \(SP_{O_2}\) enabled us to determine \(V_T\) at \(SP_{O_2} = 90\% (V_{90})\) 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 \(V_E\) measurements made at PET\(_{CO_2} = 46\) and 54 mmHg during hyperoxia. The slope and \(V_E\) at PET\(_{CO_2} = 46\) mmHg (\(V_{46}\)) 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 \(V_{46}\) of the steady-state hypercapnic response and slope, \(V_{50}\), and \(V_{90}\) 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 sequela as a result of participation in the
DIPHENHYDRAMINE AND VENTILATORY DRIVE

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

<table>
<thead>
<tr>
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<th>Prediphenhydramine</th>
<th>Postdiphenhydramine</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Low CO₂</td>
<td>High CO₂</td>
</tr>
<tr>
<td>PETCO₂ (mmHg)</td>
<td>46.0 ± 0.1</td>
<td>54.0 ± 0.2</td>
</tr>
<tr>
<td>Slope (l·min⁻¹·%SpO₂⁻¹)</td>
<td>0.88 ± 0.28</td>
<td>1.28 ± 0.33</td>
</tr>
<tr>
<td>V̅₉₀ (l/min)</td>
<td>15.3 ± 1.9</td>
<td>31.2 ± 3.1</td>
</tr>
<tr>
<td>V₁₉₀(l)</td>
<td>1.07 ± 0.10</td>
<td>1.98 ± 0.16</td>
</tr>
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Values are mean ± SE.
* P < 0.05 versus corresponding prediphenhydramine value.

study. After diphenhydramine, subjects were mildly sedated but remained fully responsive. PETCO₂ readings were stable within ± 1 mmHg of their target values and did not differ between pre- and postdiphenhydramine studies.

Pre- and postdiphenhydramine values for V̅₉₀, V₁₉₀, and the slope of the hypoxic ventilatory response appear in table 1. At PETCO₂ = 46 mmHg, diphenhydramine did not affect any of these variables (fig. 1). In contrast, at PETCO₂ = 54 mmHg, diphenhydramine caused the slope of the hypoxic ventilatory response to increase from 1.28 ± 0.33 to 2.13 ± 0.61 l·min⁻¹·%SpO₂⁻¹ (P < 0.05, fig. 2), while V̅₉₀ increased from 31.2 ± 3.1 to 43.1 ± 5.4 l·min⁻¹ (P < 0.05); V₁₉₀ was not affected.

Before diphenhydramine, the slope of the steady-state ventilatory response to carbon dioxide was 1.35 ± 0.39 l·min⁻¹·mmHg⁻¹; after the drug it was 1.80 ± 0.24 l·min⁻¹·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·kg⁻¹ (PRE-D and POST-D, respectively), responses did not differ significantly.

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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 actu-
ally 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 antag-
onist, 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 diphenhy-
dramine. However, it is commonly prescribed post-
operatively 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, di-
phenhydramine might potenitate this effect via its sed-
ative properties. Although the current findings suggest
that diphenhydramine may actually stimulate the
interaction between central and peripheral ventilatory
control mechanisms, it is conceivable that diphenhy-
dramine 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

![Graph showing the relationship between minute ventilation (L/min) and P_{ET}CO_2 (mmHg).](http://anesthesiology.pubs.asahq.org/pdfaccess.ashx?url=/data/journals/jasa/931306/)

Central nervous system $H_1$ receptors, where they result
in central nervous system depression or excitation, de-
pending on the dose.$^8$ Central depression is the result
of therapeutic doses of $H_1$ antagonists, especially the
ethanolamine group to which diphenhydramine be-
longs. 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 di-
phenhydramine, 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 di-
phenhydramine. Studies evaluating this drug as a noc-
turnal hypnotic have shown clinical activity different
from placebo but not an increasing effect with increas-
ing dose.$^{10,12}$ This limited effect is consistent with the
observation that excitement is occasionally seen when
diphenhydramine is used for sedation and that diphen-
hydramine 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 con-
sciousness is the most common finding after overdose,
the clinical picture may include a cataleptic 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 car-
bon 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 aug-
mentation of this response strongly suggests an action
on the peripheral chemoreceptors or their immediate
central connections.

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

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suggests that there are several drugs that do affect the carotid body. Dopamine, for example, is an important neurotransmitter that modulates carotid chemoreceptor sensitivity.\textsuperscript{18} Dopamine infusion has been found to decrease hypoxic ventilatory response in humans\textsuperscript{19} and in laboratory animals,\textsuperscript{20} whereas droperidol, a dopamine antagonist, augments the ventilatory response to hypoxia.\textsuperscript{21} Prochlorperazine, another dopamine antagonist, augments the ventilatory response to hypoxia without altering the responsiveness to hypercapnia.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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 rhinorhea 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.\textsuperscript{25}

The chemoreceptor cells of the carotid body have both nicotinic and muscarinic cholinergic receptor sites.\textsuperscript{26} Dinger et al. have localized muscarinic receptors to the type 1 parenchymal cells in the rabbit carotid body and found that these receptors inhibit the nicotine evoked release of catecholamines.\textsuperscript{27} Earlier studies by Monti-Bloch and Eyzaguirre\textsuperscript{28} and by Docherty and McQueen\textsuperscript{29} showed that muscarinic drugs such as acetylcholine and pilocarpine inhibit chemoosensory 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.\textsuperscript{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.\textsuperscript{30} Seerveringhaus 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.\textsuperscript{31} On the other hand, phystostigmine, an anticholinesterase resulting in increased concentrations of acetylcholine, does penetrate the central nervous system and significantly depresses ventilatory drive in both cats and humans.\textsuperscript{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\textsubscript{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·kg\textsuperscript{-1} suggested respiratory stimulation,\textsuperscript{34} whereas Gasser and Bellville found the drug to be a mild respiratory depressant after intravenous administration of 75 or 150 mg.\textsuperscript{35} Benzquinamide (Emetec-con, Roerig) is a mild sedative used principally as an antiemetic; animal studies have demonstrated anticholinergic and antihistaminic effects of this compound.\textsuperscript{36} Benzquinamide is a ventilatory stimulant in human studies; Mull and Smith\textsuperscript{37} and Steen and Yates\textsuperscript{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 $P_{ETCO_2} = 46$ 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.\textsuperscript{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. The recent report by Temp et al. suggests that isoflurane sedation similarly depresses the sustained ventilatory response to hypoxemia and hypercapnia more than to either stimulus alone. 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. In the current study, we have gone one step further, measuring hypoxic ventilatory response at two different PETCO2 levels. We chose 46 mmHg because it lies at the beginning of the linear portion of the carbon dioxide response curve, and a PETCO2 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 euapnia. However, this method may not accurately predict the effects of diphenhydramine on ventilatory drive at PETCO2 = 40 mmHg.

In the current study, as in many previous studies of drug effects on ventilatory drive, 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. 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.

References


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