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Diphenhydramine Increases Ventilatory Drive during Alfentanil Infusion

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Background: **Diphenhydramine is used as an antipruritic and antiemetic in patients receiving opioids. Whether it might exacerbate opioid-induced ventilatory depression has not been determined.**

Methods: **The ventilatory response to carbon dioxide during hyperoxia and the ventilatory response to hypoxia during hypercapnia (end-tidal pressure of carbon dioxide [$P_{ET_{CO_2}}$] ≈ 54 mmHg) were determined in eight healthy volunteers. Ventilatory responses to carbon dioxide and hypoxia were calculated at baseline and during an alfentanil infusion (estimated blood levels ≈ 10 ng/ml) before and after diphenhydramine 0.7 mg/kg.**

Results: **The slope of the ventilatory response to carbon dioxide decreased from 1.08 ± 0.38 to 0.79 ± 0.36 $l \cdot min^{-1} \cdot mmHg^{-1}$ ($\bar{x}$ ± SD, $P < 0.05$) during alfentanil infusion; after diphenhydramine, the slope increased to 1.17 ± 0.28 $l \cdot min^{-1} \cdot mmHg^{-1}$ ($P < 0.05$). The minute ventilation ($\dot{V}_E$) at $P_{ET_{CO_2}}$ ≈ 46 mmHg ($\dot{V}_E$46) decreased from 12.1 ± 3.7 to 9.7 ± 3.6 l/min ($P < 0.05$) and the $\dot{V}_E$ at 54 mmHg ($\dot{V}_E$54) decreased from 21.3 ± 4.8 to 16.6 ± 4.7 l/min during alfentanil ($P < 0.05$). After diphenhydramine, $\dot{V}_E$46 did not change significantly, remaining lower than baseline at 9.9 ± 2.9 l/min ($P < 0.05$), whereas $\dot{V}_E$54 increased significantly to 20.5 ± 3.0 l/min. During hypoxia, $\dot{V}_E$ at S_pO_2 = 90% ($\dot{V}_E$90) decreased from 30.5 ± 9.7 to 23.1 ± 6.9 l/min during alfentanil ($P < 0.05$). After diphenhydramine, the increase in $\dot{V}_E$90 to 27.2 ± 9.2 l/min was not significant (P = 0.06).**

Conclusions: **Diphenhydramine counteracts the alfentanil-induced decrease in the slope of the ventilatory response to carbon dioxide. However, at $P_{ET_{CO_2}}$ = 46 mmHg, it does not significantly alter the alfentanil-induced shift in the carbon dioxide response curve. In addition, diphenhydramine does not exacerbate the opioid-induced depression of the hypoxic ventilatory response during moderate hypercarbia. (Key words: Conscious sedation; epidural opioids; subarachnoid opioids.)**

DIPHENHYDRAMINE commonly is prescribed as a sedative, an antipruritic, and an antiemetic agent. When administered alone, it modestly stimulates ventilation by augmenting the interaction of hypoxic and hypercarbic ventilatory drives.[1] Because diphenhydramine often is used in combination with systemic or neuraxial opioids to control nausea and pruritus, we designed this study to evaluate the effect of diphenhydramine on the ventilatory responses to carbon dioxide and isohypercapnic hypoxia during alfentanil infusion.

Materials and Methods

Eight nonsmoking healthy volunteers (three women and five men), ranging in age from 23 to 38 yr and in weight from 55 to 91 kg, consented to participate in this institutional review board–approved study. The volunteers abstained from using alcohol and caffeine for 24 h and took nothing by mouth for at least 8 h before the study began. To minimize the effect of auditory stimulation during ventilatory testing, the supine volunteers listened to quiet classical music *via* headphones. We monitored blood pressure, electric activity of the heart, and arterial oxygen saturation (S_pO_2) with an Ohmeda (Louisville, CO) model 3700 oximeter (ear probe, fast mode). A Datex (Helsinki, Finland) Capnomac II, calibrated with three reference mixtures of carbon dioxide in oxygen, continuously monitored the end-tidal pressure of carbon dioxide ($P_{ET_{CO_2}}$) and fractional concentration of oxygen in inspired gas ($F_{I_{O_2}}$) from a sampling port built into the face mask in front of the volunteers' mouths. Subjects breathed *via* mask from a to-and-fro circuit with variable carbon dioxide absorption.[2] By continuously monitoring $P_{ET_{CO_2}}$ on a breath-by-breath basis and adjusting the flow of gas through the carbon dioxide absorber accordingly, we kept $P_{ET_{CO_2}}$ constant despite changes in the volunteers' ventilatory patterns. A Hans-Rudolph (Kansas City, MO) 3700 heated pneumotacho-

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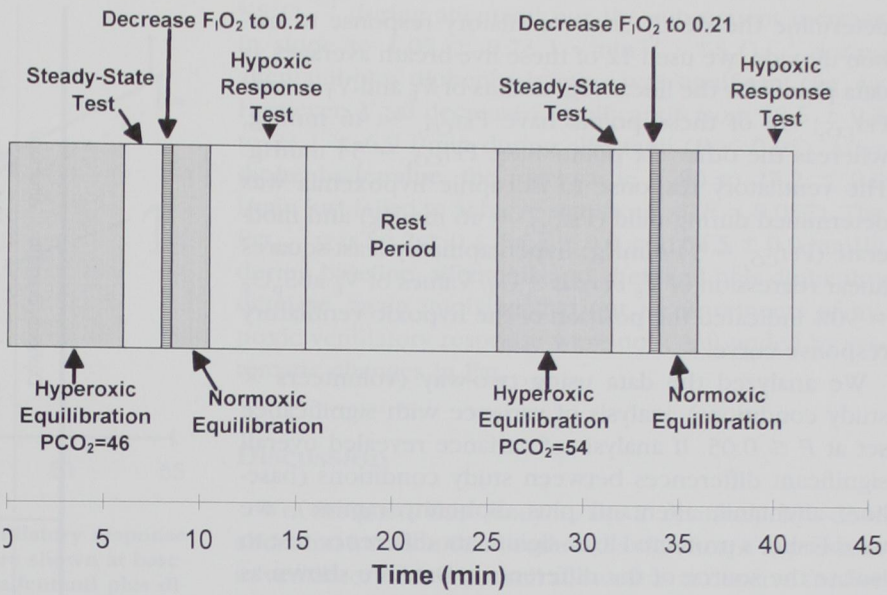

Fig. 1. Timeline showing the sequence of events during a set of ventilatory response measurements in odd-numbered volunteers. For even-numbered volunteers, the sequence of carbon dioxide tensions was reversed. Three sets of data were obtained for each volunteer: baseline, alfentanil, and alfentanil plus diphenhydramine.

graph with a Validyne (Northridge, CA) DP45 differential pressure transducer and electronic integrator determined ventilatory volumes at body temperature and ambient pressure. Before each set of measurements, we performed a three-point volume calibration and linearity check using a Collins (Braintree, MA) 3200 3-l super syringe. An analog to digital converter and computer recorded breath-by-breath measurements of minute ventilation ($\dot{V}_E$), tidal volume (V_T), S_pO_2, and $P_{ET_{CO_2}}$.

To determine the steady state ventilatory response to carbon dioxide, the volunteers breathed hyperoxic mixtures ($F_{I_{O_2}} > 0.6$) of oxygen in nitrogen with $P_{ET_{CO_2}}$ held constant at approximately 46 or 54 mmHg for alternate volunteers. After a 6-min equilibration period, we recorded the steady state $\dot{V}_E$ and $P_{ET_{CO_2}}$ during 30 breaths. Then we 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 $F_{I_{O_2}}$ within the breathing circuit to 0.21 and allowing subjects to equilibrate for 2 additional min, we discontinued oxygen inflow to the circuit. As metabolic oxygen consumption progressively decreased $F_{I_{O_2}}$, we continuously recorded $\dot{V}_E$, $P_{ET_{CO_2}}$, and S_pO_2. We adjusted the nitrogen inflow to maintain a constant rebreathing bag volume, and we varied the carbon dioxide absorber flow to maintain a constant $P_{ET_{CO_2}}$ despite changes in ventilation. When S_pO_2 reached approximately 75% (usually 5–7 min after discontinuing oxygen inflow), we terminated data collection and administered 100% oxygen for approximately 30 s. After a 10-min recovery period, we repeated the steady state and hypoxic ventilatory measurements at the alternate carbon dioxide tension (54 or 46 mmHg), whichever was not used previously. Thus, in odd-numbered volunteers, ventilatory measurements were performed first at $P_{ET_{CO_2}} \approx$ 46 mmHg and then at 54 mmHg, whereas in even-numbered volunteers, the sequence was reversed (fig. 1).

After these baseline measurements, we administered a graded alfentanil infusion at 0.6 $\mu g \cdot kg^{-1} \cdot min^{-1}$ for 5 min, 0.18 $\mu g \cdot kg^{-1} \cdot min^{-1}$ for 10 min, and 0.05 $\mu g \cdot kg^{-1} \cdot min^{-1}$ thereafter. We previously showed that this infusion regimen provides constant plasma alfentanil levels of approximately 10 ng/ml and a modest, consistent depression of the ventilatory responses to hypercapnia and hypoxia.[2] Then we determined the ventilatory response to carbon dioxide and hypoxia using the same sequence of carbon dioxide tensions as before. As the alfentanil infusion continued, the volunteers received a single dose of diphenhydramine (0.7 mg/kg given intravenously) over 15 s. After allowing 10 min for effect-site equilibration, we determined the ventilatory response during combined alfentanil and diphenhydramine, again using the same sequence of carbon dioxide tensions.

Data Analysis

Because of breath-to-breath variability in respiratory variables, five-breath average values of $\dot{V}_E$, V_T, $P_{ET_{CO_2}}$, and percent S_pO_2 were used throughout the analysis. To

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determine the steady state ventilatory response to carbon dioxide, we used 12 of these five-breath averages as data points for the linear regressions of $\dot{V}_E$ and V_T *versus* $P_{ET_{CO_2}}$; six of these points have $P_{ET_{CO_2}} \approx 46$ mmHg, whereas the other six points have $P_{ET_{CO_2}} \approx 54$ mmHg. The ventilatory response to isocapnic hypoxemia was determined during mild ($P_{ET_{CO_2}} \approx 46$ mmHg) and moderate ($P_{ET_{CO_2}} \approx 54$ mmHg) hypercapnia by least-squares linear regression of $\dot{V}_E$ *versus* S_pO_2. Values of $\dot{V}_E$ at $S_pO_2 = 90\%$ indicated the position of the hypoxic ventilatory response curve.

We analyzed the data using two-way (volunteers × study conditions) analysis of variance with significance set at $P \leq 0.05$. If analysis of variance revealed overall significant differences between study conditions (baseline, alfentanil, alfentanil plus diphenhydramine), we used Fisher's protected least-significant difference test to isolate the source of the differences. Data are shown as mean ± SD.

Results

After receiving alfentanil, all volunteers were mildly sedated, responsive to verbal commands in a normal tone, and had mild ptosis or a "glazed" appearance of the eyes. This corresponds to a change from 5 to 4 on the Observers Assessment of Alertness/Sedation Scale.[4] The addition of diphenhydramine produced additional subjective sedation (*i.e.*, volunteers reported feeling more drowsy); however, none of the volunteers was sedated enough to meet the criteria for an Observers Assessment of Alertness/Sedation Scale score of 3 (marked ptosis or spontaneous eye closure with response to loud verbal commands) after receiving diphenhydramine.

The slope of the ventilatory response to hypercapnia decreased from 1.08 ± 0.38 to 0.79 ± 0.36 l · min^{-1} · mmHg^{-1} ($P < 0.05$, table 1) during alfentanil infusion; with the addition of diphenhydramine, the slope increased to 1.17 ± 0.28 l · min^{-1} · mmHg^{-1} ($P < 0.05$). The $\dot{V}_E$ at $P_{ET_{CO_2}} \approx 46$ mmHg ($\dot{V}_E46$) decreased from 12.1 ± 3.7 to 9.7 ± 3.6 l/min ($P < 0.05$, fig. 2) during alfentanil infusion. This resulted from a decrease in the V_T at $P_{ET_{CO_2}} = 46$ mmHg (V_T46) from 882 ± 347 to 699 ± 319 ml ($P < 0.05$) because respiratory rate was unaffected by alfentanil. After diphenhydramine, $\dot{V}_E46$ was 9.9 ± 2.9 l/min and V_T46 was 608 ± 134 ml; these values did not differ significantly from those observed during alfentanil, but they remained significantly lower than baseline ($P < 0.05$). During alfentanil infusion,

Table 1. Individual CO_2 Response Data

Subject number	Pretest							Alfentanil							Diphenhydramine + Alfentanil						
	Low CO_2			High CO_2				Low CO_2			High CO_2				Low CO_2			High CO_2			
	CO_2	V_E	V_T	Rate	Co_2	V_E	V_T	Rate	Slope	CO_2	V_E	V_T	Rate	CO_2	V_E	V_T	Rate	Slope	CO_2	V_E	V_T	Rate	Slope
1	46.4	10.7	1,478	7.2	54.2	19.2	1,334	14.4	1.09	46.5	11.0	1,441	7.6	54.2	16.8	1,370	12.2	0.73	46.7	8.2	620	13.3	53.7	16.1	1,122	14.3	1.12
2	46.1	14.1	836	16.8	54.0	24.4	1,476	16.5	1.27	45.5	9.4	734	12.8	53.5	14.8	982	15.1	0.66	45.3	12.0	789	15.1	53.0	22.0	1,220	18.1	1.29
3	45.4	16.3	1,330	12.2	53.9	25.3	2,560	9.9	1.03	44.6	9.0	720	12.5	54.0	22.0	1,736	12.7	1.37	45.4	10.0	717	14.0	53.7	22.8	1,447	15.7	1.54
4	46.2	5.9	597	9.9	54.7	16.6	1,426	11.7	1.24	49.4	6.2	500	12.5	54.2	7.8	635	12.3	0.32	47.0	8.0	500	16.0	54.1	17.5	1,314	13.3	1.28
5	45.6	12.7	645	19.7	53.6	27.4	1,253	21.9	1.83	46.4	10.9	566	19.3	55.6	20.5	1,025	20.0	1.02	45.3	9.6	514	18.7	55.2	23.6	1,110	21.3	1.39
6	45.7	16.9	819	20.6	55.5	24.3	1,032	23.5	0.77	46.1	17.3	667	25.9	55.8	21.0	921	22.8	0.38	45.8	16.0	740	21.7	55.5	21.9	891	24.6	0.61
7	45.6	11.4	846	13.5	55.7	19.8	1,163	17.0	0.83	46.9	7.7	542	14.1	55.1	17.0	1,099	15.5	1.14	44.9	9.0	583	15.4	57.1	22.7	1,349	16.8	1.08
8	46.7	8.6	504	17.0	54.9	13.5	771	17.5	0.61	45.4	6.1	421	14.6	55.4	13.1	835	15.7	0.7	45.7	6.8	404	16.7	55.4	17.1	858	19.9	1.06
Mean	46.0	12.1	882	14.6	54.6	21.3	1,377	16.5	1.08	46.3	9.7*	699*	14.9	54.7	16.6*	1,075	15.8	0.79*	45.8	9.9*	608*	16.3	54.7	20.5†	1,164	18.0†	1.17†
SD	0.5	3.7	347	4.7	0.8	4.8	529	4.6	0.38	1.4	3.6	319	5.5	0.9	4.7	340	3.8	0.36	0.7	2.9	134	2.7	1.3	3.0	211	3.8	0.28

* $P < 0.05$ *versus* pretest.
† $P < 0.05$ *versus* alfentanil.

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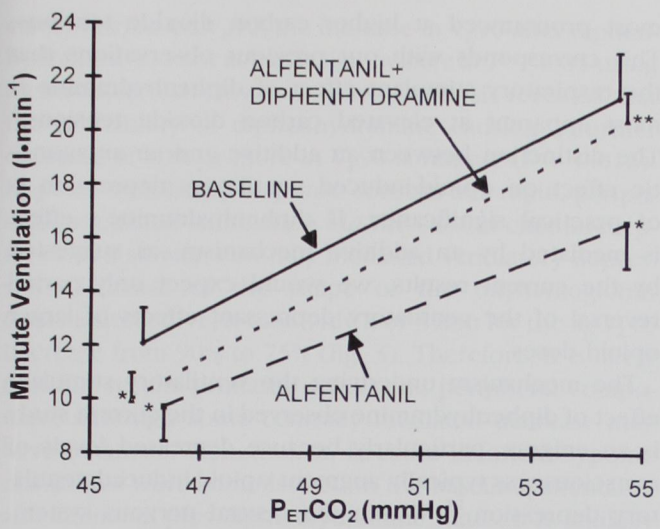

Fig. 2. Mean steady state carbon dioxide ventilatory response curves during hyperoxia ($F_{I_{O_2}} > 0.5$). Data are shown at baseline, during alfentanil infusion, and during alfentanil plus diphenhydramine administration. Error bars represent 1 SEM. (*$P < 0.05$ *vs.* baseline; **$P < 0.05$ *vs.* alfentanil.)

$\dot{V}_E54$ decreased from 21.3 ± 4.8 to 16.6 ± 4.7 l/min ($P < 0.05$); with diphenhydramine, this variable increased to 20.5 ± 3.0 l/min ($P < 0.05$). The decrease in $\dot{V}_E54$ was associated with a borderline-significant decrease in V_T from 1,377 ± 529 to 1,075 ± 340 l/min ($P = 0.08$) and no significant change in respiratory rate. In contrast, the increase in $\dot{V}_E54$ with diphenhydramine was associated with an increase in respiratory rate to 18 ± 3.8 breaths/min ($P < 0.05$), whereas the increase in V_T to 1,164 ± 211 was not significant.

During mild hypercapnia ($P_{ET_{CO_2}} \approx 46$ mmHg), the slope of the hypoxic ventilatory response did not change significantly between baseline, alfentanil, and alfentanil plus diphenhydramine trials (0.56 ± 0.38, 0.46 ± 0.27, 0.44 ± 0.21 $l \cdot min^{-1} \cdot \%S_pO_2^{-1}$, respectively). Similarly, the computed $\dot{V}_E$ at a $S_pO_2 = 90\%$ ($\dot{V}_E90$) was not significantly affected by alfentanil or diphenhydramine (11.8 ± 2.6, 10.1 ± 2.1, 10.1 ± 1.4 l/min for baseline, alfentanil, and alfentanil plus diphenhydramine, respectively). The $P_{ET_{CO_2}}$ was 45.9 ± 0.7, 46.1 ± 0.7, and 45.6 ± 0.5 mmHg during baseline, alfentanil, and alfentanil plus diphenhydramine trials, ensuring that our measurements of the hypoxic ventilatory response were not confounded by systematic changes in $P_{ET_{CO_2}}$. Figure 3 shows an example of an individual hypoxic response determination.

During moderate hypercapnia ($P_{ET_{CO_2}} \approx 54$ mmHg), neither the decrease in slope of the hypoxic ventilatory response from 1.20 ± 0.80 to 0.96 ± 0.52 $l \cdot min^{-1} \cdot \%S_pO_2^{-1}$ during alfentanil nor the subsequent increase in slope to 1.05 ± 0.73 $l \cdot min^{-1} \cdot \%S_pO_2^{-1}$ during alfentanil plus diphenhydramine was significant (fig. 4). However, $\dot{V}_E90$ decreased significantly from 30.5 ± 9.7 to 23.1 ± 6.9 l/min during alfentanil ($P < 0.05$). After diphenhydramine, the increase in $\dot{V}_E90$ to 27.2 ± 9.2 l/min just failed to achieve significance ($P = 0.057$). The $P_{ET_{CO_2}}$ was 54.2 ± 0.4, 54.4 ± 0.9, and 54.5 ± 0.9 mmHg during baseline, alfentanil, and alfentanil plus diphenhydramine, again implying that our measurements of hypoxic ventilatory response were not confounded by systematic changes in $P_{ET_{CO_2}}$.

Discussion

We designed this study using a relatively low-dose alfentanil infusion that produced a significant depression in ventilatory drive but still allowed us to observe further diphenhydramine-induced ventilatory depression if it occurred. The appropriateness of our alfentanil dose was confirmed by our observation that the decrease in ventilatory response to carbon dioxide was similar to that seen after epidural or intramuscular fentanyl,[5,6] alfentanil,[7] or morphine.[8-10]

We began the diphenhydramine plus alfentanil ventilatory measurements 10 min after diphenhydramine was administered. Although the time necessary for equilibration of diphenhydramine at its effect sites in the brain has not been reported, clinical experience in the treatment of dystonic reactions after phenothiazine administration suggests a rapid (within minutes) onset of ac-

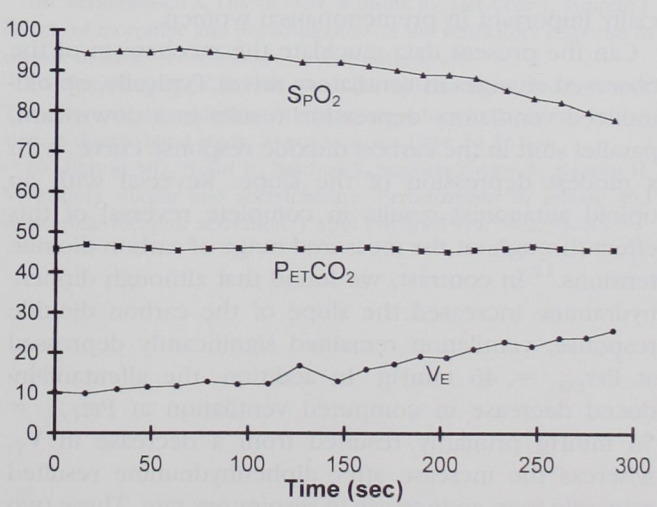

Fig. 3. Hypoxic response determination from a single volunteer at $P_{ET_{CO_2}} \approx 46$ mmHg. The hypoxic response was computed from the linear regression of minute ventilation $\dot{V}_E$ *vs.* S_pO_2.

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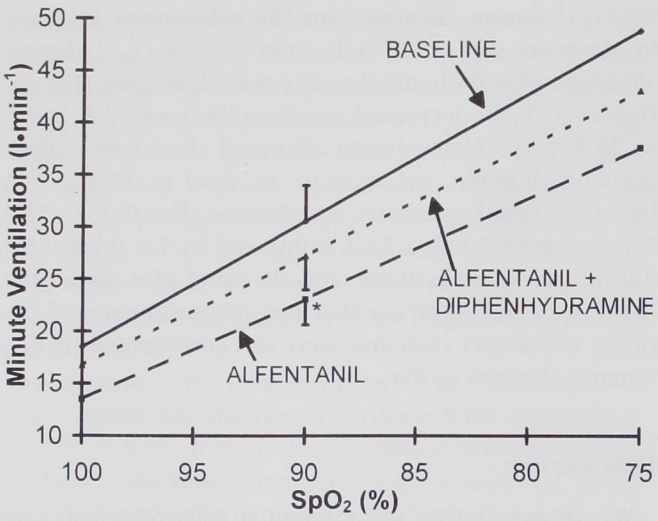

Fig. 4. The mean hypoxic ventilatory response curves at $P_{ET_{CO_2}}$ ≈ 54 mmHg. Data are shown at baseline, during alfentanil infusion, and during alfentanil plus diphenhydramine administration. Error bars represent 1 SEM. (*P < 0.05 *vs.* baseline $\dot{V}_E$90; slopes do not differ among study conditions.)

tion.[11] In addition, our volunteers seemed to reach a stable level of subjective sedation within about 5 min. Despite the sedative effect of diphenhydramine, its concomitant administration did not further depress ventilatory drive. In fact, diphenhydramine increased the slope of the ventilatory response to hypercarbia, restoring it to baseline levels, and did not further depress hypoxic ventilatory response. Each volunteer was studied on a single day; although this precluded the use of a placebo control, it avoided the problems associated with day-to-day variations in ventilatory drive, which may be especially important in premenopausal women.

Can the present data elucidate the mechanism of the observed changes in ventilatory drive? Typically, opioid-induced ventilatory depression results in a downward, parallel shift in the carbon dioxide response curve, with a modest depression of the slope. Reversal with an opioid antagonist results in complete reversal of this effect throughout the measured range of carbon dioxide tensions.[12] In contrast, we found that although diphenhydramine increased the slope of the carbon dioxide response, ventilation remained significantly depressed at $P_{ET_{CO_2}}$ = 46 mmHg. In addition, the alfentanil-induced decrease in computed ventilation at $P_{ET_{CO_2}}$ = 54 mmHg primarily resulted from a decrease in V_T, whereas the increase after diphenhydramine resulted primarily from an increase in respiratory rate. These two observations suggest that diphenhydramine has a nonantagonistic, additive effect on ventilatory drive that is most pronounced at higher carbon dioxide tensions. This corresponds with our previous observations that the respiratory stimulant effect of diphenhydramine is most apparent at elevated carbon dioxide tensions.[1] The distinction between an additive and an antagonistic effect on opioid-induced ventilatory depression is of practical significance. If diphenhydramine's effect is mediated by an additive mechanism, as suggested by the current results, we would expect only partial reversal of the ventilatory depressant effects of larger opioid doses.

The mechanism underlying the ventilatory stimulant effect of diphenhydramine observed in the current study is an enigma, particularly because decreased levels of consciousness typically augment opioid-induced ventilatory depression.[13] Within the central nervous system, histamine activation of H1 and H2 receptors increases production of cyclic adenosine monophosphate,[14] which would be expected to stimulate ventilation.[15] On this basis, H1 blockade by diphenhydramine should depress rather than augment ventilatory drive. Diphenhydramine also has central anticholinergic activity. Because ventilatory drive is proportional to acetylcholine activity in medullary respiratory centers,[16] the anticholinergic activity of diphenhydramine would be expected to further depress ventilatory drive. However, in certain circumstances, increased acetylcholine activity after physostigmine may be associated with ventilatory depression: Gesell[17] observed that physostigmine depresses phrenic nerve activity in dogs, whereas Berkenbosch *et al.*[18] described a physostigmine-induced decrease in both the central and the peripheral components of the carbon dioxide response slope in cats. In addition, Spaulding *et al.*[19] reported impaired recovery of ventilatory drive when physostigmine was administered to diazepam-sedated volunteers. Therefore, in some circumstances, muscarinic blockade might stimulate rather than depress ventilation. In fact, Burton *et al.*[20] found that selective M2 antagonism in the isolated neonatal rat brain stem stimulates phrenic nerve output. Conceivably, selective cholinergic blockade by diphenhydramine could account for the ventilatory stimulation we observed. This mechanism is also consistent with our observation that the effect of diphenhydramine was most pronounced during hypercarpnic conditions, suggesting a central rather than peripheral mechanism of ventilatory stimulation.

The effect of diphenhydramine on the hypoxic ventilatory response was less pronounced than its effect on carbon dioxide response. Although alfentanil signifi-

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cantly decreased $\dot{V}_E90$, the increase in $\dot{V}_E90$ after diphenhydramine did not achieve significance at $P = 0.05$ using a two-tailed test. However, power analysis revealed that the probability of diphenhydramine causing a further decrease of 10% or more in $\dot{V}_E90$ is remote ($P = 0.016$). Hypoxic ventilatory response consists of a rapid, peripherally mediated stimulation *via* the carotid chemoreceptors and a slower, centrally mediated ventilatory depression. Because of the shape of the oxyhemoglobin dissociation curve, it took only 2 or 3 min for the S_pO_2 to decrease from 90% to 75% (fig. 3). Therefore, it is likely that our results primarily reflect the peripheral component, although some centrally mediated decrease may have occurred. Nonetheless, because identical hypoxic challenges were administered in the baseline, alfentanil, and alfentanil plus diphenhydramine states, it is unlikely that differences in the contribution of central *versus* peripheral control mechanisms during the three study conditions significantly affected our results.

Diphenhydramine is prescribed widely as an antipruritic, an antiemetic, and a sedative in patients receiving systemic or neuraxial opioids. The current findings help to explain the long-standing record of the safety of diphenhydramine when administered to various patients for these indications.

References

1. Alexander CM, Seifert HA, Blouin RT, Conard PF, Gross JB: Diphenhydramine enhances the interaction of hypercarbic and hypoxic ventilatory drive. ANESTHESIOLOGY 1994; 80:789–95

2. Gross JB, Blouin RT, Zandsberg S, Conard PF, Häussler J: Effect of flumazenil on ventilatory drive during sedation with midazolam and alfentanil. ANESTHESIOLOGY 1996; 85:713–20

3. Rebuck AS, Campbell EJM: A clinical method for assessing the ventilatory response to hypoxia. Am Rev Respir Dis 1974; 109:345–50

4. Chernik DA, Gillings D, Laine H, Hendler J, Silver JM, Davidson AB, Schwarm EM, Siegel JL: Validity and reliability of the Observer's Assessment of Alertness/Sedation Scale: Study with intravenous midazolam. J Clin Psychopharmacol 1990; 10:244–51

5. Negre I, Gueneron JP, Ecoffey C, Penon C, Gross JB, Levron, JC, Samii K: Ventilatory response to carbon dioxide after intramuscular and epidural fentanyl. Anesth Analg 1987; 66:707–10

6. Morrisot P, Dessanges JF, Regnard J, Lockhart A: Ventilatory response to carbon dioxide during extradural anaesthesia with lignocaine, and fentanyl. Br J Anaesth 1989; 63:97–102

7. Penon C, Negre I, Ecoffey C, Gross JB, Levron JC, Samii K: Analgesia and ventilatory response to carbon dioxide after intramuscular and epidural alfentanil. Anesth Analg 1988; 67:313–7

8. Camporesi EM, Nielsen CH, Bromage PR, Durant PAC: Ventilatory CO_2 sensitivity after intravenous and epidural morphine in volunteers. Anesth Analg 1983; 62:633–40

9. Knill RL, Clement JL, Thompson WR: Epidural Morphine causes delayed and prolonged ventilatory depression. Can J Anaesth 1981; 28:537–43

10. Kafer ER, Brown, JT, Scott D, Findlay JWA, Butz RF, Teeple E, Ghia JN: Biphasic depression of ventilatory responses to CO_2 following epidural morphine. ANESTHESIOLOGY 1983; 58:418–27

11. Iserson KV: Tranquilizer overdose, Emergency Medicine. 2nd edition. Edited by Rosen P. St. Louis, CV Mosby, 1988, p 2105

12. Konieczko KM, Jones JG, Barrowcliffe MP, Jordan C, Altman DG: Antagonism of morphine-induced respiratory depression with nalmefene. Br J Anaesth 1988; 61:318–23

13. Forrest WH, Bellville JW: The effect of sleep plus morphine on the respiratory response to carbon dioxide. ANESTHESIOLOGY 1964; 25: 137–41

14. Johnson C: Histamine receptors and cyclic nucleotides, Pharmacology of Histamine Receptors. Edited by Ganellin CR, Parsons ME. Bristol, United Kingdom, John Wright & Sons, 1982, pp 192–200

15. Howell LL: Comparative effects of caffeine and selective phosphodiesterase inhibitors on respiration and behavior in rhesus monkeys. J Pharmacol Exp Ther 1993; 266:894–903

16. Burton MD, Johnson DC, Kazemi H: Adrenergic and cholinergic interaction in central ventilatory control. J Appl Physiol 1990; 68: 2092–9

17. Gesell R, Hansen ET: Eserine, acetylcholine, atropine, and nervous integration. Am J Physiol 1943; 139:371–85

18. Berkenbosch A, Olievier CN, Wolsink JG, DeGoede J, Rupreht J: Effects of morphine and physostigmine on the ventilatory response to carbon dioxide. ANESTHESIOLOGY 1994; 80:1303–10

19. Spaulding BC, Choi SD, Gross JB, Apfelbaum JL, Broderson H: The effect of physostigmine on diazepam-induced ventilatory depression: A double-blind study. ANESTHESIOLOGY 1984; 61:551–4

20. Burton MD, Nouri K, Baichoo S, Samuels-Toyloy N, Kazemi H: Ventilatory output and acetylcholine: Perturbations in release and muscarinic receptor activation. J Appl Physiol 1994; 77:2275–84

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