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Time Course of Ventilatory Response to Carbon Dioxide after Intravenous Diazepam

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Dual isohypercapnic studies of the time course of depression following intravenous diazepam permit detailed analysis of changes in the ventilatory response to carbon dioxide. The mean slope of the CO_2 response curves of eight healthy volunteers dropped from 2.38 to 1.21 $l \cdot min^{-1} \cdot mmHg^{-1}$ ($P < 0.05$) within three minutes after injection of diazepam 0.4 mg/kg. Twenty-five minutes after injection, the slope was only 1.49 $l \cdot min^{-1} \cdot mmHg^{-1}$, still significantly lower than control ($P < 0.05$). At 30 min, the slope had increased to 1.73 $l \cdot min^{-1} \cdot mmHg^{-1}$ and was no longer different from control at the 0.05 level of significance. There was also a significant correlation between the slope of the CO_2 response curve and level of consciousness ($r = 0.81$). There was little or no displacement of the response curve at any selected ventilation except as accounted for by the slope change. The authors conclude that ventilatory depression resulting from intravenous diazepam begins within one minute and lasts at least 25 min after injection. (Key words: Carbon dioxide: ventilatory response. Hypnotics: benzodiazepines, diazepam. Ventilation: carbon dioxide response.)

IN 1970, CATCHLOVE AND KAFER[1] studied the ventilatory effects of intravenous diazepam in 13 healthy volunteers. Using a modification of Read's rebreathing technique[2] they found inconsistent changes in the slope of the CO_2 response curve 15–20 min after 0.14 mg/kg diazepam. Forster *et al.*[3,4] reported in 1979 that intravenous 0.3 mg/kg diazepam reduced the slope of the CO_2 response curve from 1.85 to 1.26 $l \cdot min^{-1} \cdot mmHg^{-1}$ between four and nine minutes after injection. Unfortunately, neither of these studies delineated the time course of the diazepam-induced respiratory depression, and both are assumed to have systematically *over estimated* the slope due to a waning drug effect during the study.

The two-point isohypercapnic technique described by Zebrowski *et al.*[5] enabled us to measure the slope of the CO_2 response curve continuously after the injection of a sedative drug; our goal was to determine the time course of diazepam-induced ventilatory depression. To maximize the change, we chose a dose of diazepam which is hypnotic in most normal individuals, 0.4 mg/kg, and attempted to correlate the degree of ventilatory depression with the degree of sedation at the time of measurement.

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Methods

SUBJECTS

Eight ASA PS I, informed, consenting male volunteers ranged in age from 19 to 50 years. None had any clinical impairment of pulmonary function and none was allergic to medications of the benzodiazepine class. Subjects refrained from consuming any caffeine- or alcohol-containing beverages for 24 h prior to each study, and had nothing by mouth for at least eight hours before each test. Our institutional review committees approved the study.

PROCEDURE

After establishment of an intravenous infusion and electrocardiographic and blood pressure (Arteriosonde®) monitoring, the supine subjects breathed a mixture of oxygen and carbon dioxide from a rebreathing circuit incorporating variable carbon dioxide absorption and continuous Capnographic® carbon dioxide analysis at the mask (fig. 1). A dry spirometer (Electro/Med #780®) calibrated with a one-liter supersyringe measured ventilatory exchange. Mixtures of carbon dioxide in oxygen, standardized by microscholander analysis, served to calibrate the Capnograph. A dual servo Gilson® polygraph continuously recorded ventilation, airway CO_2 tension, and the electrocardiogram.

We obtained four-point CO_2 response curves for each subject (end-tidal CO_2 tensions of 40, 46, 52, and 58 mmHg) allowing eight minutes for equilibration at each P_{CO_2}. We then held the end-tidal CO_2 tension constant at either 46 or 58 mmHg (for alternate subjects) while injecting 0.4 mg/kg diazepam over a 15-s interval. Careful adjustment of flow through the absorber usually kept the end-tidal CO_2 tension within ±1 mmHg despite changes in the subjects' ventilatory pattern. At 30-s intervals we verbally stimulated the subjects for approximately 15 s and noted the degree of responsiveness on a five-point scale (table 1). The study was continued for 30 min; the subjects were then taken to the postanesthesia room until they were fully awake.

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A minimum of 72 h after his first study, each subject was restudied; this time we maintained an end-tidal CO_2 tension of 58 or 46 mmHg (the value not studied on the first day).

Analysis

Using the spirometer tracings, we measured minute ventilation and mean end-tidal CO_2 tension during each period of verbal stimulation and at selected periods just before stimulation; the measured ventilatory volumes were adjusted to ambient barometric pressure. For each subject, we thus obtained a series of minute ventilations at 30-s intervals, measured with end-tidal CO_2 tensions of both 46 and 58 mmHg. The line joining the minute ventilation at P_{CO_2} = 46 mmHg with the corresponding minute ventilation at P_{CO_2} = 58 mmHg defines the two-point ventilatory response curve at the time of measurement. While we attempted to keep the end-tidal CO_2 tensions constant at 46 and 58 mmHg, respectively, slight variations were inevitable; therefore, the measured end-tidal CO_2 tensions were used to construct the CO_2 response curves.

We used analysis of variance and Dunnett's test[6] to determine whether the observed changes in slope of the ventilatory response curve were significant. A value of $P < 0.05$ was taken to indicate significance. We calculated the mean slopes from the individual slopes at each time after injection, enabling us to assess the intersubject variability by calculating the associated standard deviations. The correlation between the mean slope of the CO_2 response curves and the mean awareness score at each time after injection was determined by linear regression. We compared awareness at low and high CO_2 levels using the sign test.[7]

Results

The underlying assumption of this study is that, since P_{CO_2} is held constant, the ventilation is a direct measure of the effect of the drug on the central respiratory control system. Our ability to hold CO_2 constant is indicated by the P_{CO_2} values of table 2. The range of CO_2 tensions was from 45.2 to 47.0 mmHg (low CO_2) and from 57.8 to 59.1 mmHg (high CO_2). Additionally, the slopes of the ventilatory responses were calculated from the actual individual CO_2 values at each time. This is as close to a maintained equilibrium of CO_2 as is practical.

The ventilation during the lower isohypercapnic study started at 17.0 l/min and did not change very much (see fig. 2). The lowest value of 15.0 l/min occurred 6 min after injection; the highest was 1 min after injection, when some subjects were experiencing a burning sensation in the injected limb. The ventilation did not change significantly from the nadir for the balance of the study.

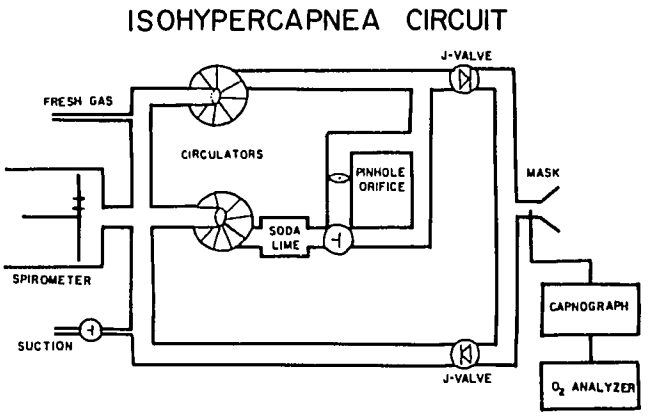

FIG. 1. Breathing circuit with variable CO_2 absorption. The upper circulator ensures rapid mixing and homogeneity of the gases within the circuit. The lower circulator is variable in speed and was adjusted manually based on breath-to-breath end-tidal CO_2 measurements to keep end-tidal P_{CO_2} within the desired range.

Ventilation at the higher carbon dioxide tension started at 46.4 l/min and fell nearly monotonically to a nadir of 31.2 l/min (67 per cent of control), also at 6 min after injection. In contrast to the lower CO_2 study, this decrease was highly significant ($P < .01$). Over the next 24 min, the ventilation improved significantly in each subject ($P < 0.01$) but reached only 80 per cent of the control value.

There was a consistent decrease in the slope of the CO_2 response within one minute of injection (table 2, and figure 3), the mean slope decreasing by 34 per cent from 2.38 to 1.56 $l \cdot min^{-1} \cdot mmHg^{-1}$ ($P < 0.05$). Three minutes after injection, the mean slope had declined nearly 50 per cent to its nadir of 1.21 $l \cdot min^{-1} \cdot mmHg^{-1}$ ($P < 0.05$). The ventilatory response to CO_2 remained depressed for the duration of our 30-min study interval, rising to only 1.73 $l \cdot min^{-1} \cdot mmHg^{-1}$ at that time ($P \approx 0.05$ compared to control). There was no significant change in slope between 3 and 10 min (encompassing the nadir of the ventilatory depression at 6 min).

As suggested in figure 4, there is a significant correlation ($r = 0.81$) between the degree of awareness and the slope of the CO_2 response curve at each time after injection. However, the degree of sedation observed varied considerably from subject to subject. While some individuals became unarousable after two minutes, others never lost consciousness, and one individual became extremely talkative during the study period.

TABLE 1. Definition of Awareness Scores

4—Awake and alert
3—Awake but drowsy
2—Asleep but opens eyes to verbal command
1—Asleep and unresponsive to verbal stimulation, lash reflex present
0—Asleep, lash reflex absent

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TABLE 2. Overall Mean Values (±SD) of Ventilatory Measurements and Awareness after Intravenous Diazepam

Time (min)	Low CO_2		High CO_2		Mean of Slopes ($l \cdot min^{-1} \cdot mmHg^{-1}$)	Awareness
	P_{CO_2} (mmHg)	V_E (l/min)	P_{CO_2} (mmHg)	V_E (l/min)		
0.0	46.6 ± 0.7	17.0 ± 5.1	58.9 ± 1.7	46.4 ± 14.7	2.38 ± 0.90	4.0
0.5	47.0 ± 0.5	17.4 ± 4.9	58.9 ± 1.7	37.2 ± 5.1	1.67 ± 0.38	3.4 ± 0.5
1.0	46.0 ± 0.5	17.9 ± 5.7	59.1 ± 3.2	37.7 ± 8.7	1.56 ± 0.52*	2.8 ± 1.0
1.5	46.0 ± 1.0	16.6 ± 5.6	58.3 ± 1.6	34.9 ± 6.4	1.50 ± 0.25*	2.6 ± 1.0
2.0	45.4 ± 0.8	16.7 ± 5.9	58.4 ± 1.7	33.9 ± 8.5	1.34 ± 0.36†	2.5 ± 0.9
2.5	45.6 ± 1.3	15.8 ± 6.2	58.1 ± 1.7	33.7 ± 9.6	1.46 ± 0.43*	2.4 ± 0.9
3.0	45.6 ± 1.0	16.7 ± 6.8	57.9 ± 1.6	31.7 ± 8.7	1.21 ± 0.48†	2.3 ± 0.9
3.5	45.8 ± 0.6	15.5 ± 5.6	57.9 ± 1.9	33.0 ± 11.3	1.47 ± 0.62*	2.2 ± 0.9
4.0	46.0 ± 0.9	15.4 ± 4.6	58.2 ± 2.0	33.2 ± 11.6	1.50 ± 0.76*	2.1 ± 1.0
4.5	46.4 ± 0.9	15.3 ± 7.0	58.0 ± 2.1	34.1 ± 10.9	1.65 ± 0.62	2.1 ± 1.0
5.0	45.8 ± 1.0	15.4 ± 5.6	58.0 ± 1.4	33.8 ± 10.7	1.54 ± 0.60*	2.1 ± 0.9
6.0	46.0 ± 1.0	15.0 ± 5.4	57.9 ± 2.0	31.2 ± 9.7	1.44 ± 0.65†	2.1 ± 1.0
8.0	46.1 ± 0.7	15.7 ± 7.2	58.4 ± 1.5	32.6 ± 10.9	1.38 ± 0.54†	1.8 ± 1.1
10.0	45.7 ± 0.7	16.3 ± 8.3	58.6 ± 1.8	33.7 ± 12.0	1.34 ± 0.48†	2.0 ± 1.2
12.0	45.7 ± 0.7	15.1 ± 5.1	58.5 ± 1.6	32.2 ± 10.7	1.35 ± 0.61†	2.1 ± 1.1
15.0	45.4 ± 0.7	14.8 ± 5.9	58.2 ± 1.8	31.5 ± 7.5	1.31 ± 0.41†	2.1 ± 1.2
18.0	45.2 ± 0.6	15.2 ± 5.0	58.3 ± 1.5	32.9 ± 10.2	1.36 ± 0.57†	2.1 ± 1.3
20.0	45.2 ± 0.6	16.1 ± 6.2	58.1 ± 1.8	31.4 ± 9.4	1.19 ± 0.53†	2.1 ± 1.3
25.0	45.3 ± 0.8	15.8 ± 6.9	58.4 ± 2.0	34.8 ± 7.7	1.49 ± 0.48*	2.1 ± 1.5
30.0	45.6 ± 0.9	15.8 ± 6.3	57.8 ± 0.7	37.0 ± 10.0	1.73 ± 0.45	2.6 ± 1.0

* $P < 0.05$ compared to control.

† $P < 0.01$ compared to control.

Some individuals demonstrated different awareness scores at the same time after injection during their two studies; however, the scores were within ±1 in all but seven of 158 pairs of observations. Increased P_{CO_2} was associated with increased awareness in 57 pairs of observations, and decreased awareness in only 15 pairs of observations ($P < 0.05$).

Discussion

Diazepam, when given intravenously in hypnotic doses, causes a significant depression of the ventilatory response to CO_2 in normal volunteers. This finding is, of course, in agreement with the findings of Catchlove and Forster. We have shown, in addition, that this de-

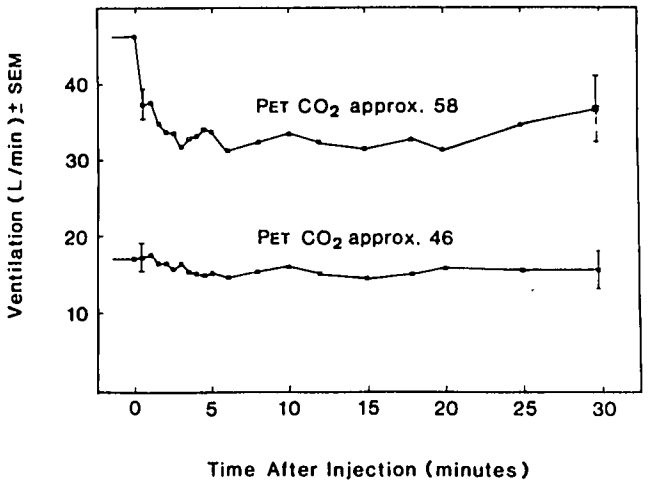

FIG. 2. Mean (±SEM) minute ventilation after 0.4 mg/kg diazepam measured with end-tidal P_{CO_2} maintained at approximately 46 and 58 mmHg.

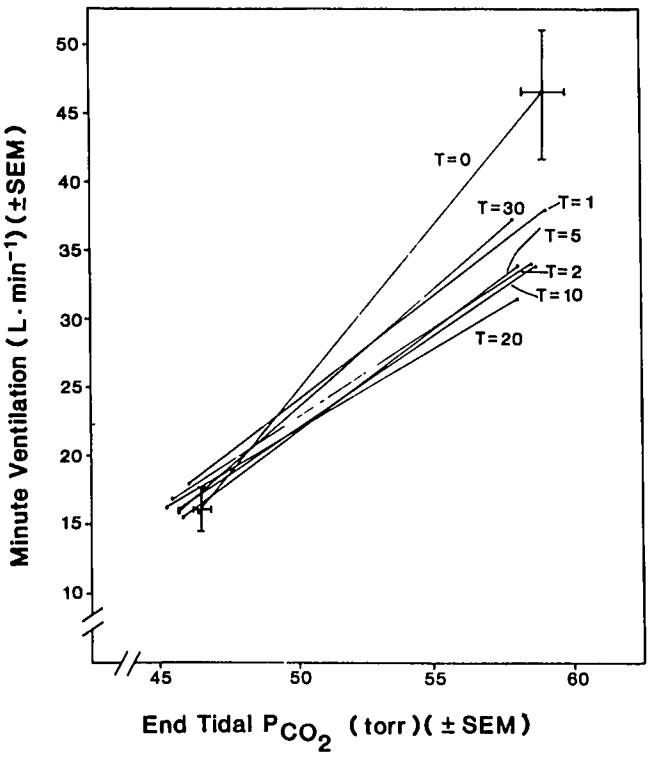

FIG. 3. Constructed two-point CO_2 response curves for eight subjects before (time = 0) and at representative times after intravenous diazepam (0.4 mg/kg).

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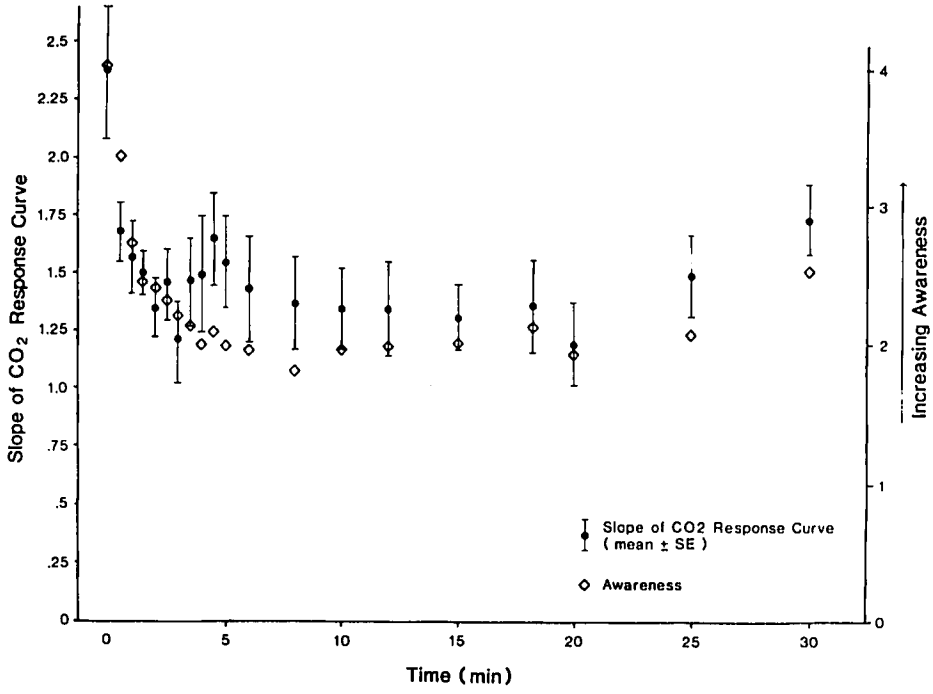

FIG. 4. Slope of CO_2 response curves (±SEM) ($l \cdot min^{-1} \cdot mmHg^{-1}$) and awareness scores during the 30 min following the intravenous injection of diazepam.

pressant effect begins within one minute of injection, peaks at three minutes, and lasts for at least 30 minutes after injection.

We have also shown that there was a correlation between the degree of ventilatory depression and the state of consciousness of our subjects. It should be noted that we measured minute ventilation during intervals when our subjects were stimulated verbally, to provide a consistent environment for our measurements. As expected, ventilation was even more depressed in the absence of stimulation. Thus, a patient who is ventilating adequately in the immediate postoperative period, might hypoventilate when removed from the stimulating environment of the operating and recovery rooms. Additionally, a mild arousal by elevated CO_2 tensions systematically increases the slope as we calculate it; this error also exists with the Read rebreathing studies of Catchlove and Forster. Although stimulation did not change the mean slope of the ventilatory response to CO_2 significantly, ventilation in individual subjects was increased consistently after stimulation ($P < 0.05$).

General anesthesia, as shown by many different groups of investigators, decreases the slope of the ventilatory response by 35 to 50 per cent in light planes.[8] We observed a similar degree of depression after diazepam, but the subjects were for the most part not anesthetized: *i.e.*, they were still responsive. Thus, intravenous diazepam in sedative doses (0.4 mg/kg) is no less of a respiratory depressant than modern inhalational anesthetics.

The depressant effect of intravenous 0.4 mg/kg diazepam lasts a minimum of 30 min. Our findings therefore suggest that the indiscriminant use of intravenous diazepam in suboptimally monitored situations by physicians not skilled at airway management might entail considerable risk, as significant depression of both mental state and ventilatory drive can occur within one minute of injection.

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