Respiratory Depression Following Diazepam: Reversal with High-dose Naloxone


The authors compared the effects of naloxone and saline solution on the respiratory changes following diazepam in a double-blind crossover trial in six subjects. Following baseline measurements of respiration, each subject was given diazepam, 15 mg, intravenously. Sixty and ninety-five minutes later each subject received either two doses of naloxone, 15 mg, intravenously, or two doses of the equivalent volume of saline solution. Forty-five minutes after diazepam administration the slopes of the curves of the ventilatory responses to rebreathing carbon dioxide (Vd/PETCO2) were depressed to 55 per cent of control (P < 0.05). Following the two doses of naloxone, the slopes of Vd/PETCO2 recovered, until, 120 minutes after the second dose of naloxone, slopes had returned to control values. After saline solution, however, slopes remained depressed at 68 per cent of control (P > 0.05). A similar recovery following naloxone was observed in the PETCO2 intercept of the Vd/PETCO2 response curve and in the slope of the mouth-occlusion-pressure response curve to rebreathing carbon dioxide. End-tidal carbon dioxide during quiet breathing and during inspiratory resistive-loaded breathing (60 cm H2O/l/s) showed small increases after diazepam, which were not significantly reduced by naloxone. The results of this study show that diazepam produces respiratory depression, and that this may be relieved by large doses of naloxone. (Key words: Antagonists, narcotic; naloxone. Hypnotics, benzodiazepines: diazepam. Ventilation: anesthetics, effects of; carbon dioxide response.)

The specificity and mode of action of the opiate antagonist naloxone suggest that it is unlikely to reverse the central nervous system depressant effects of non-opiate drugs. However, there are two reports of reversal by naloxone of coma and of respiratory depression following diazepam. The reported effects of diazepam on depression of ventilation are also conflicting. Several groups10–13 have demonstrated significant respiratory depression after diazepam in doses of 5–15 mg/70 kg, while others16–13 found no significant respiratory depression in doses as high as 56 mg/70 kg. We therefore studied, under controlled conditions, the respiratory changes produced by diazepam, and investigated the actions of naloxone and a saline placebo on these changes.

Methods

Six healthy male volunteers, aged 25–45 years, gave informed consent for this study, which was approved by the Hospital Ethical Committee. Each subject was studied on two days separated by approximately a week. On both days diazepam, 15 mg/70 kg, was given intravenously. On one of the days naloxone, 15 mg/70 kg, was given intravenously 60 min and again 95 min after diazepam administration. On the other day, equivalent volumes of saline solution were given at the same time intervals. The injections of naloxone and saline solution were administered in a double-blind manner, the subjects being allocated to receive naloxone or saline solution in a random order.

The course of events throughout the day was as follows. After a light breakfast, each subject arrived at the laboratory at 9.00 A.M. and rested for 45 min, during which time a cannula was inserted in a large vein in the forearm. A series of control measurements of respiration (described below) followed. The subject was then given diazepam, 15 mg/70 kg, iv, mixed with 1 ml of solubilizing agent (20 per cent v/v Cremophor EL, BASF) in 20 ml saline solution. The diazepam was injected over 5 min to reduce the pain of injection and the likelihood of producing thrombophlebitis. Twenty minutes after the injection, the respiratory measurements were repeated, and 60 min after diazepam administration either naloxone, 15 mg/70 kg, or saline solution (38 ml/70 mg) was infused over 5 min through the cannula. Respiratory measurements were again repeated, and 95 min after diazepam administration a further dose of either naloxone, 15 mg/70 kg, or saline solution, 38 ml/70 kg was given. The sequence of respiratory tests was then repeated four times at 45-min intervals.

Four tests were used to evaluate the respiratory effects of these drugs:

Test 1. The ventilatory response to hypercapnia (Vd/PETCO2) was determined by a modified Read rebreathing method similar to that developed by Millidge et al.14 Subjects breathed 50 per cent oxygen for 5 min before being connected to a rebreathing circuit with a capacity of 6 liters, which was primed with a gas mixture of 5 per cent carbon dioxide, 44 per cent nitrogen, and 50 per cent oxygen. Rebreathing was continued until the carbon dioxide concentration increased to 8.5 per cent or until ventilation increased to 70 l/min, whichever occurred first. An electrical spirometer (Ohio Ltd. Model 840) provided an output that was proportional to volume, and this signal was processed to derive continuous minute ventilation. End-
tidal carbon dioxide tension (P_{ETCO2}) was measured using an infrared analyzer (Godart Ltd., Capnograph) that sampled gas at the mouthpiece and then returned it to the circuit. Minute volume was plotted against P_{ETCO2} on an XY recorder (Bryans Southern Instruments Ltd., Model 26000). The rebreathing test was performed in triplicate before diazepam administration and in duplicate thereafter.

Test 2. The mouth-occlusion-pressure response to carbon dioxide was measured simultaneously with test 1, using the same rebreathing circuit. This test, originally described by Whitelaw, Derenne and Milic-Emili, involves occluding the inspiratory limb of the rebreathing circuit for 0.12 sec on occasional breaths during the rebreathing test. The occlusions were produced by activation of a solenoid valve, which was operated by the investigator at 20–30-sec intervals. The subjects were unaware of when the occlusions were to occur. The subatmospheric pressure (P_{0.1}) developed by the inspiratory muscles 0.1 sec after the start of an inspiration was measured by a purpose-built electronic system and plotted automatically against P_{ETCO2} on an XY recorder (Bryans Southern Instruments Ltd., Model 26000). The increase in P_{0.1} resulting from an increase in P_{ETCO2} was expressed as the slope of the mouth-occlusion-pressure response to carbon dioxide (P_{0.1}/P_{ETCO2}).

Test 3. The end-tidal carbon dioxide tension (P_{ETCO2}) was measured with the subjects breathing room air via a nonrebreathing valve (Hook and Tucker, Ltd.) over a period of 7 min. The mean P_{ETCO2} during each 1-min interval was derived electronically.

**Test 4.** In an attempt to simulate the effect of obstructive pulmonary disease on ventilation in sedated patients, the effect of an inspiratory resistive load of 80 cm H2O/l/s on the regulation of ventilation was assessed from measurements of P_{ETCO2} over 7 min. The load was connected to the inspiratory limb of the nonrebreathing valve.

During the tests great care was taken to ensure that the subjects were comfortable and undisturbed. They remained supine throughout and listened to music via headphones. At least 5 min were allowed to elapse between successive rebreathing tests. Periods of 5-min also separated the rebreathing tests and measurements of P_{ETCO2} during resting breathing.

The data from each of the tests were analyzed in the following manner. The slopes of V_E/P_{ETCO2} and P_{0.1}/P_{ETCO2} response curves were determined by drawing a line of best fit (assessed visually) through the linear portion of each curve. The intercepts were determined by extrapolating these lines to zero ventilation and zero pressure for the ventilation and mouth-pressure responses, respectively. The control data used were the means of triplicate measurements made at the start of each day. Slopes measured at intervals following the injection of diazepam were then compared with control data by calculating:

\[
\log_{10} \text{test slope} - \log_{10} \text{mean control slope}
\]

Logarithms of the slopes were used to permit the application of Student's t tests to the data because the distribution of V_E/P_{ETCO2} slopes in the population is skewed (log normal). Our data from this and previ-

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* Saline solution and naloxone were each administered at 60 min and at 95 min.
NALOXONE REVERSAL OF DIAZEPAM RESPIRATORY DEPRESSION

Fig. 1. Mean changes from control (± 1 SEM) in the slopes of the ventilatory response curves to CO₂ shown against time elapsed after diazepam injection. The scale on the right represents the ratio of test and control slopes, expressed in percentages, while that on the left expresses this ratio as a logarithm. Changes from control that are significant are indicated by: *P < 0.05; **P < 0.02 (t test for paired data). Values measured after naloxone treatment that differed significantly from those obtained after administration of saline solution are indicated by: †P < 0.05; ††P < 0.01 (t test for paired data).

Ours studies suggest that P₆/P₆-CO₂ slopes also show a skewed distribution (log normal). Intercepts were compared with control data by calculating (test intercept - mean control intercept). Values of P₆-CO₂ measured at intervals following diazepam administration were compared with P₆-CO₂ prior to diazepam administration by calculating (test P₆-CO₂ - mean control P₆-CO₂). Test P₆-CO₂ was compared with control P₆-CO₂ during breathing with the inspiratory resistive load in a similar way (test P₆-CO₂ [loaded] - mean control P₆-CO₂ [loaded]).

In order to compare data obtained at intervals following diazepam administration with control values, the means of the V₆/P₆-CO₂ slopes and intercepts, and P₆-CO₂ measurements, were calculated at each time interval. Differences between these values and control values were obtained as described above and tested using the t test for paired data. The effects of naloxone and saline solution on the respiratory changes after diazepam were also compared using the t test for paired data.

Results

The Ventilatory Response to Hypercapnia

Table 1 shows the slopes of the V₆/P₆-CO₂ plots for the six subjects throughout both days of the study. The group mean results (fig. 1) showed marked depression (P < 0.05) of the V₆/P₆-CO₂ slope 45 min after diazepam administration. The magnitudes of depression of slopes on the two days of the study were similar. The slope remained significantly depressed (P < 0.05) following the injections of saline solution, but recovered towards control after the naloxone injections. The t test for paired data showed that V₆/P₆-CO₂ slopes during the three-and-a-half hour period after naloxone administration were significantly less depressed than those found after injection of saline solution (P < 0.05).

The P₆-CO₂ intercept of the V₆/P₆-CO₂ response curve showed a shift towards lower P₆-CO₂ following diazepam (fig. 2). On the occasions when saline solution was given, the shift in intercept was significant both 120 min and 165 min after diazepam administration (P < 0.05). The t test for paired data showed that 165
and 210 min following diazepam injection, the shift was significantly less with naloxone than with saline solution \( (P < 0.01)\).

**The Mouth-occlusion-pressure Response to Hypercapnia**

There were significant \( (P < 0.05)\) reductions in the \( P_{\text{ETCO}_2}/P_{\text{ETCO}_2} \) slopes 45 min after diazepam administration that were similar on the two days (fig. 3). Slopes remained significantly depressed after injection of saline solution \( (P < 0.05)\) 120 and 165 min after diazepam administration, and showed more of a tendency to return towards control following naloxone injections. Although mean \( P_{\text{ETCO}_2}/P_{\text{ETCO}_2} \) slopes were less depressed with naloxone than with saline solution, the \( t \) test for paired data showed no significant differences between these slopes. Mean changes in the intercept of the \( P_{\text{ETCO}_2}/P_{\text{ETCO}_2} \) curve were less than 2.2 torr, and there was no significant effect of diazepam, naloxone, or saline solution.

**\( P_{\text{ETCO}_2} \) while Breathing at Rest**

Following diazepam administration there was a small increase in \( P_{\text{ETCO}_2} \) which was significant only on the day saline solution was given \( (P < 0.05)\) (fig. 4). This increase remained after injection of saline solution, and the differences in \( P_{\text{ETCO}_2} \) with naloxone and with saline solution did not achieve statistical significance.

**\( P_{\text{ETCO}_2} \) while Breathing with the Inspiratory Load**

More variability in \( P_{\text{ETCO}_2} \) measurements was encountered during loaded breathing compared with unloaded breathing (fig. 5). None of the changes in \( P_{\text{ETCO}_2} \) was significant, and the \( t \) test for paired data showed no significant difference in values of \( P_{\text{ETCO}_2} \) found with naloxone and with saline solution.

**Discussion**

**The Effects of Diazepam**

Experimental studies of the effects of diazepam on respiration in man have produced conflicting results. Several groups\(^{10–15}\) found no significant respiratory depression when diazepam was administered by the intravenous route in doses as high as 56 mg/70 kg. One
group\textsuperscript{13} even suggested that diazepam reversed respiratory depression produced by meperidine. In contrast, others\textsuperscript{14-18} have shown significant respiratory depression following diazepam in doses of 5–15 mg/70 kg. In one study,\textsuperscript{19} respiratory arrest occurred in three of 15 patients given diazepam (2.5–10 mg) during anesthesia with nitrous oxide, oxygen and halothane. There are several case reports\textsuperscript{19-21} of apnea occurring when diazepam was administered to conscious patients in doses between 2.5 mg and 10 mg. There is one report\textsuperscript{19} of respiratory arrest when diazepam, 5 mg, was given following meperidine (50 mg).

The failure of certain groups\textsuperscript{10-13} to show that diazepam has depressant effects on respiration may be due in part to insensitivity of their methods, and also to the variability in individual responses to diazepam. None of these workers\textsuperscript{10-12} used the slope of the ventilatory response to carbon dioxide in their analyses. On the basis of our study, there seems little doubt that diazepam does have a respiratory depressant action. The depression of the slope of the curve of the ventilatory response to carbon dioxide following diazepam was in fact greater than the depression we observed when morphine, 10 mg, was given to a similar group of volunteers in an earlier trial.\textsuperscript{22} We also observed a significant shift to the left of the zero-ventilation intercept of the ventilatory response curve to carbon dioxide after diazepam, which confirms a previous report.\textsuperscript{8} This shift to the left of the $V_{E}/P_{ETCO_2}$ curve may have compensated for the depression of the $V_{E}/P_{ETCO_2}$ slope so that resting $P_{ETCO_2}$ was little affected —our measurements showed an increase in $P_{ETCO_2}$ of only 1.7 torr at 20 min. The effect of diazepam on the mouth-occlusion-pressure response to carbon dioxide has not been previously reported. We showed that after diazepam there was significant depression of $P_{O_2}/P_{ETCO_2}$ slope, reflecting the changes in $V_{E}/P_{ETCO_2}$ slope. The effects of diazepam on breathing with the inspiratory load showed variable results, and there was nothing to suggest that diazepam interfered with the regulation of breathing against a large resistive load. This is in agreement with the findings of Catchlove and Kafer,\textsuperscript{6,7} who showed that no greater respiratory depression was observed after diazepam in patients with chronic obstructive pulmonary disease than in patients without such disease.

The Effect of Naloxone on Respiratory Changes after Diazepam

Naloxone was shown to reduce significantly both the depression of slope and the displacement of the ventilatory response to carbon dioxide caused by diazepam. It would appear from these findings that large doses of naloxone do act to reverse the respiratory effects of diazepam. In this study it was apparent that these large doses of naloxone were necessary to provide effective reversal, since naloxone, 15 mg/70 kg, only partially reversed the respiratory effects. Furthermore, in a pilot trial in one volunteer, 2.8 mg naloxone produced no apparent change in the respiratory effects of diazepam.

These doses of naloxone are much larger than those that proved effective clinically in reversing coma\textsuperscript{4} and respiratory depression\textsuperscript{5} following diazepam administration (0.4 mg/70 kg and 1.2 mg/70 kg, respectively). These small doses provided rapid reversal of the central nervous system depression, whereas the larger doses used in this trial produced slower recovery. It is possible that in these large doses, naloxone has effects on the central nervous system other than those of a specific opiate antagonist. Naloxone may be acting as a respiratory stimulant at this dose. There are few reports on the effects of large doses of naloxone on respiration. One group\textsuperscript{23} found that doses as high as 1 mg/kg given to dogs produced no significant effect on respiration, and that 1.5 mg/kg produced slight increases in respiratory rate and minute ventilation in rabbits. A study of the pharmacology and abuse potential of naloxone in man\textsuperscript{24} showed that 90 mg naloxone daily had no effect on respiratory rate, the only respiratory variable measured. Another group\textsuperscript{23} reported that 7.5 mg naloxone given to volunteers had no effect on the intercept of the $V_{E}/P_{ETCO_2}$ response curve, but showed a tendency to increase the slope of the $V_{E}/P_{ETCO_2}$ response, although this was not significant.
Although this trial has shown that large doses of naloxone counteract the respiratory effects of diazepam, effective reversal of the central nervous system depression caused by diazepam by use of physostigmine has been demonstrated, and this may be a more appropriate antidote, if one is deemed necessary in clinical use.

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