

Effect of nitrazepam and flurazepam on the ventilatory response to carbon dioxide

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Geddes, D. M., Rudolf, M., and Saunders, K. B. (1976). *Thorax*, 31, 548–551. **Effect of nitrazepam and flurazepam on the ventilatory response to carbon dioxide.** Ventilatory response to CO₂ was measured before and after two different benzodiazepine hypnotics in both chronic bronchitics and patients without chest disease. Flurazepam, but not nitrazepam, produced a significant decrease in CO₂ sensitivity, although there was no significant change in FEV₁ or mixed venous PCO₂. This is the first unequivocal evidence of central depression of respiration by a benzodiazepine and may be the mechanism by which benzodiazepines cause deterioration in patients with respiratory failure.

It is generally accepted that any form of sedative may cause deterioration in a patient with respiratory failure. This has been attributed to depression of central respiratory drive, and impaired ventilatory response to carbon dioxide has been well demonstrated with both morphine and barbiturates (Weil *et al.*, 1975; Gasser, Kaufman, and Bellville, 1975). Benzodiazepines have been reported to cause deterioration in patients with chronic respiratory failure during an acute exacerbation (Clark, Collins, and Tong, 1971), but the effect of these drugs on such patients when they are in a stable state is less well established and the mechanism of the respiratory depression is unknown. In one of the patients reported by Clark *et al.* (1971), administration of nitrazepam was followed by a severe worsening of respiratory failure although that patient had taken the same drug on previous occasions without ill-effect. It was suggested that acute pulmonary infection might increase the susceptibility to respiratory depression. There is, however, no good evidence that benzodiazepines are respiratory depressants in normal subjects or in patients with stable chronic respiratory disease.

We have therefore conducted a double-blind cross-over trial using nitrazepam, flurazepam, and placebo in patients with and without respiratory disease in order to investigate the effects of these drugs on the ventilatory response to CO₂. In Britain, nitrazepam (Mogadon) is the most widely prescribed non-barbiturate hypnotic. Flurazepam

(Dalmane) is a more recently available benzodiazepine which has theoretical advantages since more rapid recovery of skilled performance after equipotent doses of this drug and nitrazepam has been demonstrated (Borland and Nicholson, 1975).

PATIENTS AND METHODS

PATIENTS Twelve patients were studied. The procedure and purpose of the experiment were fully explained to them, and informed consent was obtained. The study had been approved by the hospital's Clinical Investigation Panel. Six patients (4 male, 2 female, aged 49–68) had chronic bronchitis as defined by the Medical Research Council (1965) with spirometric evidence of fixed airways obstruction. All these patients had smoked 10 or more cigarettes per day for more than 10 years. Mixed venous carbon dioxide tension was normal in four and slightly raised in two patients. The remaining six patients (2 male, 4 female, aged 17–69) had no evidence of respiratory disease and were in hospital for the investigation of other unrelated conditions.

METHODS Ventilatory response to CO₂ was measured using the rebreathing technique of Reed (1967), and the result was expressed as the slope of the line obtained by performing least squares regression analysis of the minute ventilation on end-tidal CO₂ tension, ignoring the first 30 seconds of breathing. The intercept of the slope at zero ventilation was also calculated.

Forced expired volume in one second (FEV₁) was measured before each rebreathing procedure using a Vitalograph spirometer, and the best of three attempts was recorded. The mixed venous carbon dioxide tension (P \bar{V} CO₂) was estimated before each rebreathing test according to the method of Campbell and Howell (1962).

PROTOCOL Each patient performed FEV₁, P \bar{V} CO₂, and CO₂ rebreathing tests at least twice before the trial in order to become familiar with the equipment. Measurements were made in the morning with the patient fasting. No drugs were given on the morning of the test, and all patients had taken no form of sedative or hypnotic during the two weeks before the test. FEV₁ and rebreathing P \bar{V} CO₂ were measured. The patient then rested for at least five minutes, after which the ventilatory response to CO₂ was measured. A tablet was then given and observed to be swallowed. The patient rested for two hours without further drugs, coffee, tea or cigarettes, and the measurements were then repeated. Subsequently the measurements were repeated using the other tablets with intervals of at least 48 hours between experiments. The tablet order was randomized and double-blind.

The tablets contained nitrazepam, 5 mg, flurazepam, 15 mg, or placebo.

Differences between pre- and post-drug values were analysed for significance using Student's *t* test for paired data.

RESULTS

VENTILATORY RESPONSE TO CO₂ The results are shown in Table I. There were no significant differences between the control values obtained before each of the three tablets was taken. Neither placebo nor nitrazepam produced any significant change in ventilatory response. However, after flurazepam CO₂ sensitivity was significantly decreased ($P < 0.02$), and indeed no ventilatory response could be detected in two patients after taking this drug. No significant differences between the intercepts at zero ventilation were found.

The bronchitic group had a lower mean ventilatory response than the non-respiratory group, but there was no difference between the two groups in the effect of the drugs on CO₂ responsiveness and they were therefore combined for statistical analysis.

TABLE I
VENTILATORY RESPONSE TO CO₂ EXPRESSED AS
l min⁻¹ kPa⁻¹

Group	Placebo		Nitrazepam		Flurazepam	
	Pre	Post	Pre	Post	Pre	Post
Bronchitic	8.87	10.70	11.23	11.49	9.84	9.08
	1.83	3.78	3.49	2.17	3.05	2.57
	3.06	2.93	3.47	3.41	3.46	0
	2.30	2.85	—	—	1.61	0
	5.85	6.48	5.27	5.79	4.34	5.78
	16.37	12.02	12.16	13.98	14.00	12.61
Non-respiratory	13.94	10.96	—	—	16.22	9.64
	14.15	12.88	11.88	15.90	16.47	13.64
	8.08	9.01	7.68	10.58	10.64	7.97
	7.27	8.40	5.42	3.42	6.53	3.45
	7.20	7.49	10.34	5.20	5.75	7.47
	12.08	7.73	13.62	6.14	11.18	8.08
Mean	8.42 ¹	7.94 ²	8.46 ¹	7.81 ³	8.59 ¹	6.69 ³
SEM	1.40	1.00	1.22	1.53	1.51	1.28

¹No significant difference between pre-drug values.

²No significant difference between pre- and post-drug values.

³Significant decrease in post-drug value ($P < 0.02$).

MIXED VENOUS CO₂ AND FEV₁ The mean values for the two groups are shown in Table II. The bronchitics had a significantly lower mean FEV₁ than the patients without respiratory disease ($P < 0.01$, unpaired *t* test), but there were no significant changes in FEV₁ or P \bar{V} CO₂, after placebo or either drug.

TABLE II
MEAN VALUES FOR FEV₁ (litres) AND P \bar{V} CO₂ (kPa)

	Group	Placebo		Nitrazepam		Flurazepam	
		Pre	Post	Pre	Post	Pre	Post
FEV ₁	Bronchitic	1.48 ¹	1.43 ¹	1.43 ¹	1.45 ¹	1.49 ¹	1.53 ¹
	Non-respiratory	2.78	2.81	2.83	2.86	2.83	2.82
	All subjects	2.13	2.12	2.13	2.15	2.16	2.17
P \bar{V} CO ₂	Bronchitic	6.96	6.45	6.03	6.19	6.84	6.80
	Non-respiratory	6.43	6.43	6.27	6.35	6.03	6.18
	All subjects	6.69	6.44	6.15	6.27	6.43	6.55

¹FEV₁ for bronchitic group significantly less than for non-respiratory group ($P < 0.01$). No significant differences between pre- and post-drug values of FEV₁ or P \bar{V} CO₂ for either group or for the combined data on all subjects.

DISCUSSION

When benzodiazepines became available for clinical use they were thought not to depress respiration. The drugs were therefore considered safe for use in patients with respiratory failure. This view was supported when Matthew *et al.* (1969) reported 27 patients who had taken overdoses of nitrazepam with no evidence of respiratory depression. There was, however, only one chronic bronchitic among these patients. Rao *et al.* (1973)

found slight depression of ventilation after diazepam but this was comparable to that occurring during normal sleep. Clark *et al.* (1971) reported three patients with acute on chronic respiratory failure in whom nitrazepam had apparently caused dangerous deterioration. This effect was confirmed by Pines (1972). All these patients deteriorated within hours of the drug being taken. In 1973 Model reported two further patients whose respiratory failure deteriorated following nitrazepam but only after the drug had been taken for nine days in one case and for 21 days in the other. It is not clear from this last report whether the drug was the sole factor responsible for the deterioration or whether an acute infection also played some part.

Gaddie *et al.* (1972) performed a double-blind cross-over trial to study the effect of nitrazepam, 10 mg, on patients with chronic respiratory failure in a stable state. There was no significant change in arterial tensions of oxygen or carbon dioxide but the FEV₁ fell significantly at two hours after ingestion of the drug. This raised the possibility that the respiratory depression previously reported might be due to an effect on skeletal muscle rather than a direct suppression of the central drive to ventilation.

Similar results were obtained by Model and Berry (1974), who showed that regular oral chlordiazepoxide caused a significant fall in FEV₁, associated with a rise in P_vCO₂, in patients with acute on chronic bronchitis.

The simplest way to assess the central drive to respiration is by measuring the ventilatory response to CO₂. With this method ventilatory depression has been shown with opiates (Weil *et al.*, 1975) and barbiturates (Gasser *et al.*, 1975). There have been some previous studies of the effect of benzodiazepines on the ventilatory response, although none using nitrazepam or flurazepam. Sadove, Balagot, and McGrath (1965) demonstrated respiratory depression with pethidine which was not worsened by the simultaneous administration of intravenous chlordiazepoxide or diazepam. This was confirmed by Steen and his co-workers (Steen *et al.*, 1966; Steen *et al.*, 1967), who measured also the ventilatory response to CO₂ after the administration of chlordiazepoxide and diazepam, both alone and with pethidine, in normal volunteers. No depression of CO₂ sensitivity could be demonstrated with these benzodiazepines.

Using the rebreathing method of Read (1967) to assess ventilatory response to CO₂, Cohen,

Finn, and Steen (1969) were unable to show any depression as a result of intravenous diazepam in normal subjects, and there was even a suggestion that diazepam antagonized the respiratory depression induced by pethidine. More detailed studies were done by Catchlove and Kafer (1971) both in normal subjects and in patients with chronic bronchitis after intravenous diazepam. The CO₂ sensitivity was reduced in some patients but unchanged and even increased in others. There was no significant change for either group overall. Gasser *et al.* (1975) showed marked reduction in ventilatory response to CO₂ after pentobarbitone and pentazocine but no significant change after lorazepam.

The significant depression of CO₂ sensitivity by flurazepam shown in our study is, to our knowledge, the first unequivocal evidence of central depression of respiration by a benzodiazepine. The lack of any change in FEV₁ argues against the muscle relaxant properties of the drug being significant and implies true depression of central drive. We were unable to demonstrate any significant change after nitrazepam, which raises the possibility of different behaviour among the different drugs of this group. The doses given are approximately equal in hypnotic effect. The failure of both this study with nitrazepam and the previous studies quoted above to demonstrate respiratory depression implies that such an effect cannot be very great. It may then be important only in patients when an acute exacerbation of respiratory failure causes a deterioration in respiratory function such that any small change in central drive or muscular power becomes critical. This is supported by our observation that in spite of a change in CO₂ sensitivity there was no significant change in P_vCO₂.

Our results refer to the effects of a single dose of benzodiazepine, not to long-term administration. We believe that the administration of sedatives or hypnotics to patients with acute respiratory failure, or an acute exacerbation of chronic respiratory disease, is always contra-indicated. The position for patients with chronic stable respiratory failure and CO₂ retention is less certain, but we feel that the indication for sedatives, if prescribed, should be compelling, and the patient should be under close observation.

There is no good evidence that chronic bronchitis with a normal arterial carbon dioxide tension will come to harm after a single dose of a benzodiazepine. However, should such a drug be prescribed it would be reasonable to prefer

nitrazepam to flurazepam in view of the results of this study.

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