Depression of central respiratory drive by nitrazepam

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Nitrazepam (Mogadon), a benzodiazepine, is now regarded as the hypnotic of choice in this country (British Medical Journal, 1976). There have been several case reports of the apparent precipitation by nitrazepam of respiratory failure in patients with pre-existing pulmonary disease (Clark et al., 1971; Hilton, 1971; Pines, 1972; Model, 1973), but the mechanism of this respiratory depression is unclear (Gaddie et al., 1972).

We have shown that a single 5-mg dose of nitrazepam fails to produce any significant depression of central respiratory drive (as assessed by the ventilatory response to carbon dioxide) either in subjects without lung disease or in patients with chronic bronchitis (Geddes et al., 1976). Since repeated administration of nitrazepam at 24-hour intervals is known to produce a steady rise in plasma levels of the drug over the first four to five days (Reider and Wendt, 1973), cumulative effects might be anticipated. We have, therefore, studied the effect of repeated doses of nitrazepam on respiratory drive in a group of patients with chronic bronchitis over a period of five days.

Patients and methods

Patients
Twelve patients (8 male, 4 female, age range 46–76) were studied. All had smoked more than 20 cigarettes a day for more than 15 years, had chronic bronchitis as defined by the Medical Research Council (1965) with spirometric evidence of fixed airway obstruction, and were in a clinically stable state. Three of the subjects had chronic hypercapnia.

Informed consent was obtained from every patient, and the study was approved by the hospital’s ethical committee.

Methods
Central respiratory drive was assessed by measuring the increase in ventilation produced by progressive hypercapnia, using the rebreathing technique of Read (1967). Ventilation was measured by integrating the flow signal from a pneumotachograph, and Pco2 was continuously monitored with a Beckman infra-red CO2 analyser. The resulting ventilatory response to CO2 was expressed as the slope of the line obtained by performing least squares regression analysis of the minute ventilation on end-tidal Pco2, ignoring the first 30 seconds of rebreathing. The theoretical intercept of the slope at ‘zero’ ventilation was also calculated.

Arterial blood samples were obtained when the patients were at rest breathing room air, and the arterial oxygen and carbon dioxide tensions (Pao2 and Paco2) and pH were measured on standard Radiometer electrodes. All measurements were performed in duplicate, and the electrodes were calibrated immediately before and after each sample with standard gases and buffers.

Forced expired volume in one second (FEV1) was measured on a Vitalograph spirometer, and the best of three attempts was recorded.

Protocol
All patients had previously performed the CO2 rebreathing test on at least one occasion in order to familiarise themselves with the procedure. Arterial blood gases, spirometry, and ventilatory response to CO2 were measured, and nitrazepam, 10 mg, was...
then given at 2200 hours for the next five nights, with
repeat measurements, always at the same time of day,
made on the first, third, and fifth days. No change in
any concurrent drug therapy was made throughout
the trial and no other sedatives or hypnotics were
given.

Differences between the values obtained on the
different days were analysed for statistical signi-
ficance using Student's t test for paired data.

Results

ARTERIAL BLOOD GASES
The daily carbon dioxide tensions in all patients are
shown in the Figure. In two of the patients treat-
ment had to be discontinued because PaCO₂ rose by
1 kPa (7.5 mmHg) or more; both of these patients had
been hypercapnic before receiving nitrazepam. Eight
of the remaining 10 patients had an increase in
PaCO₂ at the end of their five days' treatment, and
there was a steady rise in mean PaCO₂ over the five
days, as shown in the Table. (The results in the two
subjects who were withdrawn from the study are not
included in these mean values.) The mean PaCO₂
on every day of nitrazepam treatment was signi-
ficantly greater than the control value (p < 0.05 for
day 1, p < 0.01 for days 3 and 5), and the mean levels
on days 3 and 5 were also significantly higher than on
day 1 (p < 0.05).

Reciprocal changes occurred in the mean arterial
pH levels. There were no significant changes in mean
Pao₂, and clinically important hypoxaemia was not
precipitated in any patient.

SPIROMETRY
There were no significant changes in spirometry, and
FEV₁ remained unchanged in the two patients who
developed severe hypercapnia.

VENTILATORY RESPONSES TO CARBON DIOXIDE
CO₂ response fell by one-third in both of the patients
who had to be withdrawn from the study. The mean
response for the remaining 10 patients fell steadily
over the five days (Table) and was significantly
lower at the end of the study (p < 0.05). All eight
subjects whose PaCO₂ had risen showed a decrease in
ventilatory response. No significant differences
between the intercepts at zero ventilation were
found.

Discussion

Although some benzodiazepines have been shown
to cause respiratory depression in both animals and
humans (Flórez, 1971; Gasser and Bellville, 1976;
Conversion factor: 1 kPa = 7.5 mmHg
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Geddes et al., 1976), the only previous evidence that nitrazepam might depress the central drive to breathing is that, when given intravenously to decerebrate cats, it raises arterial PCO\textsubscript{2} and depresses the ventilatory response to carbon dioxide (Flórez, 1971). The results of the present study show that nitrazepam does indeed depress the central respiratory drive in man.

Measurement of the ventilatory response to CO\textsubscript{2} is a rapid and easily performed method of assessing the effects of drugs on the respiratory control system and, as long as lung mechanics remain constant, any change in this response represents a change in central drive. Opiates, barbiturates, and other benzodiazepines have been shown to depress central respiratory drive using this technique (Gasser et al., 1975; Weil et al., 1975; Gasser and Bellville, 1976; Geddes et al., 1976). The steady decrease in mean CO\textsubscript{2} response over the five days of the study suggests that nitrazepam-induced suppression of ventilatory drive is a cumulative effect. However, whereas this fall in CO\textsubscript{2} sensitivity did not attain statistical significance until the fifth day, the increase in mean Paco\textsubscript{2} was statistically significant by day 1. Although this can be explained by the greater variance of the former measurement, it does raise the possibility that something other than depression of respiratory drive might have been causing these changes in Paco\textsubscript{2}.

Two possible explanations are (1) that Paco\textsubscript{2} may have risen as a result of increasing maldistribution:perfusion ratios throughout the lung (West, 1963), and there is some evidence that diazepam, another benzodiazepine, can cause this (Catchlove and Kafer, 1971a, 1971b), and (2) that the respiratory depression may have been produced, not by an effect on central drive, but by the known ability of benzodiazepine drugs to cause muscle relaxation and consequent impairment of ventilatory capacity (Gaddie et al., 1972; Model and Berry, 1974). The absence of any significant changes in either Pao\textsubscript{2} or FEV\textsubscript{1} in our study argues against both these possibilities, and we believe that the increase in Paco\textsubscript{2} that we observed was most likely due to the decrease in central drive rather than to any other cause.

Although sedatives and hypnotics are generally considered always to be contraindicated in patients with acute respiratory failure, their position in the treatment of patients with chronic stable respiratory failure is less certain. It is often tempting to use such drugs, especially when nocturnal dyspnoea and insomnia are problems, and, in the absence of any previously proven respiratory depressant effect, nitrazepam has been assumed to be comparatively safe in these circumstances. We feel that the results of this study make this assumption no longer justified, and that the presence of chronic hypercapnia should make one strongly resist the temptation to prescribe nitrazepam or any other hypnotic.

The chronic bronchitics with normal arterial PCO\textsubscript{2} showed blood gas changes which, although statistically significant, were small and of little clinical relevance. Nevertheless it would seem sensible to exercise caution in prescribing nitrazepam to these patients since the drug-induced depression of central respiratory drive might well become of critical importance when acute exacerbations of the disease occur.

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References


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