

Effect of diazepam on sleep in patients with chronic airflow obstruction

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ABSTRACT The effect of a single dose of diazepam on sleep and respiration was studied in nine patients with chronic airflow obstruction with moderate arterial hypoxaemia but no hypercapnia. Diazepam improved sleep duration without exacerbating nocturnal hypoxaemia and there was no change in the number of apnoeic events after a single 5 mg dose at night.

Diazepam has been advocated as a treatment for breathlessness in patients with chronic airflow obstruction.¹ Previous studies have suggested that the benzodiazepine hypnotic flurazepam can cause sleep disordered breathing, with nocturnal oxygen desaturation, an increased frequency of apnoeic episodes and reduced rapid eye movement (REM) sleep.²⁻⁴ The effects of diazepam on respiration at night have not, however, been evaluated.

We have therefore performed a double blind, placebo controlled study to investigate the effects and safety of a small nocturnal dose of diazepam on sleep quality and respiration at night in patients with chronic airflow obstruction and moderate arterial hypoxaemia.

Methods

We studied nine patients (eight of them men) in the sleep laboratory (mean age 67.6 (SD 6.18) years and weight 62.8 (17.5) kg) with stable chronic airflow obstruction (mean FEV₁ 1.13 (0.47) l and FVC 2.38 (0.86) l) and moderate arterial hypoxaemia (mean arterial oxygen tension (PaO₂) 9.05 (0.73) kPa) but no hypercapnia (mean arterial carbon dioxide tension (PaCO₂) 4.97 (0.40) kPa).

After an initial acclimatisation night in the sleep laboratory, the subjects were studied on two further nights, between 2200 and 0700 h, at least five days apart. Each subject received diazepam 5 mg orally on one night and a matched placebo on the other night in a randomised double blind fashion. Airflow was monitored with a laryngeal microphone and chest and abdominal wall motion was recorded by inductance plethysmography. Arterial oxygen saturation (Sao₂) was measured continuously during the night with a Hewlett Packard 47201A ear oximeter and an electrocardiogram was recorded simultaneously. Sleep was staged with an electroencephalogram (C4/A1), electro-oculogram, and submental electromyogram by standard methods. Apnoea and hypopnoea were defined as previously described.⁵ The FEV₁ and forced vital capacity (FVC) were

Sleep events and arterial oxygen saturation (Sao₂) on the placebo and diazepam nights (medians with ranges in parentheses)

	Placebo	Diazepam
FEV ₁ (l)	1.05 (0.5-1.6)	1.0 (0.56-1.55)
Forced vital capacity (l)	2.32 (1.2-4.0)	2.15 (1.5-2.95)
Total sleep time (min)	176.4 (23.3-389.3)*	261.3 (190.8-403.8)*
REM sleep (min)	32.5 (0-68.5)	50.0 (8.9-82.7)
No of hypopnoeic or apnoeic episodes	13.0 (0-204)	20.0 (2-123)
No of arousals	6.0 (2-11)	4.7 (2-10)
Awake Sao ₂ (%)	93.0 (91-95.7)	92.7 (89.9-95.4)
Asleep Sao ₂ (%)	91.9 (86.8-95.2)	91.1 (88.8-95.3)
REM Sao ₂ (%)	90.9 (84.7-94.5)	90.6 (82.6-92.8)
Minimum nocturnal Sao ₂ (%)	87.7 (75-93)	87.0 (76-90)

*p < 0.02.

measured with a Morgan dry spirometer and blood gas tensions, taken from the radial artery, were estimated with a Radiometer ABL 1 analyser.

The study was approved by the London Hospital ethics committee and informed consent was obtained from the patients. The patient groups were compared by means of the Wilcoxon matched pairs signed ranks test and the Mann-Whitney U test.

Results

The sleep events during the placebo and diazepam nights are shown in the table. During the diazepam nights the patients slept for a longer period (median 261.3 (range 190.8-403.8) min during stages 2, 3, and 4 and REM sleep) than during the placebo nights (median 176.4 (range 23.3-389.3) min; p < 0.02). The difference in the duration of REM sleep in the two groups was not significant. The numbers of hypopnoeic and apnoeic events were not statistically different on the two nights, and there was no change in the frequency of arousals.

There was a small fall in the median nocturnal Sao₂ during sleep in both groups (diazepam: awake 92.7%, asleep 91.9%; p < 0.01), but there was no significant difference in the median awake or asleep Sao₂ between the diazepam and the placebo nights. The lowest nocturnal Sao₂ recorded was similar on the two nights. There were no differences in sleep or nocturnal Sao₂ between the patients who received diazepam on the first night and those who initially received the placebo. There was no change in the FEV₁ and FVC values on the two study nights.

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Discussion

This study shows that low dose oral diazepam (5 mg) increases sleep duration in patients with chronic airflow obstruction and moderate arterial hypoxaemia but without hypercapnia. There was a similar fall in the arterial oxygen saturation on the two nights, suggesting that nocturnal hypoxaemia was not exacerbated by diazepam, and there was no difference in the number of apnoeic events.

By contrast, flurazepam 30 mg has been reported to increase the frequency of sleep disordered breathing both in symptom free subjects and in patients with chronic airflow obstruction.^{3,4} Flurazepam 15 mg has been shown to cause greater depression of the ventilatory response to carbon dioxide than other benzodiazepines, such as nitrazepam 5 mg,⁶ perhaps explaining the increased incidence of sleep related events. Previous studies have shown variable reduction of the ventilatory response to carbon dioxide with diazepam.¹⁷ Catchlove and Kafer⁷ showed that intravenous diazepam 7.5 mg affected the ventilatory response in half of the patients with chronic airflow obstruction, but there were no obvious factors that predicted the individual response. Some of the variability in the results, however, may be related to differences in dosages of benzodiazepines in the various studies. No dose-response studies of the effects of benzodiazepines in modulating ventilatory drive have been reported.

A single dose of diazepam at night prolongs sleep with no adverse effects in patients with moderate hypoxaemia. Repeated daily use of diazepam, however, may lead to accumulation of the drug and produce respiratory depression. Although a single dose of nitrazepam 5 mg appeared safe,⁶ repeated doses may cause respiratory depression.^{8,9} Further studies are required to assess the consequences of prolonged regular treatment with diazepam on respiration during sleep. All benzodiazepines are contraindicated in patients with respiratory failure and during exacerbations of chronic airflow obstruction.¹⁰ The use of diazepam should be

restricted to patients who are clinically stable and have no current or previous hypercapnia.

In this study a single dose of diazepam 5 mg did not increase the risk of sleep disordered breathing in patients with chronic airflow obstruction. Diazepam may be useful in relieving dyspnoea and anxiety in these patients,¹ but further studies are required to assess its safety at night after repeated dosages.

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