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# Nitrazepam in patients with sleep apnoea: a double-blind placebo-controlled study

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*Nitrazepam in patients with sleep apnoea: a double-blind placebo-controlled study. U. Höijer, J. Hedner, H. Ejnell, R. Grunstein, E. Odelberg, M. Elam. ©ERS Journals Ltd 1994.*

**ABSTRACT: We wanted to assess whether benzodiazepines worsen sleep apnoea, since their use in such patients has been controversial.**

**Fourteen male patients with mild to moderate obstructive sleep apnoea were investigated in a placebo-controlled, double-blind study evaluating the influence of nitrazepam (NIT) on apnoea frequency and severity. Each patient was given oral nitrazepam 5 or 10 mg, or corresponding placebo, in a randomized order on three separate nights. Wash-out time was one week. A complete sleep study was undertaken at each study night. Eleven patients completed the study.**

**Although there were individuals with marked variability in apnoea index between the three study nights, there was no significant change in apnoea index or minimum arterial oxygen saturation with any of the two nitrazepam dosages studied. Only 3 out of 11 patients had a higher apnoea index after both nitrazepam doses compared to placebo, and in these patients the increase in sleep-disordered breathing was of marginal clinical significance. Nitrazepam caused a modest increase in total sleep time and a decrease in rapid eye movement (REM) sleep.**

**These results demonstrate that nitrazepam does not worsen sleep apnoea in patients with mild to moderate sleep apnoea. The previously reported sleep apnoea promoting effects of benzodiazepines may be restricted to a small subgroup of patients with sleep-disordered breathing.**

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A number of sedative agents have inhibitory effects on breathing and respiratory control, potentially leading to the development or worsening of sleep apnoea (SA) [1]. Such agents are typically central nervous system depressants and may worsen SA by a number of mechanisms, including reduction of upper airway muscle tone [2], and impaired arousal responses to airway occlusion or hypoxia [3, 4].

Benzodiazepines are commonly prescribed central nervous system depressants. In Sweden, national drug sale statistics indicate that, at any one time, 2.6% of the population are receiving benzodiazepine prescriptions specifically for sleep problems [5]. A number of studies have reported that benzodiazepines slow the arousal response to a variety of stimuli, including hypercapnia [6], and airway occlusion [4]. However, despite their frequent use, there is only limited and conflicting information on the effect of benzodiazepines on SA. Although several workers have reported worsening of SA following benzodiazepine use [7–10], other groups have found no or minimal change in indices of sleep-disordered breathing severity [11]. Nevertheless, many reviews of the management of SA patients state that benzodiazepines are contraindicated in such patients [12, 13].

There are a number of potential indications for benzodiazepines in SA. Sleep disruption [12] and a variety of psychiatric symptoms [14] are common complaints in SA, and in addition benzodiazepines may be prescribed as premedication for surgical procedures, in particular uvulopalatopharyngoplasty. To examine whether the commonly prescribed benzodiazepine, nitrazepam (NIT), influences breathing in sleep we performed a placebo-controlled, double-blind, cross-over polysomnographic study of two dose levels of NIT in patients with mild to moderate SA.

## Material and methods

### *General study protocol*

Patients with diagnosed obstructive SA (OSA) were recruited for a double-blind study of NIT (Nitrazepam, Kabi Pharmacia, Stockholm, Sweden). The patients were randomized into one of three groups with different order of medication in order to avoid influence of a first night effect. Data were analysed on an intent to treat basis. Study nights were separated in time by a minimum of one week. NIT, 5 or 10 mg tablets, or corresponding placebo, was given 30 min prior to start of the sleep study. Regular intake of benzodiazepines, theophylline, antipsychotic agents or alcohol (>30 mg·day$^{-1}$) were

exclusion criteria. Other exclusion criteria were impaired renal or hepatic function.

In the morning, following each study night, patients were instructed to assess subjective sleep quality, current sleepiness, presence of headache, and the degree of general physical and mental fitness on a 10 cm visual analogue scale. Patients were questioned regarding adverse drug effects. All study participation followed informed oral consent. The study protocol was approved by the Ethics Review Committee of the University of Gothenburg.

*Subjects*

We recruited 14 consecutive patients (12 males and 2 females), found to have mild to moderate OSA (60–180 apnoeas per 6 h of self-reported sleep time) on a screening sleep study night (for method see below) at the Sleep Laboratory, Renströmska Hospital, Gothenburg, Sweden. The mean number of apnoeas per hour of self-estimated sleep time was 15 (±5.0) and mean overnight minimum arterial oxygen saturation ($Sa_{O_2}$ min) was 80 (±6.4)%. Mean age of the study population was 47 (±7.5) yrs, and body mass index was 27 (±3.3) $kg \cdot m^{-2}$. One patient was withdrawn from the study due to poor co-operation. In two patients, sleep data were insufficient for analysis due to technical failure, leaving interpretable data from 11 patients who completed the study. Patient characteristics are given in table 1.

*Overnight screening recording*

The initial screening study prior to recruitment consisted of an overnight continuous recording of transcutaneous $Sa_{O_2}$ and heart rate using a pulse oximeter and a finger probe (BIOX 3700, Ohmeda, Louisville, CO, USA). Nasal and oral airflow were recorded *via* a thermistor. Respiratory and body movements were monitored *via* a static charge sensitive bed (Bio-matt, Biorec Inc., Finland). Signals were amplified and recorded on a filter pen recorder (Kipp & Zonen, Holland). A sleep-related event (apnoea) was scored when $Sa_{O_2}$ dropped by ≥4% from the immediately preceding baseline in association with absence of nasal and oral airflow for ≥10s. All patients were heavy snorers and had predominantly obstructive apnoeas. All scoring was made manually from the chart record. The diagnosis of mild to moderate SA was based on an overnight recording with more than 6 h of self-reported sleep duration and 60–180 apnoeas according to the criteria cited above.

Table 1. – Physical characteristics of patients studied and results from sleep studies based on the screening night recording

| Patient No. | Sex | Age yrs | BMI $kg \cdot m^{-2}$ | AI* $n \cdot h^{-1}$ | $Sa_{O_2}$min % |
|---|---|---|---|---|---|
| 1 | M | 60 | 31 | 15 | 87 |
| 2 | M | 46 | 27 | 25 | 77 |
| 3 | M | 48 | 22 | 25 | 84 |
| 4 | M | 43 | 32 | 16 | 84 |
| 5 | M | 36 | 26 | 15 | 80 |
| 6 | M | 36 | 27 | 15 | 81 |
| 7 | M | 55 | 24 | 12 | 66 |
| 8 | M | 53 | 23 | 14 | 85 |
| 9 | M | 45 | 25 | 10 | 75 |
| 10 | F | 53 | 30 | 10 | 90 |
| 11 | M | 55 | 24 | 12 | 79 |

*: index calculated based on self-estimated sleep time (see Methods section). M: male; F: females; BMI: body mass index; AI: apnoea index (number of apnoeas per hour of sleep); $Sa_{O_2}$min: minimum oxygen saturation reached during the overnight sleep recording.

*Sleep studies*

Sleep studies were performed between 2300 and 0600 h. The automatic sleep scoring (Oxford Medilog 9000, Oxford Medical, Abingdon, UK) was based on a bipolar electroencephalogram ($C_3$ - $A_2$), two electrooculograms (EOG), and a submental electromyogram (EMG). Although automated analysis with this device has been demonstrated to correlate well with visual scoring [15], our experience is that epochs of rapid eye movement (REM) sleep may be markedly overestimated. Therefore, manual scoring of raw data, according to previously described terminology [16], was performed for all epochs analysed as REM sleep by the Medilog 9000 device. Data reported in this study refer to sleep scoring obtained after such manual correction. Respiratory variables were recorded both on the Oxford system (airflow, oximetry and impendance) and on a separate pen recorder (static charge sensitive bed and oximetry). Respiratory events recorded on the Oxford system were printed out separately for later analysis. Apnoeas detected by the Medilog 9000 automatic analysis system were cross-checked against the printed data on the pen recorder and inconstant data were corrected. In particular, all signals obtained were used to discriminate between central and obstructive apnoeas by manual analysis. Although a specific definition of hypopnoeas was not used, episodes where the airflow or the impedance signal were diminished and >4% desaturation occurred, were considered as apnoeas. The apnoea index (AI) refers to the number of these events per hour of total sleep time.

*Statistics*

All values are given as mean (±SD). Comparisons between treatments were analysed by means of analysis of variance, controlling for measurements within subjects. A nonparametric confirmation was obtained by reanalysis of the ordered responses. Confidence intervals are presented for differences between placebo and either treatment.

## Results

Average AI during the placebo night was 18 (±15) compared with 21 (±20) and 12 (±9) after 5 mg and 10 mg of NIT, respectively (fig. 1). Mean $Sa_{O_2}$min was identical, 85%, on all three study nights (fig. 2). In several patients, there was marked intraindividual variability between consecutive study nights, but this could not be attributed to a first night or drug effect. For example,

in one patient (patient No. 3), there was a 20 fold decrease in AI following 10 mg NIT compared to placebo. In contrast, in patient No. 1 there was a three fold increase in AI following 5 mg NIT but no difference between placebo and 10 mg NIT (fig. 1). Patients Nos. 1, 6 and 11 were the only patients with a higher AI during both nights of active medication compared with placebo (fig. 1). All patients had predominantly obstructive apnoea and the relative proportion of central and obstructive SA was not different between placebo and drug studies. In three patients, AI was <10 during one or several of the recording nights.

The mean total sleep time was 300±42 min h during the placebo night (table 2). Although sleep time was longer on both drug nights, the increase in sleep time was significant only after 10 mg NIT. The proportion of Stage 1 sleep remained unchanged after NIT. Stage 2 sleep increased and Stage 3+4 sleep decreased, however, not significantly, after NIT. A decrease of REM sleep ($p<0.05$) was found after 5 mg NIT (table 2). AI and relative proportion of sleep stages did not differ between the first, second and third study night (data not shown), indicating that there was no systematic first night effect.

The difference or absence of differences between placebo and NIT 5 mg or 10 mg remained when comparisons were based on confidence intervals (table 3, data not shown for sleep variables).

Subjective sleep quality, morning sleepiness, presence of headache, and the degree of general physical or mental fitness rated on a visual analogue scale were not significantly different after placebo, NIT 5 mg or 10 mg. No adverse drug effects were reported.

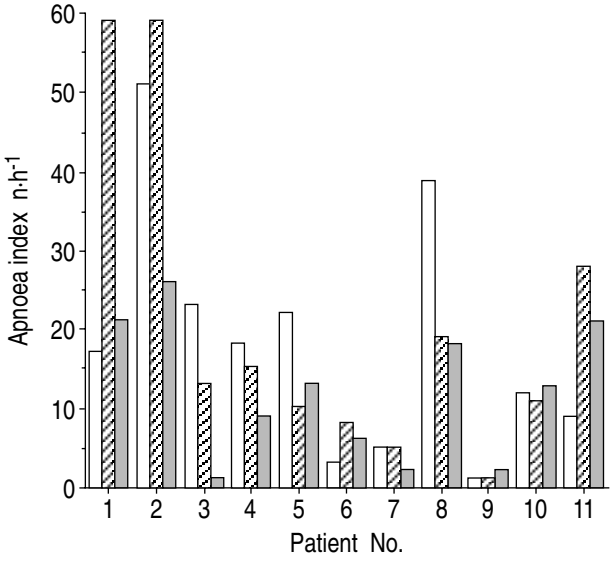


Fig. 1. – Individual apnoea index in the 11 patients investigated during the three study nights after placebo (▭), 5 mg nitrazepam (▨) or 10 mg nitrazepam (▬).

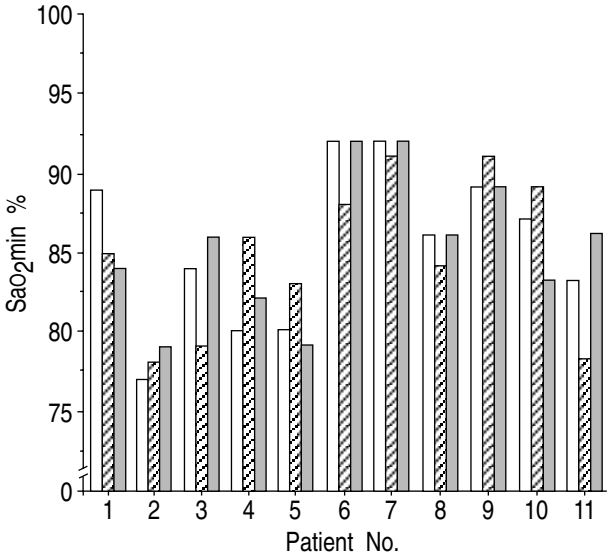


Fig. 2. – Individual minimum arterial oxygen saturation ($Sao_2min$) in the 11 patients investigated during the three study nights after placebo (▨), 5 mg nitrazepam (▬) or 10 mg nitrazepam (▭). Note that the vertical axis is magnified and cut off from zero.

Table 2. – Sleep architecture in the patients investigated during the three study nights

| Pat. No. | Dose | Stage 1 % | Stage 2 % | Stage 3+4 % | REM % | TST min |
|---|---|---|---|---|---|---|
| 1 | P | 20 | 68 | 1 | 11 | 357 |
| | 5 | 26 | 69 | 1 | 4 | 411 |
| | 10 | 19 | 71 | 2 | 8 | 400 |
| 2 | P | 14 | 57 | 1 | 28 | 316 |
| | 5 | 16 | 67 | 0 | 17 | 370 |
| | 10 | 14 | 67 | 3 | 16 | 344 |
| 3 | P | 40 | 57 | 0 | 3 | 333 |
| | 5 | 44 | 53 | 0 | 3 | 324 |
| | 10 | 25 | 65 | 0 | 10 | 372 |
| 4 | P | 20 | 53 | 4 | 23 | 277 |
| | 5 | 25 | 59 | 2 | 14 | 339 |
| | 10 | 36 | 46 | 3 | 15 | 397 |
| 5 | P | 22 | 58 | 10 | 10 | 332 |
| | 5 | 11 | 73 | 2 | 14 | 335 |
| | 10 | 11 | 71 | 5 | 13 | 320 |
| 6 | P | 36 | 41 | 13 | 10 | 310 |
| | 5 | 17 | 72 | 12 | 0 | 259 |
| | 10 | 14 | 72 | 9 | 1 | 268 |
| 7 | P | 41 | 25 | 16 | 18 | 278 |
| | 5 | 43 | 54 | 3 | 0 | 239 |
| | 10 | 15 | 79 | 1 | 5 | 300 |
| 8 | P | 8 | 65 | 19 | 8 | 225 |
| | 5 | 20 | 63 | 7 | 10 | 244 |
| | 10 | 39 | 37 | 25 | 0 | 290 |
| 9 | P | 7 | 56 | 22 | 15 | 275 |
| | 5 | 9 | 65 | 14 | 12 | 354 |
| | 10 | 15 | 50 | 19 | 16 | 334 |
| 10 | P | 14 | 58 | 20 | 8 | 308 |
| | 5 | 21 | 53 | 26 | 0 | 273 |
| | 10 | 19 | 56 | 20 | 5 | 331 |
| 11 | P | 21 | 61 | 18 | 0 | 295 |
| | 5 | 26 | 64 | 7 | 3 | 318 |
| | 10 | 33 | 65 | 2 | 0 | 362 |
| **Mean (SD)** | | | | | | |
| | P | 22 (12) | 54 (12) | 11 (8) | 12 (8) | 303 (42) |
| | 5 | 23 (11) | 63 (7) | 7 (8) | 7 (6)* | 315 (55) |
| | 10 | 22 (10) | 62 (13) | 8 (9) | 8 (6) | 334 (38)* |

The relative amount (% of total sleep time) of sleep stage 1, 2, 3+4 and REM as well as total sleep time (TST) are presented. Pat: patient; P: placebo; 5, 10: 5, 10 mg nitrazepam; REM: rapid eye-movement. *: $p<0.05$ compared to placebo.

Table 3. – Confidence intervals for differences in apnoea index (AI) and overnight minimum arterial oxygen saturation ($Sa_{O_2}$min) between placebo and either treatment with nitrazepam

| Treatment comparison | Confidence intervals | |
|---|---|---|
| | AI | $Sa_{O_2}$min |
| Placebo-nitrazepam 5 mg | -2.70–3.98 | -13.53–8.44 |
| Placebo-nitrazepam 10 mg | -2.34–4.34 | -4.80–17.17 |
| Nitrazepam 5 mg-10 mg | -2.98–3.70 | -2.26–19.71 |

## Discussion

The principal finding of this study was that NIT had no consistent effect on the severity of sleep-disordered breathing in patients with mild to moderate SA. There were intraindividual differences in several patients with both increase and decrease in apnoea index following NIT. However, for the entire group there was no change either in apnoea index or minimum oxygen saturation. Total sleep time increased only with the higher dose of NIT.

Centrally-acting depressants may influence breathing in sleep by several mechanisms. These include altered upper airway tone, modification of chemoreceptor function [17], or changes in arousability to respiratory stimuli. For example, acute ethanol intake selectively decreases genioglossal muscle activity by an inhibitory effect on the genioglossus motor nucleus in the medulla oblongata [2], impairing upper airway stability [18]. Ethanol also decreases the chemoreceptor response to hypoxia and hypercapnia and prolongs the time to airway occlusion in non-rapid eye movement (NREM) sleep [3, 19]. A likely consequence of these inhibitory effects on breathing is the previously recognized phenomenon of exacerbation of snoring and SA following acute alcohol ingestion [18].

Amongst its other pharmacological actions, ethanol facilitates gamma-aminobutyric acid (GABA)-ergic transmission in the central nervous system [20]. Interestingly, the central nervous pharmacological action of benzodiazepines is also mediated *via* an interaction with the GABA/benzodiazepine receptor complex [21]. GABA-receptor activation has been shown to result in a reduction in central nervous chemosensitivity and a ventilatory depression, in several different species [22]. GABA-synthesis is increased during global hypoxia [23, 24], thereby potentially resulting in a state of self-sustained inhibition of respiration during hypoventilation-induced hypoxia.

Despite the profound effects of GABA on breathing, there are conflicting data concerning the ventilatory effects of benzodiazepines in normal subjects. Some studies have failed to demonstrate ventilatory depression after intravenous [25], or oral [26], midazolam administration, whilst other investigators have found a weakly dose-dependent decrease in tidal volume but not minute ventilation after this agent [27]. In the decerebrate cat, hypoventilation has been demonstrated following diazepam, nitrazepam and clonazepam [28].

There are also conflicting data on the influence of benzodiazepines on breathing in sleep. Previous case reports [7, 8] suggest that severe SA may occur after therapeutic doses of benzodiazepines. In addition, flurazepam has been demonstrated to increase AI in an elderly population without previously documented apnoea [9], as well as in asymptomatic patients [29]. However, the increase in AI after flurazepam in these studies was relatively modest. Individual data were reported only in the study of the elderly [9], and in this group increases in AI were confined to a subgroup of subjects with an AI exceeding 5 on the control night. Although both these studies used placebo controls, they were only single-blind and, thus, may be subject to observer bias. In contrast to these studies, we were unable to find an effect of a benzodiazepine on sleep-disordered breathing in patients with mild to moderate SA. Moreover, there was no evidence of a dose-dependent effect or of an effect on SA severity. The reason for the different results of the present study and previous work may be related to study design or to the use of different benzodiazepines. However, our findings are consistent with the observations of CIRIGNOTTA *et al*. [11], who were unable to demonstrate any significant increase in AI after flurazepam. It is also important to recognize that benzodiazepines may produce an increase in upper airway resistance without overt apnoea or desaturation. Such events may be associated with increased sleep fragmentation [30], but we observed no change in sleep structure in the current study. Even though there may have been an increase in hypopnoeas and upper airway resistance with arousal, no major impact on breathing during sleep was observed.

The present cross-over study was based on data from 11 patients with OSA. The accuracy by which we may disregard impairment of sleep-disordered breathing after NIT depends on the statistical power of the analysis used for comparison between groups. In order to acertain the appropriate power of the comparison, a non-parametric confirmation was obtained by reanalysis of the ordered responses. Since all confidence limits obtained, excluding total sleep time and REM, contained only possible differences which were too small to be of clinical interest, our data suggest that NIT has no significant effect.

It is possible that benzodiazepines exert an unfavourable effect on ventilatory drive in susceptible patients. MODEL and BERRY [31] found an increase in mixed venous carbon dioxide tension in respiratory failure patients after therapeutic doses of chlordiazepoxide. However, other investigators observed minimal adverse effects of benzodiazepines on respiration in a group of patients with stable chronic obstructive airway disease [32]. In patients with central SA, without daytime respiratory failure, benzodiazepines reduce central apnoea and do not induce obstructive apnoea [33]. Benzodiazepines do not affect chemosensitivity in sleep in normal subjects [6], but prolong the time to arousal following airway occlusion [4]. Taken together, these various findings suggest that benzodiazepines would predominantly influence sleep and breathing in patients with pre-existing impaired chemosensitivity and/or arousability.

Such alteration in respiratory control would occur in patients with severe obstructive SA, typically with carbon dioxide retention or other causes of ventilatory failure.

In summary, nitrazepam did not adversely influence apnoea intensity or severity in patients with mild to moderate sleep apnoea, although predictable changes were found in sleep architecture and sleep efficiency. This suggests that previous recommendations contraindicating benzodiazepine use in sleep apnoea may be valid only for patients with severe sleep apnoea.

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