A comparison of the effects of zolpidem and placebo on respiration and oxygen saturation during sleep in the healthy elderly

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1 In a double-blind placebo controlled trial, zolpidem 10 mg, a new imidazopyridine hypnotic drug, was administered to 10 elderly female patients and placebo to 11, all recovering from hip and knee replacement surgery. Respiratory monitoring with an inductance plethysmograph and pulse oximeter showed that treatment over a 4 night period did not increase significantly the severity, frequency or duration of hypoxaemic episodes leading to $\text{SaO}_2 < 90\%$ or $< 85\%$ when compared with placebo. Confidence intervals (corrected for baseline differences) for the median differences between the two groups on night 7, the fourth night of treatment, were from -1.85 to 0.480 and from -1.07 to 0 respectively for the frequency, and from -0.76 to 0.15 and -0.5 to 0 for the duration of the hypoxaemic episodes. The incidence of sleep related respiratory disturbances was not significantly increased compared with placebo on any night.

2 Respiratory monitoring using a simple inductance plethysmograph and pulse oximeter is acceptable to patients and staff.

3 The evaluation of all hypnotic and sedative drugs should include their effects on respiration during sleep.

Keywords zolpidem hypnotic sleep respiration sleep apnoea

Introduction

Hypnotic drugs are amongst the most widely prescribed to the elderly (Catalan & Gath, 1985; Purpura, 1981). The acute respiratory effects of the commonly used agents have been extensively studied (Catchlove & Kafer, 1971; Cohn, 1983). Their efficacy as sleep inducing and maintaining agents has also been investigated in detail (Committee on the Review of Medicines, 1980; Roth *et al.*, 1981). Little attention has been paid to the effects of hypnotics on the incidence and severity of sleep disordered breathing in the elderly, although such disturbances are known to be common and to increase with age (Carskadon & Dement, 1981; Smallwood *et al.*, 1983).

Zolpidem is a new imidazopyridine hypnotic which has been shown to be an effective sleep inducer (Nicholson & Pascoe, 1986; Wheatley *et*

al., 1988). It binds selectively at benzodiazepine (BDZ)₁ receptors (Omega 1) and thus may have less myorelaxant effect than the benzodiazepines and less propensity to induce or worsen sleep apnoea (Langer & Arbilla, 1988; Lloyd & Zivkovic, 1988; Sanger *et al.*, 1987). A previous study suggested that in patients with obstructive sleep apnoea, zolpidem and flurazepam resulted in a small but not statistically significant increase in the apnoea/hypopnoea index (AHI episodes/hour of sleep) (Cirignotta *et al.*, 1988). A further study showed that the AHI was increased when compared with the preceding placebo night following a dose of zolpidem 10 mg but the difference was not detectable after 7 nights of treatment (Kurtz *et al.*, 1986).

The present study was designed to investigate

the effects of zolpidem 10 mg on respiration and oxyhaemoglobin saturation (SaO_2) during sleep in the healthy elderly. A double-blind, placebo controlled design was used over 4 treatment nights. Respiration and oxygenation were monitored using a simple inductance plethysmograph and a pulse oximeter.

Methods

Male and female patients aged 65 years and over, within 25% of the ideal body weight for their age and height and of American Society of Anesthesiologists status grades I and II (American Society of Anesthesiologists, 1963), recovering from hip and knee replacement surgery, gave their written informed consent for the study. The protocol was approved by the district Ethics Committee. Patients were excluded if they had any cardiac, renal or hepatic dysfunction, known respiratory insufficiency, sleep apnoea, or marked biochemical or haematological abnormalities. They were also excluded if they were drug or alcohol dependent, allergic to benzodiazepines or if they were receiving any hypnotic or psychotropic drug apart from triazolam 0.125 mg. This short-acting benzodiazepine was prescribed if a hypnotic was requested by the patient, until 48 h prior to the start of the study. No sedatives were permitted during the study period apart from the study medication. We intended to recruit 30 subjects of both sexes into the study, and regarded a doubling of the frequency of hypoxaemic events as clinically relevant. Assuming a within group standard deviation of 0.5 events per hour and a level of significance of 0.05, the power of recognising such an increase in a sample of this size would have been 99%.

The study was started on the fourth or fifth postoperative day, at least 48 h after the last dose of opiate analgesic. Paracetamol or a nonsteroidal anti-inflammatory drug was permitted if analgesia was required. Placebo tablets were given at night to all patients for the first 3 nights of the study (nights 1–3). Patients were then randomly allocated to two groups for treatment with either placebo or zolpidem 10 mg for a further 4 nights (nights 4–7). The placebo tablets were identical in appearance to the zolpidem. All treatments were given at approximately 22.00 h when the other patients in the ward were receiving their night sedation and the ward lighting was dimmed.

Respiration was monitored using a simple single coil respiratory inductance plethysmograph (GVT, PK Morgan Ltd.) (Frater & Hanning, 1986). Oxyhaemoglobin saturation (SaO_2) was monitored with a pulse oximeter (Ohmeda Biox

III) using an ear probe. The signals from both instruments were recorded continuously on a four channel instrumentation tape recorder (Store 4 FM, Racal) and were subsequently transcribed onto a two channel chart recorder (PL2500, JJ Instruments) for analysis.

The instruments were applied on night 2 (placebo for both groups) to permit acclimatisation to the monitoring equipment but no recordings were made. Recordings were then made on night 3, the baseline night when placebo was given to both groups, and nights 4 and 7, the first and fourth treatment nights. Recording was commenced immediately after the drug had been administered and continued until the patient woke spontaneously in the morning. A trained nurse observer (P.P.) was present throughout all recording nights supervising the equipment and noting any periods of waking, sleeping, snoring and other events.

Analysis of results

Following transcription onto chart paper the number and duration of episodes of hypoxaemia ($\text{SaO}_2 < 90\%$) and severe hypoxaemia ($\text{SaO}_2 < 85\%$) were recorded by an observer who was blinded to the treatment group. Each episode of hypoxaemia was related to the respiratory pattern recorded at the same time. Abnormal respiration was distinguished from normal by the shape of the respiratory waveform and classified into one of the following categories.

Obstructive apnoea (OA) Partial or complete obstructive apnoea of >15 s duration terminated by an arousal.

Obstructive pause (OP) As for OA but <14 and >6 s duration.

Partial obstruction (PO) Respiratory waveform indicating partial obstruction not terminated by an arousal.

Central apnoea (CA) Cessation of respiration for >15 s duration.

Central pause (CP) As for CA but <14 and >6 s duration.

Central hypoventilation (CH) Normal respiratory pattern of amplitude less than 50% of control before sleep onset.

Periodic breathing (PB) Unobstructed respiration with cyclical variation in tidal volume.

Normal respiration (NR).

A fuller description of the technique of analysis can be found in a previous paper (Frater *et al.*, 1989).

Statistical analysis included Student's *t*-tests for data with a normal distribution, Wilcoxon Signed Rank test and Rank Sum test for paired

Table 1 Demographic data and hours of sleep (mean $\pm$ s.e. mean)

	Placebo	Zolpidem
Age (years)	72.5 (1.28)	72.2 (0.996)
Weight (kg)	68.1 (2.68)	66.9 (2.75)
Height (m)	1.64 (0.018)	1.6 (0.02)
Sex	11 female	10 female
Operation	6 hip 5 knee	5 hip 5 knee
<i>Hours of sleep</i>		
Night 3 (baseline)	7.0 (0.13)	6.7 (0.29) (placebo)
Night 4	7.1 (0.14)	7.1 (0.2) (zolpidem)
Night 7	7.3 (0.15)	7.2 (0.23) (zolpidem)

and unpaired data for the respiratory results, non-parametric confidence intervals, and Fisher's exact test and Chi Square test where appropriate.

Results

Twenty-nine patients entered the study. Seven patients subsequently withdrew or were withdrawn by the investigators before the study was completed, all on placebo nights (nights 1 or 2). Two found the recording equipment intolerable; one had diarrhoea (in company with several other patients on the same ward); one developed severe indigestion and one developed 'pains all over'. Physical examination of this patient was

normal but the patient nevertheless withdrew from the study. Two were withdrawn by the investigators; one received an opiate analgesic and another had a postoperative haemoglobin of 7.8 g dl^{-1} due to bleeding from the operation site. A further patient in the placebo group completed the study but was subsequently excluded as he was found to have clinically significant obstructive sleep apnoea on the placebo night recording (night 3). Only two men agreed to take part and they were amongst the withdrawals.

The demographic data for the remaining 21 female patients, 10 of whom received zolpidem and 11 placebo, are given in Table 1. All values are given as mean $\pm$ s.e. mean. The two groups were evenly matched for age, weight, height and operation.

Table 1 also shows the duration of sleep on each recording night for the two groups. There was no significant difference in the mean duration of sleep between the two groups on any night. The duration of sleep in the zolpidem group was significantly increased on night 7 (after four doses of zolpidem 10 mg) compared with night 3 (placebo), $P < 0.05$.

Table 2 shows the numbers of patients in the two groups developing or still experiencing episodic hypoxaemia on nights 4 and 7, when compared with their saturations for night 3 the baseline night (placebo for both groups). Statistical analysis using the Chi-squared distribution showed there to be no significant difference in the number of patients becoming hypoxaemic

Table 2 Numbers of subjects in the placebo and zolpidem groups becoming or remaining hypoxaemic ($\text{SaO}_2 < 90\%$ and $< 85\%$) on nights 4 and 7 when compared with their baseline night, night 3

<i>Number of patients on night 3 with $\text{SaO}_2 >$ or $< 90\%$ and 85%</i>		<i>Number of patients becoming or remaining hypoxaemic on nights 4 and 7 compared with night 3</i>	
	<i>Night 3</i>	<i>Night 4 ($\text{SaO}_2 < 90\%$)</i>	<i>Night 7 ($\text{SaO}_2 < 90\%$)</i>
<i>Placebo</i>			
$\text{SaO}_2 > 90\%$	5	2	3
$\text{SaO}_2 < 90\%$	6	5	5
<i>Zolpidem</i>			
$\text{SaO}_2 > 90\%$	4	0	0
$\text{SaO}_2 < 90\%$	6	6	5
		<i>($\text{SaO}_2 < 85\%$)</i>	<i>($\text{SaO}_2 < 85\%$)</i>
<i>Placebo</i>			
$\text{SaO}_2 > 85\%$	8	0	3
$\text{SaO}_2 < 85\%$	3	3	3
<i>Zolpidem</i>			
$\text{SaO}_2 > 85\%$	6	3	0
$\text{SaO}_2 < 85\%$	4	3	2

Table 3 Mean frequency (+ range) of hypoxaemic events per hour of sleep for $\text{SaO}_2 < 90\%$ and $< 85\%$ with 95% confidence intervals for the median differences (nights 4 and 7 corrected for baseline differences)

	Placebo group	Zolpidem group	Median differences	95% C.I.	Wilcoxon rank sum
<i>SaO₂ < 90%</i>					
Night 3	1.7 (0–6.93) s = 6	1.3 (0–6.18) s = 6	0	–1.54 to 0.26	NS
Night 4	1.3 (0–5.14) s = 7	1.6 (0–4.92) s = 6	0.23	–0.27 to 2.29	NS
Night 7	2.1 (0–7.96) s = 8	0.9 (0–5.44) s = 5	–0.21	–1.85 to 0.48	NS
<i>SaO₂ < 85%</i>					
Night 3 (baseline)	0.2 (0–0.91) s = 3	0.4 (0–2.18) s = 4	0	0 to 0.54	NS
Night 4	0.2 (0–1.14) s = 3	0.3 (0–1.29) s = 4	0	–0.13 to 0.22	NS
Night 7	0.5 (0–2.09) s = 6	0.2 (0–1.39) s = 2	–0.15	–1.07 to 0	NS

s = number of subjects experiencing hypoxaemia.

C.I. = confidence interval.

NS = no significant difference.

(with $\text{SaO}_2 < 90\%$ and $< 85\%$) on nights 4 and 7 in either the placebo or zolpidem groups, compared with their baseline night (night 3). The lowest SaO_2 recorded in the placebo group was 72.5% on night 4, and the lowest in the zolpidem group was 51% also on night 4.

The frequency of hypoxaemic events of $\text{SaO}_2 < 90\%$ and $< 85\%$ per hour of sleep is given in Table 3, together with confidence intervals for the median differences (expressed as zolpidem minus placebo values and corrected for baseline differences). There was no significant difference between the zolpidem and placebo groups on nights 3, 4 or 7. The duration of hypoxaemic episodes (min h^{-1} of sleep) is shown in Table 4, with confidence intervals for the median differences (nights 4 and 7 corrected for baseline differences). There was no significant difference on any night between the zolpidem and placebo groups for $\text{SaO}_2 < 90\%$ and $< 85\%$. The respiratory events associated with the hypoxaemic episodes are shown in Table 5. There were no significant differences between the two groups for any respiratory event leading to $\text{SaO}_2 < 90\%$ on any night, with nights 4 and 7 again corrected for baseline differences. However, OA occurred

more frequently and in more subjects in the zolpidem group compared with placebo on night 4 (first treatment). For respiratory events leading to $\text{SaO}_2 < 85\%$ the only significant difference was an increase in the frequency of total obstructive episodes (OP + OA + PO) in the placebo group compared with zolpidem on night 7, $P < 0.01$.

Within group comparisons were also made between nights 4 and 7 (corrected for baseline differences), firstly for the zolpidem group and then the placebo group. For the zolpidem group, there was no significant difference between nights 4 and 7 for the frequency or the duration of hypoxaemia. There was however, a significant increase in the frequency of OA leading to $\text{SaO}_2 < 90\%$ on night 4 (first treatment) compared with night 7 (fourth treatment), with a difference between the sample medians of 0.16 and a 91.5% confidence interval from 0 to 0.75 and an associated P value of 0.05. No differences were found for any other respiratory event. For the placebo group, the only significant results were for $\text{SaO}_2 < 85\%$ when the frequency was significantly increased on night 7 compared with night 4, with a median difference of -0.108 , a 95.8%

Table 4 Duration of hypoxaemic episodes $\text{SaO}_2 < 90\%$ and $< 85\%$ (mean + range) expressed as minutes per hour of sleep with 95% confidence intervals for the median differences (nights 4 and 7 corrected for baseline differences)

	Placebo group	Zolpidem group	Median differences	95% C.I.	Wilcoxon rank sum
<i>SaO₂ < 90%</i>					
Night 3 (baseline)	4.2 (0–30.07) s = 6	0.5 (0–1.36) s = 6	0	–3.35 to 0.09	NS
Night 4	1.7 (0–8.94) s = 7	3.7 (0–28.86) s = 6	0.29	–0.05 to 3.32	NS
Night 7	2.1 (0–9.69) s = 8	0.4 (0–2.54) s = 5	–0.05	–0.76 to 0.15	NS
<i>SaO₂ < 85%</i>					
Night 3 (baseline)	0.7 (0–6.86) s = 3	0.2 (0–0.88) s = 4	0	0 to 0.38	NS
Night 4	0.4 (0–3.54) s = 3	2.3 (0–18.62) s = 4	0	0 to 0.33	NS
Night 7	0.6 (0–3.91) s = 6	0.1 (0–1.20) s = 2	–0.13	–0.5 to 0	NS

s = number of subjects experiencing hypoxaemia.

C.I. = confidence interval.

NS = no significant difference.

confidence interval from -0.915 to 0 and an associated P value of <0.05 , and the duration significantly longer, with a difference between the sample medians of -0.145 , a 95.8% confidence interval from -0.145 to 0 , and an associated P value of <0.05 . There was also a significant increase in the frequency of PO leading to $\text{SaO}_2 < 90\%$ on night 4 compared with 7, with a median difference of -0.29 , a 95.8% confidence interval from -2.425 to -0.075 , and an associated P value of <0.02 .

Few adverse effects were reported. In the placebo group, one patient complained of epigastric discomfort (night 7) and one complained of dizziness (nights 4–7). The ECG of this lady was normal. In the zolpidem group, two patients complained of nausea and indigestion on night 3, a placebo night. The symptoms responded to antacid therapy. One lady developed a deep venous thrombosis on night 7 for which she received heparin therapy. This is a complication not infrequently seen following hip and knee joint replacement surgery.

Discussion

Hypnotic drugs may affect respiration during sleep by several mechanisms. Firstly they may reduce hypoxic and hypercarbic drives. Secondly they may impair the arousal from sleep induced by airway obstruction, hypercarbia or hypoxia. Thirdly, they may change the pattern of sleep, increasing the proportion of those stages where respiratory abnormalities are most common. Finally, they may relax the pharyngeal musculature increasing the likelihood of obstructive events. The first mechanism is readily tested in the laboratory and is part of the standard investigation of any new drug. The latter mechanisms are more difficult to test and are probably best examined by observing normal sleep. There is some evidence that hypnotic drugs may worsen or induce sleep apnoea (Dolly & Block, 1982), and that the use of hypnotics is associated with an increased mortality (Fancourt & Castleden, 1986). As hypnotics are widely prescribed for the elderly despite exhortations to the contrary,

Table 5 Mean frequency of respiratory events per hour of sleep leading to $\text{SaO}_2 < 90\%$ and $< 85\%$ for all subjects

	$\text{SaO}_2 < 90\%$				$\text{SaO}_2 < 85\%$			
	Placebo		Zolpidem		Placebo		Zolpidem	
	f	s	f	s	f	s	f	s
<i>Night 3 (baseline)</i>								
OP	0.04	2	0.05	2	—	—	0.02	1
OA	0.07	2	0.49	5	0.01	1	0.18	4
PO	0.21	6	0.33	3	0.05	2	0.09	3
CP	0.01	1	0.06	1	—	—	—	—
CA	—	—	0.27	1	—	—	0.13	1
CH	0.04	2	—	—	—	—	—	—
PB	0.86	3	0.09	3	0.05	2	—	—
NR	0.49	2	—	—	0.05	1	—	—
<i>Night 4</i>								
OP	0.05	2	0.06	2	0.01	1	0.01	1
OA	0.04	2	0.54	6	—	—	0.12	2
PO	0.33	5	0.7	5	0.06	3	0.11	4
CP	0.05	2	—	—	0.03	1	—	—
CA	—	—	—	—	—	—	—	—
CH	0.08	1	—	—	0.04	1	—	—
PB	0.36	4	0.20	4	0.01	1	0.01	1
NR	0.41	4	0.07	2	0.03	1	0.03	2
<i>Night 7</i>								
OP	—	—	—	—	—	—	—	—
OA	0.09	4	0.19	3	0.01	1	0.06	1
PO	1.08	7	0.39	3	0.38	5	0.06	1
CP	—	—	—	—	—	—	—	—
CA	0.03	2	—	—	0.01	1	—	—
CH	—	—	—	—	—	—	—	—
PB	0.50	5	0.19	2	0.06	2	0.05	1
NR	0.32	3	0.17	2	0.01	1	0.06	2

OP = Obstructive pause; OA = Obstructive apnoea; PO = Partial obstruction; CP = Central pause; CA = Central apnoea; CH = Central hypoventilation; PB = Periodic breathing; NR = Normal respiration.

f = mean frequency of respiratory events per hour of sleep.

s = number of subjects displaying the respiratory event.

it is important that those drugs which are prescribed have as little effect on respiratory events as possible.

The study shows that zolpidem 10 mg does not increase the incidence or duration of episodes of hypoxaemia $\text{SaO}_2 < 90\%$ and $< 85\%$ in female patients over four nights treatment compared with placebo. There were no significant differences between the two groups for the frequency or duration of the hypoxaemic episodes (corrected for baseline differences) either on first treatment (night 4) or after accumulated dosage (night 7—fourth treatment). Analysis of the confidence intervals also seems to exclude any increase in the frequency and duration of such episodes in the zolpidem group. Similarly zolpidem did not significantly increase the incidence

of sleep related respiratory disturbances leading to hypoxaemia $\text{SaO}_2 < 90\%$ compared with placebo either on night 4 or night 7. Indeed, the frequency of total obstructive episodes (OP + OA + PO) was less in the zolpidem patients on night 7 ($P < 0.01$). Several within group comparisons for the placebo group of patients (the frequency and duration of hypoxaemic episodes $\text{SaO}_2 < 85\%$, and the frequency of PO leading to $\text{SaO}_2 < 90\%$) proved to be significantly greater on night 7 than night 4. As these patients had placebo only on each night, the most likely explanation is that they arose by chance simply because of the large number of comparisons made.

Within the zolpidem group of patients, the frequency of OA leading to $\text{SaO}_2 < 90\%$ was

significantly greater on night 4, the first treatment, than night 7, $P = 0.05$. This observation is in accord with an earlier study (Kurtz *et al.*, 1986).

Zolpidem is an imidazopyridine and is chemically unrelated to the benzodiazepines. It has been shown to be an efficient sleep inducer and does not significantly alter sleep patterns (Cirignotta *et al.*, 1988; Nicholson & Pascoe, 1986). It has been shown to have an affinity predominately at the BDZ₁ (Omega 1) receptors with little affinity for the other BDZ receptors. This selectivity of action is probably the explanation for its lesser myorelaxant effect compared with the benzodiazepines (Depoortere *et al.*, 1986) and may thus be the explanation of its lack of effect on sleep disordered breathing demonstrated in this study. The drug has a short elimination half-life of approximately 2.5 h and has no active metabolites. It may thus be assumed that the maximal effect would have been reached before the end of this study.

Patients recovering from orthopaedic surgery were chosen for two reasons. Firstly, they are commonly given hypnotic drugs as part of normal management. Triazolam was permitted if requested and sufficient time, 48 h, allowed for its elimination before the start of the study. Secondly, they are nursed in the supine position as part of the orthopaedic management thus eliminating the effect of changes in sleeping position on the incidence of apnoea. All surgery was on the lower limbs and thus it was unlikely that any residual effects of anaesthesia on the functional

residual capacity and oxygenation would be present. It was intended that patients of both sexes would be recruited. However, very few male patients met the entry criteria and of those who did a greater proportion refused to participate. Sleep disordered breathing is more common in men and further studies will be necessary to investigate the effect of zolpidem and other hypnotics in this group.

The recording apparatus has been shown to be effective and reliable in previous studies in the postoperative period and for investigation of sleep apnoea (Hanning, 1982; Hanning *et al.*, 1986). Its simplicity makes it acceptable to patients and staff. Sleep staging was not possible and night to night differences in sleep pattern cannot be excluded. However, the complexity of EEG and EOG recording would make it impractical in the ward setting. Patients were permitted an acclimatisation night (night 1) so that there should have been little effect of the apparatus and associated activities on the sleep pattern (Wittig *et al.*, 1984).

We conclude that zolpidem in a dose of 10 mg is an effective hypnotic which does not increase the frequency or severity of sleep related disordered breathing in healthy elderly women. Similar studies should form part of the evaluation of all hypnotic and sedative drugs.

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