Effect of temazepam on oxygen saturation and sleep quality at high altitude: randomised placebo controlled crossover trial

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Abstract

Objective: To determine the effects of temazepam on the quality of sleep and on oxygen saturation during sleep in subjects at high altitude.

Design: Randomised, blinded, crossover, placebo controlled trial.

Setting: Base camp at Mount Everest (altitude 5300 m).

Subjects: 11 members of British Mount Everest Medical Expedition recently arrived at base camp.

Intervention: Participants were randomly allocated to receive either temazepam 10 mg or placebo on their first night at base camp and the other treatment on the second night.

Main outcome measures: Quality of sleep (assessed subjectively), mean arterial oxygen saturation value, and changes in saturation values (as measure of periodic breathing) while participants taking temazepam or placebo.

Results: All participants noted subjective improvements in sleep. Mean saturation value remained unchanged when temazepam was compared with placebo (74.65% *v* 75.70%, $P=0.5437$). There were fewer changes in oxygen saturation when participants took temazepam and when measured as decreases $>4\%$ below the mean value of saturation each hour ($P=0.0036$, paired Student's *t* test (two tailed)).

Conclusions: Participants taking temazepam at 5300 m showed no significant drop in mean oxygen saturation values during sleep. Both the number and severity of changes in saturation during sleep decreased and the quality of sleep improved. This may be a result of a reduction in the number of awakenings and might lead to greater respiratory stability and fewer episodes of periodic breathing. This has the effect of improving the quality of sleep and reducing the number of periods of desaturation during sleep.

Introduction

Sleep is impaired in people who have recently arrived at high altitude.^{1,2} Impairment is caused by a combination of factors, which include being in a new environment, the low temperature, general discomfort, and development of acute mountain sickness. A feature of sleep at high altitude is periods of awakening or arousal that are associated with pronounced oxygen desaturation and periodic breathing.³⁻⁷ These episodes of periodic breathing may cause more unconsolidated sleep, which may lead to further episodes of periodic breathing.⁸ Consequently, daytime symptoms of drowsiness and reduced performance may occur.⁹ The use of benzodiazepine hypnotics may lessen the effects of periodic breathing and desaturation.^{7,8}

This study compared the effects of a comparatively low dose (10 mg) of the short acting benzodiazepine temazepam with placebo on the sleep patterns of subjects recently arrived at high altitude.

Subjects and methods

Shortly after arrival at 5300 m on Mount Everest nine men and two women (age range 26-46) were randomly selected from the 78 members of the British Mount Everest Medical Expedition. All participants gave informed consent. The study was approved by the Oxford regional ethics committee. A coin was tossed to randomly allocate participants to either temazepam (Norton Pharmaceuticals, Essex) or placebo (Advisory Services, London) on the first night followed by the other treatment on the second night. Participants were unaware which treatment they were given. However, the investigator was aware of participants' allocation at the time treatment was given because of the different sizes of tablets, but was not aware when data were analysed. Arterial oxygen saturation was measured continuously during the night (every 5 s) with a pulse oximeter and finger probe (Minolta Pulseox 7, De Vilbiss, Middlesex). Each morning quality of sleep was appraised subjectively by direct questioning.

The data on saturation and pulse rate were downloaded to a computer and analysed to find the mean saturation values and variation in saturation (the number of times saturation dropped $>4\%$ below mean value). Values were analysed with a paired, two tailed Student's *t* test (Statview SE and Graphics, version 1.04, Abacus Concepts, Berkeley, CA). $P<0.05$ was considered significant.

Results

Six participants took temazepam on the first night and placebo on the second and five took placebo on the first and temazepam on the second. The mean duration of recordings made during sleep was 408 minutes (SD 35 min). Length of recording was limited by sleep duration or oximeter battery life (whichever was shorter).

Mean arterial oxygen saturation—Temazepam had no significant effect on mean oxygen saturation during sleep when compared with placebo (table). The difference of 1.05% was not significant using a paired *t* test ($P=0.54$, $df=10$, 95% confidence interval -4.73 to 2.65). However, when participants took temazepam there was a significant decrease in the number of times that saturation fell $>4\%$ below the mean ($P=0.0036$); there were 25.81 fewer falls per hour that were $>4\%$ below the mean when participants took temazepam when compared with placebo ($df=10$, 10.7 falls per hour on temazepam *v* 40.9 falls per hour on placebo). The effect was more pronounced in the early hours of sleep. These effects were found regardless of

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Mean arterial oxygen saturation in 11 participants at high altitude who took placebo or temazepam

	Placebo	Temazepam	Difference	P value (two tailed)
Mean % (SE) oxygen saturation	75.70	74.65 (1.55)	-1.05 (1.66)	0.54
No of times per hour (SE) saturation fell >4% below mean value	100.79	74.98 (12.25)	25.81 (6.78)	0.0036

SE=standard error.

whether participants were assigned to take temazepam or placebo first (figure).

Subjective changes in sleep—All participants reported an improvement in sleep when taking temazepam. Improvements noted included a quicker onset of sleep, better quality of sleep, fewer awakenings and less awareness of periodic breathing, and feeling more rested the next day. No participants complained of drowsiness the day after taking temazepam.

Discussion

In this study the use of temazepam during sleep at high altitude improved the subjective quality of sleep without reducing arterial oxygen saturation. The use of various benzodiazepines at high altitude has been considered in several previous studies.^{10–14} Many of these have used high doses and long acting preparations which led to heavy sedation and marked desaturation.^{11–14} There is, however, evidence that small doses of

Key messages

- Poor sleep at high altitude is common and may be due to a combination of physiological and physical factors
- Frequent arousals, periodic breathing, and episodes of oxygen desaturation lead to poor sleep and daytime symptoms of drowsiness and reduced performance
- In this study 10 mg temazepam improved subjective reports of the quality of sleep and reduced episodes of arterial desaturation, with no significant effect on mean oxygen saturation during sleep

benzodiazepines may be beneficial in reducing central sleep apnoeas in susceptible patients.⁸

The reduction in the number of episodes of desaturation is in part due to the sedative effects of temazepam; these effects produce longer periods of consolidated sleep and lead to fewer of the arousals that are usually associated with sleep apnoea.⁸ By stabilising sleep and reducing the number of arousals, episodes of periodic breathing are similarly reduced. This leads to an improvement in the quality of sleep and a reduction in both the number of times desaturation occurs during sleep and the amount of desaturation that occurs. In this study the reduction in desaturation was more pronounced in the earlier hours of sleep when temazepam has its strongest effect. By the end of sleep its effect has weakened and saturation values become similar to those found in participants taking placebo.

Though this study suggests an important role for temazepam in reducing periods of desaturation during sleep at altitude it does not elucidate the mechanism by which this occurs. The dose required to produce an effect on desaturation is lower than that needed to produce adequate sedation for sleep at sea level. Although the sedative role of temazepam is important, temazepam is probably affecting desaturation by another pharmacological action. It may act directly by suppressing respiratory receptors or indirectly by affecting cerebral pH. This is analogous to the improvements in saturation found using carbonic anhydrase inhibitors such as acetazolamide.¹³

Conclusion

Until recently, medical advice has been to avoid using hypnotic drugs at altitude. This advice has been based on the assumption that because they have depressant effects on the respiratory system they may cause desaturation of arterial oxygen and might provoke acute altitude sickness, pulmonary oedema, or cerebral oedema. The longer acting benzodiazepines and barbiturates might have these effects.¹³ However, this study supports the conclusions of other studies which found that small doses of short acting benzodiazepines actually improve the subjective quality of sleep and reduce changes in saturation without changing mean oxygen saturation.^{10–12}

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Arterial oxygen saturation during 8 hours of sleep in one participant while taking placebo or temazepam. Each horizontal bar represents 1 hour of sleep

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Conflict of interest: None.

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Case-control study of risk of cerebral sinus thrombosis in oral contraceptive users who are carriers of hereditary prothrombotic conditions

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Abstract

Objective: To investigate whether users of oral contraceptives who are carriers of a hereditary prothrombotic condition (factor V Leiden mutation, protein C, S, or antithrombin deficiency) have an increased risk of cerebral sinus thrombosis.

Design: Comparison of a prospective series of cases of cerebral sinus thrombosis with population data.

Setting: Neurological teaching hospitals from different regions in the Netherlands (cases) and a representative sample of the non-institutionalised Dutch population (controls).

Subjects: 40 women aged 18-54 years with cerebral sinus thrombosis (cases) and 2248 women aged 18-49 years (controls).

Main outcome measure: Current use of oral contraceptives at the time of the thrombosis (cases) or at the time of the questionnaire (controls). Prevalences of a hereditary prothrombotic condition in patients and in the population with odds ratios.

Results: 34 of 40 (85%) women with cerebral sinus thrombosis used oral contraceptives, versus 1007 of 2248 (45%) of the control women; the age adjusted odds ratio was 13 (95% confidence interval 5 to 37). Seven of 36 patients (19%) had a prothrombotic deficiency, versus 7% expected in the population; this corresponds to a threefold to fourfold increase in risk. In women who used oral contraceptives and also carried a prothrombotic defect, the odds ratio for cerebral sinus thrombosis was about 30 relative to women who had neither risk factor.

Conclusion: The use of oral contraceptives and being a carrier of a hereditary prothrombotic condition increase the risk of and interact in a multiplicative way in the development of cerebral sinus thrombosis.

Introduction

Epidemiological studies have shown that oral contraceptives carry a small but increased risk of venous thromboembolism (deep vein thrombosis and pulmonary embolism).¹ Furthermore, women who use oral contraceptives and carry the factor V Leiden mutation have a higher risk of venous thromboembolism than expected from the mere addition of these risks.² Although the association between oral contraceptives and venous thromboembolism is generally accepted, there remains discussion about possible sources of bias that might influence the magnitude of the risk.

Cerebral venous sinus thrombosis is a relatively rare disease, often with cerebral infarcts, which may lead to seizures, other neurological symptoms, or death. Patients with sinus thrombosis, however, may recover completely.³ Oral contraceptives and hereditary prothrombotic conditions, such as protein C, S, and antithrombin deficiency and factor V Leiden mutation, have been reported as possible causes of cerebral sinus thrombosis.⁴

We compared a series of patients with cerebral venous sinus thrombosis from a prospective treatment trial with population data from the Netherlands to investigate the risk of oral contraceptive use and prothrombotic conditions for cerebral sinus thrombosis.

Patients and methods

Cases

Cases were patients with cerebral sinus thrombosis (newly diagnosed) who participated in a treatment trial from July 1992 to November 1996 that compared low molecular weight heparin in a therapeutic dose with placebo in a randomised double blind design. Patients

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