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Psychomotor, pulmonary and exercise responses to sleep medication

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1 Athletes may use benzodiazepines before events to improve sleep, but these drugs may adversely affect performance.
2 Nitrazepam (10 mg) and temazepam (30 mg) were compared with placebo in 27 physical education students, (14 males, 13 females). Treatments were administered at night, using a double-blind, double dummy protocol, for 9 nights. Observations were made in the morning after night 2 and night 9. At least 2 weeks interval was allowed between each treatment.
3 At each examination lung mechanics were measured, a Leeds Sleep Evaluation Questionnaire completed, recognition reaction time, choice reaction time and the critical flicker fusion threshold test were used to assess psychomotor activity and an exercise test was performed. The subject exercised to exhaustion on a bicycle ergometer while ventilation, gas exchange and heart rate were recorded on an FM tape unit for off-line digital analysis.
4 The questionnaire indicated that both drugs were equally effective in promoting and maintaining sleep, but nitrazepam had a marked 'hangover' effect. The psychomotor activity and lung mechanics however seemed unaffected. On day 2, maximum exercise levels attained using either drug were comparable to placebo whilst on day 9 temazepam and placebo were significantly higher than nitrazepam.
5 Heart rate was significantly increased at each exercise level with both drugs.
6 Although there may be some effect of these drugs on athletic performance this is likely to be small especially with temazepam.

Keywords psychomotor performance exercise testing nitrazepam temazepam

Introduction

Athletes think they need undisturbed sleep before competition in order to perform optimally. However, they may have to contend with fatigue as a result of crossing different time zones in order to attend international sports meetings and this may have an important effect upon athletic performance. One solution to this problem is to use hypnotics such as the benzodiazepines to improve sleep quality, however these may be detrimental due to the continued effect ('hangover') of the drug on waking.

Two commonly used benzodiazepines are temazepam and nitrazepam. The former is presented as a gelatine capsule, it is rapid acting,

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peak plasma concentrations occurring about 50 min after oral administration with a half-life of 5.3 h (Fuccella *et al.*, 1977). By contrast nitrazepam is presented as a tablet with a peak plasma concentration at about 80 min and a half-life of 30 h (Breimer *et al.*, 1977).

Clinical studies have suggested that temazepam produces fewer side effects than other commonly prescribed hypnotics (Fowler, 1977; Carrington & Hindmarch, 1980). Two studies have suggested that jet-lag may be reduced or eliminated through the use of temazepam (Hutson, 1983; Ball, 1983).

This paper describes two separate double-blind studies each involving the administration of temazepam (Euhypnos, Farmitalia Carlo Erba Ltd), nitrazepam (Mogadon, Roche) or placebo on separate occasions. In a preliminary study (Study 1), on eight subjects, medication was given for two nights only before the evaluation. In addition to considering the symptomatic response to medication, changes in lung mechanics and ability to perform a standard exercise test have been examined. A more involved investigation was performed in study 2 using twenty-seven athletic subjects, where medication was continued for 9 nights with measurements being made after the second and ninth nights.

Methods

All subjects gave negative histories of cardiac and pulmonary disease, all gave written consent before beginning the study, the procedures of which conformed to the ethical requirements of the Institute. The subjects practiced the techniques before the study in order to familiarise themselves.

Temazepam was presented as soft green capsules, nitrazepam as a white tablet. In view of the different physical appearance of these compounds a double-blind, double dummy randomised three-period crossover design was used to allocate the drugs. The medication each night consisted of 5 units, 3 capsules and 2 tablets, subjects receiving one of the following treatments: (period 1) temazepam 30 mg: 3 × 10 mg soft gelatin capsules plus 2 placebo tablets; (period 2) nitrazepam 10 mg: 2 × 5 mg tablets plus 3 placebo capsules; (period 3) placebo: 3 matching capsules and 2 tablets.

A 2 week washout was allowed between each period of drug administration. No restrictions were placed on the time of going to bed and medication was taken 0.5 h before retiring. Subjects were asked not to consume alcohol whilst on medication; no other restrictions were imposed. All studies were, as far as possible, performed at the same time of day, usually during the morning following the second and ninth night (Study 2) of medication.

The quality of sleep was assessed using the Leeds Sleep Evaluation Questionnaire (Hindmarch, 1975) which uses a number of 100 mm analogue scales. The four indices are: ease of getting to sleep, GTS; quality of sleep, QOS; awaking from sleep, AFS; integrity of behaviour following wakefulness, BFW, (relating to the degree of clumsiness).

Psychomotor performance was assessed using the Leeds Psychomotor Unit (Hindmarch, 1975). Recognition reaction time, RRT and choice reaction time, CRT, were measured in ms as the mean of 50 values after 20 practice attempts. The critical flicker fusion threshold test (ascending, CFFa and descending, CFFd) was also performed, with nine determinations (Hz) in each direction after three practice attempts.

Lung mechanics were evaluated using spirometry and whole body plethysmography. Measurements included relaxed and forced vital capacity (VC and FVC), one second forced expiratory volume (FEV_1), peak expiratory flow (PEF), maximum expiratory flow rates at 50 and 75% FVC ($\dot{V}_{50}$ and $\dot{V}_{75}$), airway resistance and thoracic gas volume (Raw and Vtg). The last two readings were expressed as specific airway conductance (sGaw) and transformed logarithmically as the distribution is skewed (Guyatt & Alpers, 1968).

Exercise was performed using an electrically braked ergometer (Elema-Schonander Ergometry System 380). The subjects sat on the bicycle breathing into a valvebox (Lloyd type) and measurements were made of flow rate using screen pneumotachographs (Mercury Electronics model F1000 L) with variable reluctance transducers (Validyne model 45-1). Carbon dioxide and oxygen were continuously measured at the mouth by a mass spectrometer (Centronics MGA 200) the sample delay time being determined using a calibration pump (Crisp *et al.*, 1982). Heart rate was measured by an analogue rate meter (Hewlett Packard model 78201B) using a lead II position ECG signal.

The signals were recorded on an analogue FM tape unit (Racal Thermionic Store-7) and analysed off-line by computer (Varian 73) after digitising at 50 Hz real time. Breath by breath measurements were made of tidal volume, Vt; minute volume, $\dot{V}_E$; carbon dioxide production, $\dot{V}_{CO_2}$; oxygen consumption, $\dot{V}_{O_2}$ and heart rate, HR.

In study 1, eight non-smoking male university students were investigated (18–24 years).

Medication was given for 2 nights before visiting the Institute, where quality of sleep, psychomotor performance and lung function were assessed. The following exercise programme was then performed: 2 min rest; 10 min at 120 watts. Subjects then cycled to exhaustion with the work load being increased by 20 watts each minute.

For study 2, 27 physical education students were studied (14 male, 13 female, aged 18–22 years). Medication was given for 9 nights, with measurements being made after the second and ninth nights. At each visit to the Institute, quality of sleep, psychomotor performance and lung function were assessed. Following 1 min of rest subjects then cycled for 4 min at 50, 100 and 150 watts respectively and then onto exhaustion as in study 1.

In the first study the data were compared for each treatment group using paired *t*-tests. For the exercise data, all subjects reached a level of 220 watts so separate comparisons were made for each index and exercise level between 120 and 220 watts inclusive.

A fuller analysis was possible on the second study in view of its larger size. The data were examined using an analysis of variance which incorporated tests of the normality of the data and consistency of variance. The exercise data was only analysed at the 50, 100 and 150 watts level since not all the subjects reached 170 watts on all occasions.

Results

Symptomatic and psychomotor responses

The mean results are shown in Table 1 for both studies and all three regimes. Due to equipment failure, only 18 out of the 27 subjects in study 2 completed psychomotor tests for all three treatments. Using this smaller number of subjects, the evaluation of sleep (first four indices, a high value indicating an adverse result) was similar for both studies and there was no significant change in the second study between the two sets of observations.

There were very similar changes in getting to sleep and quality of sleep indices for both drugs (highly significant falls in both compared with placebo data). However there was a marked difference between the drugs with the indices of awaking from sleep and integrity of behaviour following wakefulness. Temazepam and placebo gave similar values for awaking from sleep and

Table 1 Summary of symptomatic and psychomotor measurements

Index	*GTS (mm)*	*QOS (mm)*	*AWS (mm)*	*BFW (mm)*	*CRT (ms)*	*RRT (ms)*	*CFF,d (Hz)*	*CFF,a (Hz)*
Study 1, day 2								
Placebo	50.0 **	50.1	49.8	49.9	492.9	333.5	33.9	32.9
Temazepam	32.9 **	39.1 *	52.0 ***	55.1 ***	493.6	340.6	34.6	33.0
Nitrazepam	32.5	30.7	72.6	68.8	522.4	347.1	33.6	33.4
Study 2, day 2								
Placebo	45.9 ***	49.7 ***	52.5	50.7	500.0	327.9	34.0	31.0
Temazepam	25.4 ***	32.4 ***	54.7 *	55.3 *	514.8	334.2	33.5	31.5
Nitrazepam	34.3	33.0	64.6	65.0	517.6	337.9	34.3	31.5
Study 2, day 9								
Placebo	45.0 ***	47.2 ***	59.1	57.5	502.6	331.2	33.4	32.2
Temazepam	25.5 ***	35.3 ***	58.4 *	57.1 *	504.3	326.4	33.0	31.3
Nitrazepam	31.7	32.7	70.1	67.4	517.0	342.4	33.8	31.6

All values shown are the mean for the group, eight subjects in study 1, 18 in study 2. The first four indices are from the Leeds Sleep Evaluation Questionnaire and are expressed as the mean position on a 100 mm analogue scale. The remaining indices are from the psychomotor tests. Comparing treatments with placebo, * = $P < 0.05$, ** = $P < 0.01$, *** = $P < 0.001$

integrity of behaviour following wakefulness but the nitrazepam data showed impairment in both indices ($P < 0.05$). By contrast none of the psychomotor tests showed any difference between the regimes apart from a statistically insignificant rise in the choice reaction time on nitrazepam.

Lung mechanics measurements

These are summarised in Table 2 where the mean values are shown for the two studies, different days and different regimes. Since study 1 only included males, the various lung volume measurements are higher. The only significant differences were found in study 2. There was a fall in vital capacity with all treatments between days 2 and 9 significant at the 5% level. In addition the specific airway conductance values obtained with nitrazepam were consistently lower than for temazepam or placebo. At day 2 this was significantly less than placebo and at day 9 than temazepam (at 5% level).

Maximum exercise levels

This is taken as the highest work load which could be sustained for 1 min. A summary of these data are given in Table 3. There was an overall significant difference between the treatments ($P < 0.05$, analysis of variance). The highest levels were always seen on placebo, but the differences were small, and insignificant except for the low value obtained with nitrazepam in study 2 on day 9 ($P < 0.01$) *vs* placebo and *vs* temazepam.

Table 3 Peak level of exercise sustained for 1 min (watts)

	Study 1, day 2	*Study 2, day 2*	*Study 2, day 9*
Placebo	245	257	261
Temazepam	240	255	260 **
Nitrazepam	240	255	246

All values shown are means for the group, eight subjects in study 1, 27 in study 2. Comparing treatments with placebo, ** = $P < 0.01$

Gas exchange and heart rate during exercise

In study 1, volume expired on placebo was always less than with either active treatment, but the only significant differences were with both drugs at 140 watts, with temazepam at 120 and with nitrazepam at 200. These effects are due primarily to differences in breathing frequency. In study 2 there were no systematic differences between regimes, a few significant changes in tidal volume being associated with changes in frequency in the reverse direction.

The mean oxygen consumption values from study 1 are shown in Figure 1 at rest and at levels up to 220. The temazepam values did not differ significantly from placebo at any level but the nitrazepam data were significantly higher at 140 watts and above ($P < 0.05$, paired t-test). No significant differences were seen in study 2 up to the 150 watts levels which every subject was able to complete.

Table 2 Summary of lung mechanics measurements

Index	*VC (l)*	*FEV_1 (l)*	*FVC (l)*	*PEF ($l s^{-1}$)*	*$\dot{V}_{50}$ ($l s^{-1}$)*	*$\dot{V}_{75}$ ($l s^{-1}$)*	*sGaw ($kPa^{-1} s^{-1}$)*
Study 1, day 2							
Placebo	5.06	3.86	5.19	9.82	4.31	2.20	—
Temazepam	5.02	3.85	5.16	10.22	4.16	2.16	—
Nitrazepam	5.03	3.90	5.26	10.17	3.98	1.98	—
Study 2, day 2							
Placebo	4.23	3.34	4.35	8.81	4.54	1.97	1.85
Temazepam	4.24	3.38	4.35	8.63	4.60	1.97	1.81 *
Nitrazepam	4.24	3.30	4.28	8.88	4.44	1.97	1.77
Study 2, day 9							
Placebo	4.19	3.38	4.30	9.05	4.59	1.95	1.83
Temazepam	4.19	3.32	4.28	8.85	4.60	1.98	1.87
Nitrazepam	4.15	3.36	4.32	8.88	4.68	1.92	1.78

All values shown are means for the group, eight subjects in study 1, 27 in study 2. Comparing treatments with placebo, * = $P < 0.05$

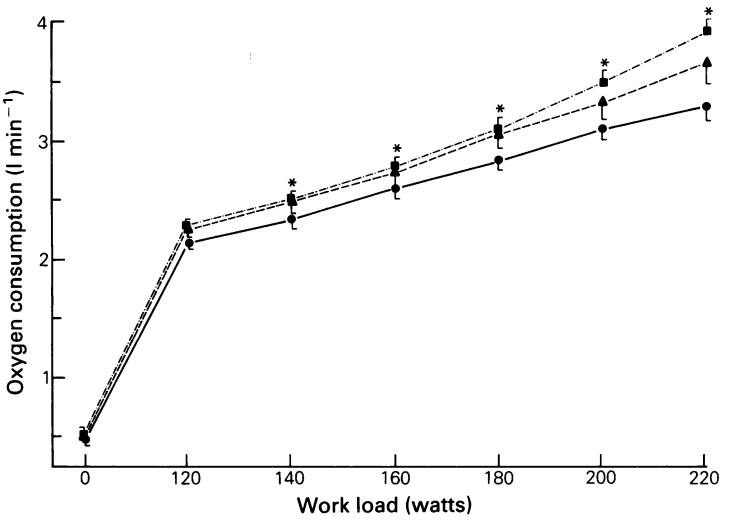

Figure 1 Mean oxygen consumption (± s.e. mean) for placebo (●——), temazepam (▲---) and nitrazepam (■—··-) at rest and with increasing levels of work load from study 1, $n = 8$. Comparison of treatments with placebo, * = $P < 0.05$.

In study 1, carbon dioxide production showed a similar pattern to volume expired, with the placebo values being the lowest, but the only significant differences were at 180 and 220 watts. In study 2 there were no significant differences.

At rest or during exercise heart rate measurements in study 1 showed no consistent pattern between drugs. In study 2 however there were very significant overall differences between all treatments at both visit 2 and visit 9 ($P < 0.001$). This difference is shown using data from Study 2, day 2 in Figure 2 which also illustrates that placebo values were always less than for the active treatments. Whilst there was no consistent difference between the two active drugs, on day 2 the highest mean heart rate was on temazepam and on day 9 with nitrazepam.

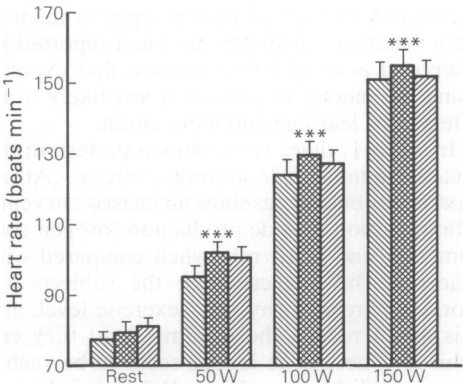

Figure 2 Mean heart rate (± s.e. mean) for placebo (▨), temazepam (▩) and nitrazepam (▨) during three levels of exercise from study 2, day 2, $n = 27$. Comparison of treatments with placebo, *** = $P < 0.001$.

Discussion

The replies to the sleep evaluation questionnaire are similar to those obtained in earlier studies (Hindmarch, 1976; Hindmarch *et al.*, 1980). The drugs were equally efficient in getting the subjects off to sleep and in providing a good quality of sleep. However nitrazepam produced a much greater hangover effect consistent with its greater plasma half life. From the measurements made in the present study there is no evidence of a cumulative effect of these drugs since in study 2 the values on day 9 are similar to those of day 2. This does, of course, not preclude the possibility that these drugs have a cumulative effect on other physiological measures. Taken overall these results provide an independent check that the subjects were taking the medication as requested.

In contrast to an earlier study (Hindmarch, 1976) the psychomotor tests do not show any marked difference between treatments in either study. This suggests that the treatments had no measurable effect on co-ordination. There were very few changes in the lung mechanics, and this is consistent with the psychomotor findings since

both types of measurement are dependent upon subject motivation and cooperation.

Reproducible measurement of vital capacity requires a sustained effort during the manoeuvre, dependent on subject motivation. The fall in vital capacity from day 2 to 9 suggests some reduction in motivation over the study period. Gaddie *et al.* (1972) showed, in a group of chronic bronchitics, a significant fall in forced expiratory volume in one second and forced vital capacity with nitrazepam. In the present study we showed no significant effect of these drugs on the measurement of forced expiratory volume in one second and forced vital capacity, in agreement with Geddes *et al.* (1976) and Rudolf *et al.* (1978). The reduction in specific airway conductance on nitrazepam suggests that this drug may produce mild bronchoconstriction.

Compared with a bicycle ergometer, the treadmill provides a more physiological form of exercise, but work output cannot be directly calculated using this method. The bicycle ergometer used in the present study, provides a constant work load, independent of the rotating speed of the wheel, and therefore provides an ideal method to compare different types of medication. Another advantage has been reported by Shephard *et al.* (1968) who state that exercise using the bicycle ergometer is less likely to be affected by learning and habituation.

In study 1, there is a common pattern in the measurements made during exercise. At all work loads both drugs show an increase in ventilation, carbon dioxide production, oxygen consumption and heart rate when compared with placebo. This suggests that the subjects are working harder at any given exercise level, and this might reduce the maximal load they can achieve. There does indeed seem to be such a decrease (Table 3, column 1) but it is not of statistical significance.

In study 2 there is a similar trend in the maximal exercise load achieved, but this only reaches significance with nitrazepam on day 9. In contrast to study 1 however there are no systematic increases in ventilation and gas exchange with the active treatments when compared with placebo.

Pleuvry *et al.* (1980) found no changes in heart rate in resting subjects taking 40 mg temazepam. Using diazepam, Rao *et al.* (1973) showed a significant rise in heart rate following acute intravenous administration of diazepam (58 mg, ± 4.9 mg s.e. mean). We failed to find any differences at rest or at exercise in study 1. However in study 2, the observation of an elevation of heart rate on both active treatments during exercise might indicate another limitation on the peak potential level.

The studies were performed usually during the morning so the reported differences between study 1 and 2 are unlikely to be a result of different time intervals between measurements.

In conclusion, although we have demonstrated the expected subjective responses to sleep medication we have failed to show any changes in psychomotor performance and little alteration to lung mechanics. While our study indicates a small effect of nitrazepam on exercise performance, we have no incontrovertible evidence of a detrimental effect on exercise performance. However, we cannot rule out the possibility that the use of these drugs could adversely affect top class athletes who require the highest levels of motivation and physical performance.

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References

Ball, M. (1983). On your marks to beat jet lag. *World Medicine*, Oct 15, 38–39.

Breimer, D. D., Bracht, H. & De Boer, A. G. (1977). Plasma level profile of nitrazepam (Mogadon) following oral administration. *Br. J. clin. Pharmac.*, **4**, 709–711.

Carrington, E. A. & Hindmarch, I. (1980). The effects of 20, 40 and 60 mg temazepam (Euhypnos) on the sleep and early morning performance of patients. *I.R.C.S. Medical Science*, **8**, 406–407.

Crisp, A. H., Cumming, G., Guyatt, A. R. & Kirkham, A. J. T. (1982). Dynamic calibration of apparatus to measure respiratory dead space. *Clin. Sci.*, **63**, 51–52p.

Fowler, L. K. (1977). Temazepam (Euhypnos) as a hypnotic: a twelve-week trial in general practice. *J. int. med. Res.*, **5**, 295–296.

Fuccella, L. M., Bolcioni, G., Tamassia, V., Ferrario, L. & Tognoni, G. (1977). Human pharmacokinetics and bioavailability of temazepam administered in soft gelatine capsules. *Eur. J. clin. Pharmac.*, **12**, 383–386.

Gaddie, J., Legge, J. S., Palmer, K. N. V., Petrie, J. C. & Wood, R. A. (1972). Effects of nitrazepam

in chronic obstructive bronchitis. *Br. med. J.*, **2**, 688–689.

Geddes, D. M., Rudolf, M. & Saunders, K. B. (1976). Effect of nitrazepam and flurazepam on the ventilatory response to carbon dioxide. *Thorax*, **31**, 548–551.

Guyatt, A. R. & Alpers, J. H. (1968). Factors affecting airways conductance: a study of 752 working men. *J. appl. Physiol.*, **24**, 310–316.

Hindmarch, I. (1975). A 1,4-benzodiazepine, temazepam (K 3917), its effect on some psychological parameters of sleep and behaviour. *Arzneimittel-Forschung*, **25**, 1836–1839.

Hindmarch, I. (1976). A sub-chronic study of the subjective quality of sleep and psychological measures of performance on the morning following night time medication with temazepam. *Arzneimittel-Forschung*, **26**, 2113–2115.

Hindmarch, I. (1978). The effects of repeated doses of temazepam taken in conjunction with alcohol on aspects of psychomotor performance the morning following night time medication. *Arzneimittel-Forschung*, **28**, 2357–2360.

Hindmarch, I., Parrott, A. C., Hickey, B. J. & Clyde, C. A. (1980). An investigation into the effects of repeated doses of temazepam on aspects of sleep, early morning behaviour, and psychomotor performance in normal subjects. *Drugs exp. clin. Res.*, **6**, 399–406.

Hutson, M. (1983). How Notts Forest lost their match but won game against time zones. *Pulse*, Oct 29, p. 54.

Pleuvry, B. J., Maddison, S. E., Obeh, R. B. & Dodson, M. E. (1980). Respiratory and psychological effects of oral temazepam in volunteers. *Br. J. Anaesth.*, **52**, 901–906.

Rao, S., Sherbaniuk, R. W., Prasad, K., Lee, S. J. K. & Sproule, B. J. (1973). Cardiopulmonary effects of diazepam. *Clin. Pharmac. Ther.*, **14**, 182–189.

Rudolf, M., Geddes, D. M., Turner, J. A. McM. & Saunders, K. B. (1978). Depression of central respiratory drive by nitrazepam. *Thorax*, **33**, 97–100.

Shephard, R. J., Allen, C., Benade, A. J. S., Davies, C. T. M., di Prampero, P. E., Hedman, R., Merriman, J. E., Myhre, K. & Simmons, R. (1968). The maximum oxygen uptake. An international reference standard of cardiorespiratory fitness. *Bull. Wld. Hlth. Org.*, **38**, 757–764.

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