Human orthostatic reflexes after taking temazepam at night

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1 Cardiovascular orthostatic reflexes have been studied at night in 12 healthy male subjects who were given two soft gelatin capsules each containing 0 or 10 mg temazepam at 21.30 h.

2 The changes in heart rate, blood pressure and forearm blood flow on consecutive 5 min exposures to lower body negative pressure (suction) at 30, 40 and 50 mm Hg were measured before and then 1.5 and 9.5 h after giving doses of 10 or 20 mg temazepam in a placebo-controlled double-blind cross-over study.

3 Pre-suction resting values were not affected by temazepam, but 1.5 h after giving the capsules there were significant differences in the responses to suction between the placebo and 20 mg temazepam experiments: the tachycardia after 20 mg temazepam was about one-third greater and the forearm vasoconstriction was about 50% less. The effect of the 10 mg dose was equivocal. No residual effects were detected the next morning.

4 These alterations in orthostatic reflexes soon after the administration of temazepam at night did not impair the maintenance of arterial blood pressure in these healthy subjects.

Keywords benzodiazepines temazepam orthostasis cardiovascular system lower body negative pressure

Introduction

Temazepam is a short-acting benzodiazepine, widely used as a hypnotic drug at night and an anxiolytic drug during the day. When given orally in doses of 10 to 40 mg at night, peak plasma concentrations are reached after less than 60 min, and after 9 h the plasma concentration has fallen to 20% of the peak value (Fuccella *et al.*, 1977; Bittencourt *et al.*, 1979).

There have been many studies of the duration of the effects of a single dose. Psychomotor tests have revealed no residual impairment the morning after taking up to 30 mg temazepam at night (e.g. Nicholson, 1979), and daytime studies have found that significant psychomotor effects persist for no longer than 4 h after a 40 mg dose (Pleuvry *et al.*, 1980). Similar findings have come from

daytime psychometric studies of drowsiness, co-ordination etc (Matejcek *et al.*, 1983), EEG changes (Matejcek *et al.*, 1983) and maximum velocity of saccadic eye movements (Bittencourt *et al.*, 1981). The use of temazepam for premedication in day-case surgery also suggests that general performance is not impaired beyond a few hours (Amarasekera, 1980; Douglas *et al.*, 1980).

There have been few studies of the effects of temazepam on the cardiovascular system in man although it is known that benzodiazepines can inhibit pressor responses to hypothalamic stimulation in cats (Antonoccio & Halley, 1975; Hockman & Livingston, 1971). Hossman *et al.* (1980) found a significant fall in blood pressure

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in five normal subjects 1.5 h after an oral dose of 20 mg nitrazepam in the day. Pleuvry *et al.* (1980) and Douglas *et al.* (1980) found no effects on resting heart rate (HR) or blood pressure (BP) after giving 20 mg temazepam, but Matecjek *et al.* (1983) reported a 10 beats min^{-1} increase in heart rate in 12 normal subjects 4 h after a 30 mg dose in the morning.

There are many circumstances in which any loss of normal orthostatic tolerance after taking temazepam would be hazardous. Baird *et al.* (1983) reported the successful use of 20 mg temazepam by military aircrew at times when getting to sleep was made more difficult by stress, time-zone changes and operational schedules, but their subjects were advised to take the hypnotic at least 8 h before flying. It has not previously been established whether any alteration of the response to gravitational forces occurs with temazepam, and if so, how long it lasts. Patients taking temazepam at night may for a variety of reasons get up from their beds earlier than expected and they could be at risk of falling if their cardiovascular responses to orthostasis have been compromised by the drug.

Orthostatic responses can conveniently be studied in supine subjects using lower body negative pressure (LBNP), i.e. exposure of parts of the body below the iliac crests to pressures less than atmospheric. We have measured the cardiovascular response to LBNP in 12 normal subjects 1.5 and 9.5 h after giving placebo and 10 and 20 mg doses of temazepam at night. A preliminary report of this work has been presented to the British Pharmacological Society (Dikshit *et al.*, 1987).

Methods

Subjects

Twelve healthy adult males (age 22.3 (range 18–33) years; height 1.80 (1.68–1.92) m; weight 73 (64–99) kg) were recruited for the study which had the approval of the Medical School Ethics Committee. The subjects gave informed consent in writing. They had a normal nychthemeral (24 h) pattern of sleep and activity and were taking no current medication. Only one was a smoker (20 cigarettes daily). They were screened for cardiovascular abnormalities, and familiarised with the procedures on a separate day before the experiments. The study was performed between June and September in an air-conditioned laboratory maintained at around 25°C.

Protocol

After preliminary resting measurements, the

cardiovascular responses to consecutive 5 min periods of lower body negative pressure (LBNP) at 30, 40 and 50 mm Hg below atmospheric pressure in the supine posture were measured three times on each of three separate nights. The subject reported in the evening having avoided caffeinated drinks in the previous 3 h, and baseline measurements of the responses to suction were made in the first hour ('evening', Phase 1). Soft gelatin capsules containing the hypnotic drug or placebo were then taken orally at a clock time within 35 min of 21.30 h, and the subject went to bed in a warm adjacent room. One hour later the subject was woken and the measurements were repeated ('late night', Phase 2). He then went back to bed and was aroused 7 h later, i.e. about 9 h after the capsules had been given the night before, and the measurements were repeated a third time ('morning', Phase 3).

At the start of the second (late night) and third (morning) phases, 5-point rating scales were used to elicit subjective measures of sleep quality and of alertness. The ends of these scales were anchored by the phrases 'very poor' (1) and 'very good' (5), and 'tired and sleepy' (1) and 'alert and fresh' (5) respectively. The subjects were asked to estimate how long it had taken them to fall asleep.

Between 2 and 7 nights separated the experiments on a given subject who was always studied at the same times. Two identical capsules were administered each evening, containing either 10 mg temazepam or a lactose placebo. The dose of 0, 10 or 20 mg temazepam was randomised among the 12 subjects in a balanced cross-over design and given double-blind.

Measurements

Measurements were made after at least 10 min of quiet rest before suction, and then in the first and fifth minutes of each LBNP exposure. Systolic and diastolic blood pressures (SBP, DBP) were measured in the left arm by auscultation, and heart rate (HR) was continuously recorded using precordial ECG electrodes. Blood flow in the right forearm (FBF) was measured by venous occlusion plethysmography. The hand was isolated with an arterial cuff inflated to 200 mm Hg throughout the period of recording, and venous occlusion was achieved by a cuff applied above the elbow. This was inflated to a pressure of 50 mm Hg for 7 s at a time every 15 s. The changes in forearm circumference following venous occlusion were measured using a mercury-in-silastic strain gauge (Whitney, 1953) and recorded on an ultraviolet recorder (SE Oscillograph). Strain gauges were selected to fit the

subject and calibrated before and after each experiment. Forearm vascular resistance (FVR) was derived from the mean arterial pressure (one-third of the pulse pressure above diastolic) and the forearm blood flow which was obtained from the average of up to four technically-acceptable recordings in the same minute.

The lower body suction was applied using a rigid box with a polythene seal at the level of the iliac crests, and the subatmospheric pressures were set and maintained at the desired level using a mercury manometer (Bennett *et al.*, 1980). The right forearm skin temperature near the strain gauge was measured throughout the experiment using a Comark microprocessor thermometer.

Analysis of variance (SPSS-X) was used to establish the statistical significance of the effects attributable to temazepam dose across the range of suction steps, using within-subject comparisons. The sequence of application of the doses was ignored as carry-over effects were presumed to have been avoided. A *P* value of less than 0.05 has been taken as indicating statistical significance.

Results

Subject compliance

Four subjects exhibited pre-syncope signs or symptoms in the fifth minute of suction at 50 mm Hg on one or more occasion, but they recovered immediately when the box pressure was raised back to atmospheric. The fifth-minute data-points were lost on those occasions. This occurred three times in phase 1 before the capsules had been given (on occasions when the laboratory temperature had inadvertently risen by 4° C), twice in phase 2 (once after 20 mg temazepam

and once after placebo), and once in phase 3 when 10 mg temazepam had been given the night before. The baseline variables and the overall pattern of responses to suction in these four subjects were otherwise very similar to those in the other eight. No subject had difficulty getting up and walking back to the laboratory for the next suction exposure.

Sleep

Table 1 summarises, for each of the two sleep periods, the subjective reporting of sleep onset, sleep quality and alertness after waking. The number of subjects falling asleep within 60 min of taking the capsules was significantly greater after temazepam than after placebo ($\chi^2 = 8.22$; d.f. = 2; *P* < 0.05) but there was no difference in time to sleep onset after the subjects had returned to bed after the late night (phase 2) measurements. The subjective quality of sleep in those subjects who actually went to sleep in the first hour was not significantly better after taking either 10 mg or 20 mg temazepam than after placebo (Kruskal-Wallis 1-way analysis of variance, *P* = 0.13). Sleep quality during the main sleep period was the same whatever capsules had been taken, and so too was alertness at both 1.5 and 9.5 h after the drug.

Effect of temazepam on resting heart rate, blood pressure and forearm blood flow

Table 2 shows the mean values for the cardiovascular variables measured in phases 2 and 3, i.e. at 22.30 h and at 06.30 h when the subjects had wakened from sleep, walked the short distance to the laboratory, and lain quietly at rest in the box for 10 min prior to testing.

Two-way analysis of variance with within-subject comparisons showed that there were no

Table 1 Effect of temazepam dose on sleep and on alertness after sleep in 12 subjects

	First sleep period Temazepam dose			Main sleep period Temazepam dose		
	Placebo	10 mg	20 mg	Placebo	10 mg	20 mg
Number of subjects asleep by 60 min	3	9	9	12	12	12
Quality of sleep (scale units)	2.0 1.0	3.0 0.3	3.7 0.4	4.0 0.2	3.8 0.4	4.3 0.3
Alertness after sleep (scale units)	3.6 0.4	3.3 0.3	3.3 0.3	3.2 0.2	3.1 0.1	3.1 0.3

The mean and s.e. mean is given for the subjective rating variables.

Table 2 Mean $\pm$ s.e. mean ($n = 12$ subjects) for the cardiovascular variables at rest before suction in phase 2 (22.30 h) and in phase 3 (06.30 h next morning) after taking placebo or 10 or 20 mg temazepam at 21.30 h

	Phase 2 (22.30 h)			Phase 3 (06.30 h)		
	Placebo	10 mg	20 mg	Placebo	10 mg	20 mg
HR (beats min ⁻¹)	57.2 2.3	58.2 2.6	60.2 2.2	55.8 2.8	57.3 1.7	58.3 1.4
Systolic BP (mm Hg)	118.8 3.1	115.2 3.6	118.2 3.5	116.8 3.7	116.2 3.3	119.7 2.8
Diastolic BP (mm Hg)	80.2 2.3	76.8 2.4	80.5 2.3	82.3 2.3	80.0 1.5	84.3 2.1
Mean BP (mm Hg)	93.1 2.3	89.6 2.7	93.1 2.4	93.8 2.6	92.1 2.0	96.1 2.3
Skin temperature (° C)	33.1 0.2	33.2 0.1	33.5 0.2	32.8 0.2	32.5 0.3	33.0 0.2
FBF (ml 100 ml ⁻¹ min ⁻¹)	3.87 0.37	3.84 0.35	4.12 0.38	2.88 0.26	3.18 0.45	3.58 0.20
FVR (mm Hg (ml/100 ml/min) ⁻¹)	26.1 2.2	25.5 2.3	24.5 2.1	35.0 2.6	34.4 3.9	27.8 1.8

significant effects of the drug on any of these variables at either measurement phase. In the morning, forearm vascular resistance (FVR) was significantly higher ($P < 0.05$) and forearm blood flow (FBF) significantly lower ($P < 0.05$) than in the evening, and the temperature of the forearm skin was 0.5° C lower ($P < 0.01$).

Baseline responses to suction

Figures 1 and 2 show the cardiovascular responses to lower-body suction measured in Phase 1 before the capsules had been taken. Each point represents the mean of three observations on each of 12 subjects except for the final point where one observation was missed for each of three subjects. Results are given for the final minute of the control period before LBNP, and for the first and fifth minutes of each suction period.

Systolic blood pressure was reduced in the first minute after each lowering of box pressure and then remained approximately constant for the next 4 min (Figure 1a). Diastolic pressure rose very slightly with progressively increasing suction. Mean arterial pressure, therefore, fell by a few mm Hg.

At each stage of suction the heart rate rose, quickly at first and then more slowly, finally reaching 25 beats min⁻¹ above the resting level in response to a fall of 15 mm Hg in systolic pressure induced by LBNP of 50 mm Hg (Figure 1b).

The forearm blood flow showed a different pattern of response to the suction protocol

(Figure 2a), falling dramatically at first and then recovering somewhat. A small part of the fall is attributable to the slight reduction in mean arterial pressure, but the major part mirrors the change in the vascular resistance of the forearm (Figure 2b). This rose sharply on the first modest reduction in box pressure but then fell partway back during the next 4 min although the box pressure was maintained. The high resistance was partially restored on subsequent increases in suction.

After the capsules had been taken, the effects of the two doses of temazepam were assessed among the 12 subjects across the periods of suction using a 3-way analysis of variance (subject, suction-period, treatment) for the late night and morning phases separately. Significant treatment-effects, indicating differences attributable to temazepam, were found only for heart rate and forearm vascular resistance, and only in phase 2 (1.5 h after temazepam had been administered), not in phase 3 the morning after.

Effect of temazepam on the heart rate response to suction

Figure 3 shows the rise in heart rate induced by progressive suction in phase 2 at 22.30 h and in phase 3 at 06.30 h. The baseline was taken as the final minute of the control period before LBNP in each respective phase. Ninety minutes after the drug had been taken, the tachycardia was 33% greater after 20 mg temazepam than after

Figure 1 The responses to progressive lower body suction in 12 subjects studied on three occasions in the evening before drug administration. Measurements during the pre-LBNP control period and during the first and fifth minutes at each level are shown: (a) systolic, mean and diastolic blood pressures; (b) heart rate. The bars show the 95% confidence limits around the mean values, and the horizontal dotted lines indicate the pre-suction baseline.

placebo ($P < 0.05$). Alternatively, 20 mg temazepam increased the heart rate at each stage of suction by an average of 5 beats min^{-1} . The 10 mg dose did not affect the response. Nine and a half hours after taking the capsules (phase 3) the tachycardia was the same whatever dose had been taken, but was greater ($P < 0.05$) both with placebo and with 10 mg temazepam than it has been in the late night phase.

Effect of temazepam on the forearm vasoconstrictor response to suction

Figure 4 shows that the rise in forearm vascular resistance (FVR) with progressive suction was less when 20 mg temazepam had been given 1.5 h before than when no temazepam had been given

Figure 2 The responses to progressive lower body suction in 12 subjects studied on three occasions in the evening before drug administration. Measurements during the pre-LBNP control period and during the first and fifth minutes at each level are shown: (a) forearm blood flow, and (b) forearm vascular resistance. The bars show the 95% confidence limits around the mean values, and the horizontal dotted lines indicate the pre-suction baseline.

($P < 0.05$). The average difference was about 8.5 mm Hg (ml/100 ml/min) $^{-1}$. After 10 mg temazepam there was an intermediate rise in FVR, which resembled the response with 20 mg at low suction pressures but resembled the placebo response at high suction. In the morning the FVR responses to suction were again independent of the dose given the night before.

Effect of temazepam on the changes in other cardiovascular variables with lower-body suction

For simplicity, the responses to suction for all the other measured and derived variables are summarised in Table 3. This gives the change between the resting pre-suction baseline (the values given in Table 2) and the values measured

Figure 3 The changes in heart rate during progressive lower body suction in 12 subjects 1.5 h (late night) and 9.5 h (morning) after taking placebo ($\circ$), 10 (Δ) and 20 mg ($\bullet$) temazepam orally.

Figure 4 The changes in forearm vascular resistance during progressive lower body suction in 12 subjects 1.5 h (late night) and 9.5 h (morning) after taking placebo ($\circ$), 10 (Δ) and 20 mg ($\bullet$) temazepam orally.

in the first minute of suction at 50 mm Hg (the last time at which values for all 12 subjects were obtained).

Except for the heart rate and forearm vascular resistance described above, there were no significant drug-effects in a 2-way analysis of variance

Table 3 Differences from baseline $\pm$ s.e. mean ($n = 12$ subjects) for the cardiovascular variables during the first minute of suction at 50 mm Hg in phase 2 (22.30 h) and in phase 3 (06.30 h next morning) after taking placebo or 10 or 20 mg temazepam at 21.30 h.

	Phase 2 (22.30 h)			Phase 3 (06.30 h)		
	Placebo	10 mg	20 mg	Placebo	10 mg	20 mg
HR (beats min ⁻¹)	20.0 2.2	20.7 2.6	26.8 3.5	25.8 1.8	26.2 2.7	26.4 2.6
Systolic BP (mm Hg)	-10.3 1.6	-11.8 1.7	-13.2 1.8	-11.5 1.8	-12.0 2.1	-7.5 2.6
Diastolic BP (mm Hg)	1.7 1.8	1.1 0.9	-2.2 1.7	2.5 1.2	-1.3 1.5	0.7 2.2
Mean BP (mm Hg)	-2.3 1.3	-3.2 1.0	-5.8 1.3	-2.2 1.2	-4.9 1.1	-2.1 2.2
Skin temperature (°C)	-0.24 0.06	-0.33 0.06	-0.18 0.05	-0.15 0.08	-0.38 0.08	-0.21 0.06
FBF (ml 100 ml ⁻¹ min ⁻¹)	-1.62 0.4	-1.42 0.3	-0.92 0.5	-0.9 0.1	-1.5 0.4	-1.3 0.2
FVR (mm Hg (ml/100 ml/min) ⁻¹)	26.9 9.1	13.8 4.2	5.3 3.1	20.3 4.5	24.6 6.4	18.5 4.1

at either measurement phase. However it should be noted that for the forearm blood flow (FBF) response after 1.5 h (phase 2), the pattern seen was the one expected from the demonstrable effect of temazepam in limiting the rise in FVR: the fall in FBF on suction was much less after 20 mg temazepam than after placebo, despite a similar fall in mean arterial pressure.

Discussion

This study has demonstrated an alteration in cardiovascular responses to supine lower body suction in the second hour after the oral administration of 20 mg temazepam at night. The tachycardia was enhanced by one-third, while the forearm vasoconstriction was reduced by half. After 9.5 h no residual effects were detectable. Blood pressure responses were not significantly affected by temazepam, and in the absence of any suction stress no cardiovascular changes attributable to the drug were seen. The 10 mg dose of temazepam did not affect orthostatic reflexes materially, although it produced similar hypnotic effects to those seen after 20 mg temazepam.

There have been two previous studies reporting the effects of temazepam on HR and BP in normal human subjects. Pleuvry *et al.* (1980) found no change in resting values during 6 h's observation after giving 20 or 40 mg temazepam in the daytime. Matejcek *et al.* (1983) also found

no daytime effect of temazepam on blood pressure measured both sitting at rest and immediately after standing up. However, heart rate in both postures was significantly raised for several hours after giving 15 and 30 mg temazepam, the tachycardia reaching 10 beats min⁻¹. They found no such tachycardia after giving equipotent doses of nitrazepam, and suggested that nitrazepam but not temazepam inhibited the 'arousal' response to the repeated awakenings that had been necessary to permit the administration of psychomotor tests. Our finding in drowsy but awake subjects of an enhancement by temazepam of the tachycardia in response to suction (Figure 3, Table 3) makes it more likely that the tachycardia reported by Matejcek *et al.* (1983) was due to a primary effect of temazepam not shared by nitrazepam. The fact that this anxiolytic drug did not reduce resting heart-rate and, rather, enhanced the tachycardia response to suction indicates that our subjects were not stressed by the procedures.

Plevry *et al.* (1980) noted that after taking temazepam several of their subjects reported feeling cold and put on extra clothing: their laboratory temperature was 19–21°C. Oral temperatures were significantly depressed by 1.3°C 2 h after giving 40 mg temazepam. We found no effect of the drug on forearm blood flow or skin temperature when our subjects were resting supine in a warm room (Table 2), but there was a marked impairment of the ability of the forearm to vasoconstrict in response to a fall in thoracic

blood volume (Figure 4, Table 3). When the hand has been excluded from the measurement, blood flow in the forearm is mostly through muscle, and the total flow in these experiments was much smaller than that found when forearm vasodilatation was induced by heating. Nevertheless, some cutaneous vasodilatation as part of the response to temazepam cannot be excluded: this might account for the extra heat loss in the subjects of Pleuvry *et al.* (1980).

The baseline values and the responses to suction in the absence of the drug show some variation between the night and morning phases. Forearm blood flow was lower and forearm vascular resistance was higher in the morning, while mean arterial blood pressure was unchanged (Table 2). The small fall in forearm skin temperature is likely to have been the consequence rather than the cause of these differences. Against these changes in baseline, the responses to suction were relatively constant between phases (Table 3). Kaneko *et al.* (1968) have previously reported circadian variations in forearm blood flow in normally active subjects. They found the flow was highest in the early evening, and lowest at 09.00 h, the time of their earliest morning measurement. Kaneko *et al.* (1968) also measured the effect of 40 mm Hg LBNP: the greatest reduction in forearm blood flow was seen in the early evening, but there was little difference between the reductions due to suction at 23.00 h and 09.00 h. Our present data are entirely consistent with those findings, but neither study identifies any cause for the evening-morning difference. Millar-Craig *et al.* (1982) found that heart rate and both systolic and diastolic blood pressures were similar at 22.30 h and 06.30 h, with a nadir during sleep between these times.

When the responses to suction in the present study are compared between evening and late night phases in the absence of temazepam (i.e. before and after placebo), it appears that the FVR rose further ($P < 0.05$) and the systolic pressure fell less ($P < 0.05$) late at night than in the evening (see Figures 2 and 4). The tachycardia that developed, however, did not differ between the phases. Because the subjects had been resting

for 2 h (some sleeping) before the second measurement but active before the first, and had taken capsules that might have been sedative in between, we have preferred to make post-drug vs post-placebo comparisons in the main analysis. Nevertheless, it is possible to interpret the effects of temazepam as a dampening of a heightened late-night response to suction of forearm vascular resistance rather than a reduction of a normal response (Figure 4).

The maintenance of arterial blood pressure is an important indication that orthostatic tolerance is adequate, and this has been demonstrated here for the period when the plasma concentration of temazepam would have been maximal. In addition, there was no preponderance of presyncope episodes at this time (i.e. during the late night exposure to suction after the 20 mg dose of temazepam). These observations therefore raise no suspicions about the overall ability of the cardiovascular system to cope with the normal demands of orthostasis after the administration of moderate clinical doses of temazepam. Nevertheless, the stability of the arterial blood pressure after temazepam is maintained in the face of an impairment of the ability of the forearm vasculature to constrict in response to a fall in central venous volume. This vasoconstriction is sympathetically mediated and triggered from the thoracic low-pressure baroreceptors (Abboud *et al.*, 1976). It is likely that temazepam affects this reflex by an action in the brain-stem, just as Bittencourt *et al.* (1981) have shown for temazepam's effects on ocular movements. The significant tachycardia seen after temazepam by ourselves and by Matejcek *et al.* (1983) may be a sign of the compensation needed to maintain cardiac output and blood pressure in face of a reduced venous return to the heart. An additional compensation by enhanced splanchnic arteriolar vasoconstriction cannot be ruled out.

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