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THE EFFECTS OF CLOBAZAM AND LORAZEPAM ON ASPECTS OF PSYCHOMOTOR PERFORMANCE AND CAR HANDLING ABILITY

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1 Laboratory tests of psychomotor performance and 'on road' assessments of car handling ability were made following repeated doses of clobazam 10 mg three times daily, lorazepam 1 mg three times daily and matching placebo 1 capsule three times daily.

2 Both active compounds produced an impairment, compared to placebo, in some mental arithmetic and letter cancellation tasks, but these effects were neither widespread nor consistent.

3 Lorazepam produced a significant impairment of car driving tasks and analogue rating scales of subjective alertness. The pronounced sedative activity of the drug was also shown in the verbal reports of side effects and in indices of early morning sedation derived from the Leeds Sleep Evaluation Questionnaire.

4 Clobazam did not produce either the objective, or the subjective impairment of performance and alertness found with lorazepam.

5 The results taken as a whole show important differences between the 1,4 benzodizaepine, lorazepam, and the 1,5 benzodiazepine, clobazam, in their effects on the integrity of psychomotor performance related to car driving ability.

Introduction

Clobazam, a 1,5-benzodiazepine derivative, has been shown to be an effective anxiolytic agent at doses which do not impair human psychomotor performance in both volunteer (Borland & Nicholson, 1974; Berry, Burtles, Grubb & Hoare, 1974; Hindmarch, 1979a, 1979b) and patient (Doongaji, Sheth & Apte, 1978; Salkind, Hanks & Silverstone 1979) studies. Clobazam is metabolized in man mainly to N-desmethylclobazam (Rupp, Badian, Christ, Hadju, Kulkarni, Taeuber, Vihlein, Bender & Vanderbeke, 1979). This has significantly less anxiolytic activity than clobazam itself with minimal effects on motor co-ordination (Fielding & Hoffman, 1979).

Lorazepam, a conventional 1,4 benzodiazepine which, although it has no active metabolites and is excreted conjugated mainly as the gluceronide, is slowly dispersed from blood plasma and has a long duration of action (Knowles, Comer & Ruselius, 1971; Elliott, Nomof, Navarro, Ruselius, Knowles & Comer 1971). It has marked sedative properties (Seppälä, Kortilla, Hakkinen & Linnoila, 1976) making it clinically useful as a hypnotic and surgical premedication (Norris & Wallace, 1971; Globus, Phoebus, Humphries, Boyd, Gaffney & Gaffney, *et al.*, 1974; Straughan, 1979). At doses between 1–4 mg lorazepam has been shown to impair performance on analogues of car driving (Sappälä *et al.*, 1976), reaction time (Harry & Richards, 1972; Turner, 1973), flicker fusion frequency (Hedges, Turner & Harry, 1971; Turner, 1973; Farhoumand, Harrison, Pare, Turner & Wynn, 1979) and sensori-motor coordination (Bell, Dickie, Stewart-Jones & Turner, 1973).

The purpose of this study is to compare the effects of clobazam and lorazepam against placebo on objective tests of psychomotor performance, measures of the skill involved in car driving and subjective evaluations of behaviour, mood states and drug-induced side effects.

Methods

Subjects

Twelve female volunteers aged between 26 and 40 years (mean age 34 years) all regular and experienced car drivers, were admitted to the study. All were in normal physical health without a history of cardiovascular, gastric, renal or hepatic disorder. Concurrent medication (excluding the contraceptive pill), actual or possible pregnancy and a history of psychiatric illness also precluded participation. All subjects used public transport and consumed no alcohol for the duration of the study.

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Materials and design

The basic cross-over design was blind to subjects, marshals administering the car driving tests and experimental assistants collecting the results. The dose regimen was chosen, from the manufacturer's prescribing information, to represent equivalent daily treatments of both clobazam and lorazepam. Subjects received clobazam 10 mg three times daily for 3 days, lorazepam 1 mg three times daily for 3 days and placebo three times daily for 3 days. All materials were contained in identical matching capsules. Active treatments were administered according to a random code on week 1 and the 'crossover' treatment on week 3 of the experimental period. All subjects received matching placebo on week 2, this was unknown to either experimental assistants or subjects. Subjects were familiarized with the car driving and psychomotor testing procedures, to preclude learning effects, before entry to the study and all completed the Middlesex Hospital Questionnaire (Crown & Crisp, 1970). Each subject then took the medication three times daily for three days and attended for testing the morning of the fourth day after taking a further single dose of medication. Individual subjects took their last capsule between 08.30–09.30 h with testing taking place 0.5 h later.

Assessments and measures

On each test morning all subjects were assessed on each of the following tasks. The order the timing of the tasks was kept constant for each subject for the duration of the study. The assessment procedures are described in full elsewhere, but summarized here for convenience.

Concept identification (Hindmarch & Parrott, 1978; Hindmarch Parrott & Lanza, 1979) was used as an index of the speed of mental processing. The performance measure recorded was the time taken to correctly identify three easy and three hard conceptual elements from parallel sets of problem diagrams.

Motor manipulation was measured on a peg board, The time taken to place thirty washers on rivets and insert them into a peg board together with the time taken to remove the rivets from the board separate the washers and thread them on a rod, was the response measure used.

Mental arithmetic ability (Hindmarch *et al.*, 1979) was measured using a serial subtraction of numbers technique. The time taken to sequentially subtract twenty 3s, 7s and 17s from a five digit number and the number of erroneous subtractions made were the assessment measures taken.

Vigilance was measured using a letter cancellation technique. Subjects were required to cancel either 1, 2, 3 or 4 letters from pages of random letters. The time taken to complete the cancellation and the number of errors made during the task were the response measures used.

Sleep The effects of the treatments on sleep and early morning behaviour were rated by the subjects on the Leeds Sleep Evaluation Questionnaire (Hindmarch, 1975; Parrott & Hindmarch, 1978): a set of 10 cm line analogue rating scales.

Analogue rating scales Subjective ratings of mood, alertness and state anxiety were obtained from a set of line analogue rating scales. Side effects were reported by the subjects and recorded verbatim. These were later analysed by independent scorers and rated for severity.

Car driving ability was measured on five car handling tasks (Betts, Clayton & Mackay, 1972; Hindmarch Hanks & Hewett, 1977). These tasks embodied the skills encountered in actual road traffic conditions and were conducted on the private roads of a Driver Training Centre. The tasks comprised:— reverse parking between two stationary cars, a three point turn, a slalom about fixed bollards, width estimation for passage between obstacles and a brake reaction test. Scores were given on a ten point scale for each measure by independent marshals of the Tockwith Driver Training Centre.

Assessments of reaction time and critical flicker fusion frequency were also made but equipment failure resulted in the loss of the last weeks results and these measures are therefore not discussed further.

Results

All subjects scored within the normal range for their age and sex on the Middlesex Hospital Questionnaire. Tables 1a and 1b give the mean scores obtained on each test for all assessment measures. The error scores obtained on the serial subtraction of numbers were too few to warrant inclusion.

Also in Table 1 are the results of an analysis of variance performed to test the effects of the three treatments and, where the three treatments differ significantly (at $P<0.05$), the results of a Duncan's New Multiple Range Test (Edwards, 1970) applied to test the significance and direction of the differences between the treatment means.

Table 1a Mean scores (with s.e. mean) obtained on each objective measure for the three treatment conditions, together with significant treatment effects derived from analysis of variance of Duncan's New Multiple Range tests.

Measure		*Lorazepam* (*L*)	*Clobazam* (*C*)	*Placebo* (P)	*Anovar* (*P*)	*Duncan's comparison*
Concept Identification: (s)	Easy	12.2(1.6)	11.5(2.0)	10.1(1.3)		
	Hard	12.7(1.4)	20.0(4.3)	14.1(3.1)		
Peg board: (s)		171.5(4.5)	165.0(5.2)	163.0(5.2)		
Serial subtraction (s)	3	35.7(4.2)	32.2(2.8)	29.3(2.9)	*	L *v* P*
	7	45.0(4.2)	42.0(3.8)	37.1(3.3)	*	L *v* P*
	17	66.2(9.8)	62.0(7.6)	62.0(7.2)		V *v* P *
Letter cancellation (s)	1	31.7(3.0)	29.0(1.6)	27.0(2.2)		
	2	47.0(3.9)	48.2(3.5)	42.0(2.1)		
	3	63.0(6.3)	62.0(5.2)	57.0(4.0)		L *v* P *
	4	75.0(5.6)	73.0(4.2)	66.0(4.3)	*	L *v* C *
Letter cancellation (No errors)	1	1.1(0.5)	1.0(0.3)	0.3(0.3)		L *v* P *
	2	3.5(0.6)	1.8(0.4)	1.4(0.3)	*	L *v* C *
	3	4.1(0.6)	3.7(0.6)	2.6(0.4)	NS	
	4	6.2(1.7)	4.3(0.9)	4.7(0.7)	NS	
Car driving scores (10 point scale)	Parking	6.0(0.3)	7.8(0.4)	7.1(0.2)	*	L *v* P *
						L *v* C *
	Braking	6.8(0.4)	8.0(0.3)	7.9(0.3)	*	L *v* P *
						L *v* C *
	3 point turn	7.2(0.3)	8.3(0.2)	8.0(0.2)	*	L *v* P *
						L *v* C *
	Slalom	7.3(0.4)	8.2(0.2)	8.2(0.5)	*	L *v* P *
						L *v* C *
	Width	7.1(0.3)	7.9(0.1)	7.8(0.3)	NS	

*$= P < 0.05$, **$= P < 0.01$.

Table 1b Mean scores (with s.e. mean) obtained on the subjective measures for the three treatment condition, together with significant treatment effects derived from analysis of variance and Duncan's New Multiple Range tests.

Measure		*Lorazepam* (*L*)	*Clobazam* (*C*)	*Placebo* (P)	*Anovar* (*P*)	*Duncan's comparison*
Leeds sleep evaluation questionnaire (mm)	Getting to sleep (GTS)	75(5)	59(6)	46(3)	*	L *v* C *
						L *v* P *
						C *v* P *
	Quality of sleep (QOS)	62(8)	59(6)	49(5)		
	Awaking from sleep (AFS)	37(5)	42(5)	51(3)	*	L *v* P *
	Behaviour following wakefulness (BFW)	30(7)	52(4)	52(5)	*	L *v* P *
						L *v* P *
Analogue rating scales (mm)	Tense	40(9)	26(6)	36(7)		
	Not alert	71(7)	27(4)	42(6)	*	L *v* P *
						L *v* C *
	Anxious	44(8)	26(7)	38(8)		
	Not calm	52(8)	33(8)	47(7)		
	Apprehensive	50(9)	38(5)	50(5)		
	Not content	47(7)	27(4)	45(5)		
	Mean total	51(4)	30(2)	43(2)	***	L *v* C **
Side effects score		22	3	4		

*$= P < 0.05$, **$= P < 0.01$, ***$= P < 0.001$.

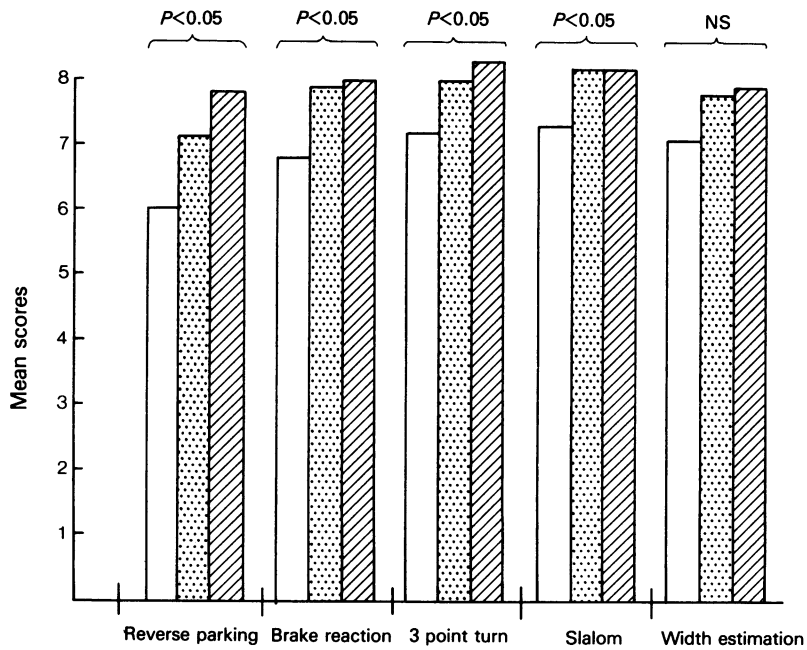

Figure 1 Performance on the car driving tests. (□ lorazepam, ⊡ placebo and ▨ clobazam).

Discussion

There are no significant differences to be found in the mean times taken to complete the concept identification task for any of the three treatment conditions and peg board completion times are also not significantly different from each other (Table 1a).

The mental arithmetic tests involving the serial subtraction of numbers show a significant difference between the three treatment means for 3s and 7s (Table 1a). It can also be seen that both clobazam and lorazepam impair performance, compared to placebo, for the serial subtraction of 7s. Lorazepam also impairs the ability to make serial subtraction of 3s, which is in accord with previous findings relating to the impairment of low interest tasks following treatment with 1,4 benzodiazepines, i.e., dipotassium clorazepate (Hindmarch & Parrott, 1979).

The increased difficulty in the subtraction of 7s following both active compounds is also manifest in the significant increase in time taken to cancel 4 letters from sheets of random letters (Table 1a). However, there does not seem to be any significant increase overall in the number of errors made on the letter cancellation test. The significant increase in errors made following lorazepam, compared to both clobazam and placebo, in the 2 letter cancellation task could be further evidence of the impairment of a low interest task or, as is more probable, an experimental artefact since there are no concordant trends from the other letter cancellation conditions.

The mean scores for four of the five driving tests all show significant treatment effects (Table 1a). A consideration of the results of the Duncan's range test clearly show the differences, on these measures of car driving, between lorazepam and placebo and between clobazam and lorazepam (Figure 1).

The lack of impairment produced by clobazam on these tests of car driving ability confirms earlier work using a repeated dose regimen (Hindmarch *et al.*, 1977), and illustrates an important difference between the two drugs.

The difference between the active treatments observed on the objective assessments of car handling ability are also manifest in the subjective ratings. A consideration of the treatment means on the analogue rating scales show that lorazepam is consistently rated as worse than placebo and clobazam better than placebo. Only one set of treatment means prove significantly different and the subsequent range tests shows that lorazepam is perceived as significantly more sedating (not alert) than either clobazam or placebo. The mean total scores on the analogue rating scales (Table 1b) are an index of the overall feelings of malaise, drowsiness, discontentedness etc. produced by the three treatments. The difference between the three treatment means is significant ($P<0.001$) and the subsequent range tests shows

clearly the significant impairment ($P<0.01$) produced by lorazepam compared to clobazam on this subjective estimate of sedation and mood.

The significant difference between the two active treatment conditions is also found in the subjects' verbal reports of side effects. The verbal reports recorded at the time of the experiment were scored for severity on a three point scale (0=felt better or no side effects; 1=mild side effects; 2=debilitating side effects) by two independent observers. The rating scores for the three treatment conditions are given in Table 1b.

A binomial comparison of the data show lorazepam to be significantly different both from placebo ($P=0.0006$) and from clobazam ($P=0.001$). Clobazam is not appreciably different from placebo. The majority of side effects reported by subjects on lorazepam referred to the sedative, drowsy, tired, uncoordinated, dizzy and nauseous consequences of taking the drug. These side effects, the analogue rating scale data and the significant impairment observed in car driving performance concur most closely and emphasize the lowering of mood, skilled behaviour and performance following medication with normal clinical doses of lorazepam.

The sedative/hypnotic properties of lorazepam are evidenced in the Leeds Sleep Evaluation Questionnaire scores (Table 1b). The ease of getting to sleep (GTS) is significantly improved following lorazepam both compared to placebo and to clobazam. This increased evaluation of hypnotic/sedative activity is at the expense of a significant reduction in estimates of the integrity of behaviour and early morning performance (AFS and BFW), and well in accord with previous work on performance decrement following administration of sedative agents (Bixler, Scharf & Kales, 1972; Bond & Lader, 1973, 1975; Hindmarch, 1975, 1976, 1977). Although clobazam is rated as significantly better than placebo in terms of sleep inducing properties (Table 1b), it is seen as no different to placebo with respect to the effects it has on early morning behaviour.

This study shows, that following repeated doses of lorazepam, performance is impaired on analogues of motor vehicle driving tasks. As well as performing significantly worse than placebo, subjects also feel 'worse', i.e. sedated, uncoordinated, clumsy. It is not determined whether the feelings of malaise following the administration of lorazepam are responsible for, or instrumental in, producing the poor performance of the subjects; or whether performance, i.e. sensori-motor coordination, is directly affected by the drug.

On the other hand the administration of clobazam, although not enitrely free from some significant effect on performance (serial subtraction of 7s), does not produce either the subjective or objective breakdown of performance, feeling and behaviour noticed following lorazepam. The lack of a persistent or generally observed effect on car handling tasks or subjective evaluations of alertness and mood following clobazam clearly distinguishes the drug from lorazepam with its widespread and consistently detrimental effects on tests of psychomotor performance.

It must be remembered that this study reports the results of a single dose administration following a period of pre-dosing and it is also recognized that pathologically anxious patients might perceive side effects differently from this present volunteer population (Malpas, Legg & Scott, 1974). However, the widespread detrimental effect of lorazepam on objective and subjective measures of performance and mood suggest that the sedative consequences following administration of acute doses of the drug would still interfere with performance of psychomotor tasks in patient populations.

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References

BELL, R.W., DICKIE, D.S., STEWART-JONES, J. & TURNER, P. (1973). Lorazepam on visuomotor coordination and visual function in man. *J. Pharm. Pharmac.*, **25**, 87–88.

BERRY, P.A., BURTLES, R., GRUBB, D.J. & HOARE, M.V. (1974). An evaluation of the effects of clobazam on human motor coordination, mental activity and mood. *Br. J. clin. Pharmac.*, **1**, 346.

BETTS, T.A., CLAYTON, A.B. & MACKAY, G.M. (1972). Effects of four commonly-used tranquillisers on low speed driving performance tests. *Br. med. J.*, **4**, 580–584.

BIXLER, E.O., SCHARF, M.B. & KALES, A. (1972). Drugs and sleep: effects of drugs on sleep stages, mood and performance and effectiveness of drugs in inducing and maintaining sleep. *N.A.T.O. Symposium: Aviemore* mimeograph).

BOND, A.J. & LADER, M. (1973). The residual effects of flurazepam. *Psychopharmacologia (Berl.)*, **32**, 223–225.

BOND, A.J. & LADER, M. (1975). Residual effect of flunitrazepam. *Br. J. clin. Pharmac.*, **2**, 143–150.

BORLAND, R.G. & NICHOLSON, A.N. (1974). Immediate

effects on human performance of a 1,5 benzodiazepine derivative (clobazam) compared with the 1,4 benzodiazepines, chlordiazepoxide hydrochloride and diazepam. *Br. J. clin. Pharmac.*, **2**, 215–221.

CROWN, S. & CRISP A.H. (1970). *Manual of the Middlesex Hospital Questionnaire*. Barnstaple: Psychological Test Publications.

DOONGAJI, D.R., SHETH, A. & APTE, J.S. (1978). Clobazam *versus* diazepam: A double-blind study in anxiety neurosis. *J. clin. Pharmac.*, **18**, 358.

EDWARDS, A.L. (1970). *Experimental Design in Psychological Research*. London: Holt, Rinehart & Winston.

ELLIOTT, H.W., NOMOF, N., NAVARRO, G., RUSELIUS, H.W., KNOWLES, J.A. & COMER, W.H. (1971). Central nervous system and cardiovascular effects of lorazepam in man. *Clin. Pharmac. Ther.*, **12**, 468–481.

FARHOUMAND, N., HARRISON, J., PARE, C.M.B., TURNER, P. & WYNN, S. (1979). The effect of high dose oxprenolol on stress-induced physical and psychophysiological variables. *Psychopharmacology*, **64**, 365–369.

FIELDING, S. & HOFFMAN, I. (1979). Pharmacology of anti-anxiety drugs with special reference to clobazam. *Br. J. clin. Pharmac.*, **1**, Suppl. 1, 75.

GLOBUS, G., PHOEBUS, E., HUMPHRIES, J., BOYD, R., GAFFNEY, D. & GAFFNEY, S. (1974). The effect of lorazepam on anxious insomniacs' sleep as recorded in the home environment. *J. clin. Pharmac.*, **14**, 192–201.

HARRY, T.V.A. & RICHARDS, D.J. (1972). Lorazepam—a study in psychomotor depression. *Br. J. clin. Pract.*, **26**, 371–373.

HEDGES, A., TURNER, P. & HARRY, T.V.A. (1971). Preliminary studies on the central effects of lorazepam, a new benzodiazepine. *J. clin. Pharmac.*, **11**, 423–427.

HINDMARCH, I. (1975). A 1,4 benzodiazepine, temazepam: its effect on some psychological aspects of sleep and behaviour. *Arzneimittel-Forsch.* (*Drug Res.*), **25**, 1836–1839.

HINDMARCH, I. (1976). A sub-chronic study of the subjective quality of sleep and psychological measures of performance the morning following night-time medication with temazepam. *Arzneimittel-Forsch.* (*Drug Res.*), **26**, 2113–2116.

HINDMARCH, I. (1977). A repeated dose comparison of three benzodiazepine derivatives (nitrazepam, flurazepam and flunitrazepam) on subjective appraisals of sleep and measures of psychomotor performance the morning following night time medication. *Acta Psychiat. Scand.*, **56**, 373–381.

HINDMARCH, I. (1979a). Some aspects of the effects of clobazam on human psychomotor performance. *Br. J. clin. Pharmac.*, **7**, 77S–82S.

HINDMARCH, I. (1979b). A preliminary study of the effects of repeated doses of clobazam on aspects of performance, arousal and behaviour in a group of anxiety rated volunteers. *Eur. J. clin. Pharmac.*, **16**, 17–21.

HINDMARCH, I. & PARROTT, A.C. (1978). The effect of a sub-chronic administration of three dose levels of a 1,5 benzodiazepine derivative, clobazam, on subjective aspects of sleep and assessments of psychomotor performance the morning following night time medication. *Arzneimittel-Forsch.* (*Drug Res.*), **28**, 2169–2172.

HINDMARCH, I. PARROTT, A.C. (1979). The effects of repeated nocturnal doses of clobazam, dipotassium clorazepate and placebo on subjective ratings of sleep and early morning behaviour. *Br. J. clin. Pharmac.*, **8**, 325–329.

HINDMARCH, I., HANKS, G.W. & HEWETT, A.J. (1977). Clobazam, a 1,5 benzodiazepine, and car driving ability. *Br. J. clin. Pharmac.*, **4**, 573–578.

HINDMARCH, I., PARROTT, A.C. & LANZA, M. (1979). The effects of an ergot alkaloid derivative on aspects of psychomotor performance, arousal and cognitive processing ability. *J. clin. Phamac.*, **19**, 726–732.

KNOWLES, J.A., COMER, W.H. & RUSELIUS, H.W. (1971). Disposition of lorazepam in humans. *Arzneimittel-Forsch.* (*Drug Res.*), **21**, 1055–1059.

MALPAS, A., LEGG, N.J. & SCOTT, D.F. (1974). Effects of hypnotics on anxious patients. *Br. J. Psychiat.*, **124**, 482–484.

NORRIS, W. & WALLACE, P.G.M. (1971). Wy 4036—a study of its use in premedication. *Br. J. Anaesth.*, **43**, 785–789.

PARROTT, A.C. & HINDMARCH, I. (1978). Factor analysis of a sleep evaluation questionnaire. *Psych. Med.*, **8**, 325–329.

RUPP, W., BADIAN, M., CHRIST, O., HADJÚ, P., KULKARNI, R.D., TAEUBER, K., UIHLEIN, M., BENDER, R. & VANDERBEKE, O. (1979). Pharmacokinetics of single and multiple doses of clobazam in humans. *Br. J. clin. Pharmac.*, **7**, 51S–67S.

SALKIND, M.R., HANKS, G.W. & SILVERSTONE, T. (1979). Evaluation of the effects of clobazam, a 1,5 benzodiazepine on mood and psychomotor performance in clinically anxious patients in general practice. *Br. J. clin. Pharmac.*, **7**, 113S–118S.

SEPPÄLÄ, T., KORTILLA, K., HAKKINEN, S. & LINNOILA, M. (1976). Residual effects and skills related to driving after a single oral administration of diazepam, medazepam or lorazepam. *Br. J. clin. Pharmac.*, **3**, 831–841.

STRAUGHAN, J.L. (1979). Which benzodiazepine, why and how? *S. Afr. med. J.* **55**, 1110–1114.

TURNER, P. (1973). Clinical pharmacological studies on lorazepam. *Curr. Med. Res. Opin.*, **1**, 262–264.

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