A placebo controlled double-blind evaluation of the pharmacodynamics of fengabine vs amitriptyline following single and multiple doses in elderly volunteers

D. B. FAIRWEATHER¹, J. S. KERR¹, S. HILTON² & I. HINDMARCH¹

¹Human Psychopharmacology Research Unit, Robens Institute, University of Surrey, Milford Hospital, Godalming GU7 1UF and ²Synthélabo Recherche (LERS), 9 John Street, London WC1N 2ES

- 1 The effects of fengabine were compared with those of amitriptyline in healthy elderly volunteers. Doses were administered double-blind and assessments were made before and after ingestion.
- 2 Psychomotor performance and cognitive ability were measured using tests of choice reaction time, tracking, critical flicker fusion threshold, memory scanning and word recognition. Subjective feelings were assessed using the Leeds sleep evaluation questionnaire (LSEQ) and line analogue rating scales (LARS).
- 3 Pharmacokinetic data suggest that fengabine may induce its own metabolism following repeated dosing.
- 4 The findings of this study show that fengabine 200 mg and 400 mg does not produce any noticeable behavioural toxicity in elderly volunteers, in contrast to amitriptyline which had a disruptive effect throughout.

Keywords fengabine amitriptyline behavioural toxicity elderly volunteers

Introduction

Over the years considerable developments have been made in the therapy of depression but there are still some problems which remain to be resolved. The therapeutic properties of antidepressants are traditionally associated with changes in monoaminergic transmission (Blackwell & Simon, 1986), and the tricyclic antidepressants (TCAs) fall into this category. The tricyclics are in fact the most widely used drugs in the treatment of depression, but are far from being the ideal treatment however, as they often produce sedation (Hanks, 1984) and behavioural toxicity, i.e. impairment of psychomotor and cognitive abilities which are necessary for the performance of everyday tasks (Hindmarch *et al.*, 1990a). A significant level of behavioural toxicity can be counter-therapeutic as it may exacerbate cognitive and psychomotor disorders (Hindmarch, 1987; Widlocher, 1983a, b). Most of the antidepressants available today are of equal clinical efficacy but may differ in the extent to which they produce behavioural toxicity. It is important therefore, to choose those drugs which possess low levels of behavioural toxicity.

The search for new antidepressants has been in response to dissatisfaction with the 'traditional' drugs. The discovery that benzylidene compounds such as probagide and fengabine are effective in relieving depressive

disorders has shed light upon the involvement of the GABA minergic system in the pathogenesis of depression. Fengabine is a novel GABA mimetic compound which has been shown to be active in behavioural models of drug action, for example it reverses passive avoidance deficit in olfactory bulbectomised rats (Scatton *et al.*, 1987). It has also been shown to exert therapeutic effects in depressed patients (Chabannes *et al.*, 1986; Lloyd *et al.*, 1989). Morselli *et al.* (1991) demonstrated that it was of equal clinical efficacy to the TCAs, but was better tolerated, particularly regarding anticholinergic side effects. Unlike the tricyclics and the monoamine oxidase inhibitors fengabine has no direct effect on monoaminergic function and has therefore been classed as an 'atypical' antidepressant (Zivkovic *et al.*, 1986).

Depression is common in the elderly and may, in part, be due to the biochemical changes in the brain which accompany ageing. Depression in the elderly may therefore present with different features than those seen in a younger population. Pharmacokinetics, i.e. the fate of the drug in the body, also alters with age. Recent studies in elderly subjects (Crome & Dawling, 1988) have shown that the half-life of tricyclics is prolonged, the clearance rate is reduced and therefore plasma drug concentrations are increased. Furthermore, Bellantuono *et al.* (1980)

reported that several drugs of the benzodiazepine class exhibit an increased half-life in the elderly, leading to greater accumulation of both parent compound and metabolites (Greenblatt *et al.*, 1982) which may cause unpleasant toxic effects. Of further consequence is the suggestion that there may be an increase in sensitivity of the brain to CNS drugs with age (Castleden *et al.*, 1977) resulting in a greater response for a given tissue concentration.

The combination of these effects may result in a significant level of behavioural toxicity. This will be of consequence in the elderly, who may already be cognitively disadvantaged, and where any additional impairment caused by antidepressants will increase the probability of accident. It is important that these factors are taken into consideration when prescribing drugs for older people.

It is for these reasons that it was deemed necessary to evaluate the effects of fengabine in an ageing population. Therefore the pharmacodynamics of fengabine were compared with those of amitriptyline (positive internal control) and placebo in healthy elderly volunteers.

Methods

Subjects

Forty healthy volunteers (20 females, 20 males), aged between 60 and 78 years old (mean 68.27), were admitted to the study. All were in good physical and medical health and met with the relevant inclusion/exclusion criteria, receiving a full medical examination before entry to the study and after completing their participation. None was receiving any concomitant medication that would interfere with CNS function. Subjects provided written informed consent and the study was approved by the Ethics Committee of the Isle of Wight Area Health Authority. Four of the male subjects were withdrawn from the study: three because of adverse reactions to amitriptyline and one due to influenza-like symptoms (unrelated to drug treatment).

Design

A randomised, double-blind, parallel group comparison of four single and multiple dose treatments was used. The treatment sequence was balanced for residual effects. The four treatments: (i) fengabine 200 mg; (ii) fengabine 400 mg; (iii) amitriptyline 25 mg or (iv) placebo were taken once on day 1 then thrice daily until day 7. The drugs and placebo were packaged in identical capsules.

Procedure

Prior to the investigation volunteers received training and familiarisation with the battery of psychomotor tests in order to preclude any learning effects.

Subjects attended the test centre on days 1, 2, 7 and 8 of the treatment period. A plastic cannula was inserted into a forearm vein on each of these mornings from which blood samples could be taken for pharmacokinetic analysis and to ensure compliance. On day 1 baseline blood sampling and psychometric testing was carried out

prior to dosing. These tests were repeated at 1, 2 and 4 h post dose after which the cannula was removed. Subjects were permitted to go home, returning the following morning for the 24 h post dose test session.

On day 2 subjects were dosed at 09.00, 15.00 and 21.00 h and were required to return to the test centre on day 7 where further tests were carried out at the appropriate time intervals. The last dose was taken at 21.00 h on day 7 and the final tests were performed on day 8.

Assessments

Critical flicker fusion threshold (CFF) CFF (Hindmarch, 1975; 1982; Hindmarch & Parrott, 1978; Hindmarch *et al.*, 1983) was used as a means of measuring the ability to distinguish discrete sensory data and was taken as an index of overall CNS activity. Subjects were required to discriminate flicker from fusion in a set of four light emitting diodes in foveal fixation at 1 metre. Individual thresholds were determined by the psychophysical method of limits of three ascending and three descending scales (Woodworth & Scholberg, 1958).

Choice reaction time (CRT) CRT (Hindmarch, 1975, 1982; Hindmarch & Parrott, 1978; Hindmarch *et al.*, 1983) was used as a measure of sensorimotor performance. Subjects were required to extinguish one of six red lights, illuminated at random, by touching the appropriate response button. The Leeds Psychomotor Tester enabled the recognition (RRT) and motor (MRT) components to be separated from the total reaction time (TRT). The mean reaction time for 20 stimulus presentations was recorded.

Tracking test This interactive task of psychomotor function entailed tracking a moving arrow on a VDU screen, using a joystick (Hindmarch *et al.*, 1983). The response measure (RMS) is the mean deviation from the track program over the 1 min trial period, with lower scores indicating more accurate tracking. In addition, a peripheral awareness task (RT) was included in which the subject had to respond to a stimulus presented in the periphery of vision, while simultaneously attending to the tracking test. The mean reaction time to ten of these stimuli over the trial period was taken as the response measure for this component of the task.

Sternberg memory scanning task This task was based on the reaction time method of memory research (Sternberg 1969, 1975). It measured the ability to retrieve information by serial search from the short term memory store. Subjects were required to judge whether a test (probe) digit was contained within a short sequence of previously memorised digits using a two button yes/no choice response box. The memorised list consisted of short sequences of either 1, 2 or 3 digits.

Word recognition task Subjects were asked to memorise a list of 14 words, presented one at a time. They were then required to indicate whether or not these words appeared in a second list, using a two button yes/no choice response box. Reaction time and error rates were recorded.

Figure 1 The structure of fengabine and some metabolites (from Ascalone & Dal Bo, 1989).

Subjective sedation Subjective ratings of drug effects were obtained from a series of 10 cm line analogue rating scales (LARS) (Hindmarch & Gudgeon, 1980). The mean score of ratings of 'tiredness', 'drowsiness' and 'alertness' (which are included amongst a number of distractor scales) was taken as a measurement of perceived sedation.

Leeds sleep evaluation questionnaire (LSEQ) The LSEQ (Hindmarch, 1975; Parrott & Hindmarch, 1978, 1980) was used to rate subjective impressions of the ease of getting to sleep (GTS), the quality of sleep (QOS), the ease of waking from sleep (AFS) and the co-ordination of behaviour following waking (BFW) on 10 cm line analogue rating scales. Subjects completed the LSEQ forms on the morning following the day of medication.

Pharmacokinetics Blood samples were collected from volunteers through a catheter which had been inserted into the forearm vein of the non-dominant arm. Samples were collected on day 1 at 0, 1, 2, 4 and 24 h post dose and on day 7 at 0, 3, 6, 9, 15, 20, 24 and 32 h post dose. The blood samples were centrifuged for 10 min at 2000 rev min⁻¹ then stored at -20° C.

Fengabine and its metabolites: SL 78.0622, SL 81.0013, SL 81.0048, SL 0196 and metabolite VI (see Figure 1) were assayed by a capillary gas chromatographic method using an electrochemical detector, with a detection limit of 1 ng ml⁻¹ for fengabine and its metabolites (Ascalone *et al.*, 1989). Amitriptyline and its metabolite nortriptyline were also assayed, the limits of detection being 1 ng ml⁻¹ and 2 ng ml⁻¹ respectively (Ascalone & Dal Bo, 1987).

Results

Psychometric data were analysed as a repeated measures analysis of variance model using differences from baseline scores. Comparisons between significant treatment means were performed *post hoc* using Tukey's HSD Test, with the significance level set at $P < 0.05$.

The CFF thresholds clearly showed the impairing effect of the positive internal control amitriptyline at all times for single and multiple dosing. In both the ascending and descending scales (Figure 2) fengabine produced no change from placebo but there was a significant improvement in CFF threshold compared with baseline with the 400 mg dose. The sedative effect of amitriptyline was evident in the recognition reaction time component of the CRT task, significantly so at 4 h post single dose, but neither dose of fengabine produced any significant effects (Table 1). Likewise the disruptive effects of amitriptyline were evident in the tracking test and again no impairment was observed with fengabine. There was no effect of fengabine in the word recognition and memory scanning tasks following single and multiple dosing. All treatments, including placebo, produced a decrease in reaction time latency during the study; this pattern of results suggests the presence of a residual/uncontrolled practice or learning effect. However, at no point did fengabine exhibit any significant trends or impairments.

The factors of the LSEQ were analysed separately. No significant differences between treatments were revealed on GTS, QOS or AFS scores. However a single dose of fengabine 200 mg produced a more negative evaluation than any of the other treatments on BFW

Figure 2 Critical flicker fusion thresholds (mean changes from baseline). ■ placebo, + amitriptyline (25 mg), * fengabine (200 mg), □ fengabine (400 mg).

Figure 3 Leeds sleep evaluation questionnaire. GTS getting to sleep, QOS quality of sleep, AFS ease of waking from sleep, BFW coordination of behaviour following waking. ■ placebo, ▨ amitriptyline (25 mg), ▩ fengabine (200 mg), ▤ fengabine (400 mg).

ratings (Figure 3). No significant effects were detected between treatments or test times on the LARS scale of subjective sedation.

Volunteers who received amitriptyline demonstrated the expected pharmacokinetic profile. Following 7 days multiple dosing amitriptyline was slowly absorbed, reaching a maximum concentration ($C_{\max}$) of 41.3 ± 14.2 ng ml $^{-1}$ at 5.6 ± 2.1 h after the final dose. Nortriptyline (metabolite of amitriptyline) reached a $C_{\max}$ of 33.8 ± 17.8 ng ml $^{-1}$ at 5.9 ± 7.2 h after the final dose.

The single dose of fengabine 200 mg reached a $C_{\max}$ of 448 ± 62 ng ml $^{-1}$ at 2.5 ± 0.3 h. Following multiple

dosing $C_{\max}$ was reduced to 152 ± 35 ng ml $^{-1}$ after 2.4 ± 0.3 h. A $C_{\max}$ of 615 ± 100 ng ml $^{-1}$ was reached with fengabine 400 mg after 1.8 ± 0.3 h on day 1 and after multiple dosing $C_{\max}$ was 239 ± 32 ng ml $^{-1}$ 2.2 h post dose.

The AUC of fengabine were proportional to dose, suggesting no dose dependency of kinetics at these doses (Table 2).

Table 2 Pharmacokinetic parameters for fengabine 200 mg, 400 mg and its metabolites following single and multiple dosing in elderly volunteers. Mean values are given with standard deviations in parentheses

	$t_{\max}$ (h)		$C_{\max}$ (ng ml $^{-1}$)		AUC_{0-32} (ng ml $^{-1}$ h)
	D1	D7	D1	D7	
Fengabine 200 mg	2.5 (0.3)	2.4 (0.3)	448 (62)	152 (35)	1092 (123)
SL81.0196	4.8 (2.1)	4.2 (1.8)	3.4 (0.6)	15.3 (1.8)	278 (23)
SL81.0048	2.6 (0.3)	2.0 (0.3)	104 (16)	50 (5)	559 (81)
SL81.0013	2.6 (0.3)	1.6 (0.3)	99 (12)	74 (9)	787 (111)
SL78.622	2.6 (0.3)	2.4 (0.8)	54 (7)	269 (53)	3566 (551)
Metabolite VI	3.0 (0.3)	3.1 (0.4)	148 (25)	450 (47)	5065 (558)
Fengabine 400 mg	1.8 (0.3)	2.2 (0.3)	615 (100)	239 (32)	1997 (294)
SL81.0196	2.7 (0.3)	4.6 (1.2)	3.7 (1.2)	19.4 (3.2)	390 (66)
SL81.0048	2.3 (0.3)	2.2 (0.3)	131 (21)	98 (16)	1084 (259)
SL81.0013	2.5 (0.2)	2.2 (0.3)	126 (19)	107 (13)	1265 (179)
SL78.622	2.1 (0.2)	2.2 (0.3)	63 (9.2)	359 (64)	5798 (1067)
Metabolite VI	2.6 (0.3)	2.6 (0.2)	217 (45)	635 (96)	7587 (1024)

Table 1 The effects of fengabine 200 mg, 400 mg and amitriptyline 25 mg on the recognition reaction time (RRT) component of the choice reaction time task in elderly volunteers. Mean values are given in ms with standard deviations in parentheses

	Placebo	Amitriptyline 25 mg	Fengabine 200 mg	Fengabine 400 mg
Day 1				
Baseline	426 (21)	453 (48)	492 (95)	457 (80)
1 h	462 (32)	439 (48)	474 (94)	469 (74)
2 h	470 (32)	478 (63)	508 (117)	484 (74)
4 h	453 (19)	550 (102)	533 (135)	463 (80)
24 h	434 (39)	437 (42)	431 (61)	410 (53)
Day 7				
0 h	432 (52)	444 (53)	435 (30)	427 (86)
1 h	437 (24)	438 (44)	497 (59)	443 (87)
2 h	452 (41)	434 (56)	508 (82)	430 (88)
4 h	456 (45)	445 (66)	464 (67)	432 (74)
24 h	406 (27)	406 (36)	458 (62)	442 (110)

Discussion

The most widely used antidepressants are the tricyclics but they are associated with objectively determined (via CFF) sedation (Hanks, 1984) and behavioural toxicity (Hindmarch *et al.*, 1990a). In the search for novel antidepressants which do not exhibit these side effects the role of the inhibitory transmitter GABA has been considered. The concept of GABA playing a role in depression was brought to light by neuropsychiatric trials with probagide, the first clinically useful GABA agonist (Bartholini *et al.*, 1978). Since then considerable developments have been made and the clinical effectiveness of GABA mimetics in the therapy of depression has been confirmed with the GABA agonist, fengabine (Chabannes *et al.*, 1986; Lloyd *et al.*, 1989).

Amitriptyline is more sedating than many of the TCAs and was therefore employed as the positive internal control to validate the test battery by acting as a verum. The detrimental effects of amitriptyline were clearly demonstrated throughout the study, but this was not the case for fengabine. With both doses of fengabine there was no difference from placebo in both scales of the CFF task suggesting that fengabine does not disrupt information discrimination. In agreement with earlier studies (Depoortere & Riou-Merle, 1986) there was no sedative effect, seen by a lack of significance in the LARS and likewise in the LSEQ. There was one exception where a single dose of fengabine 200 mg produced a more negative evaluation than any of the other treatments on BFW ratings. GABA mimetic compounds may be expected to possess sedative properties but given the pattern of results this is probably a Type I error. Fengabine had a neutral effect throughout the test battery. Due to the fact that the detrimental effects of amitriptyline have been well documented (Hanks, 1984; Hindmarch *et al.*, 1983, 1988; Hindmarch & Subhan, 1986) and that these

tests have previously been shown to be valid and reliable indicators of drug effects (Hindmarch *et al.*, 1990b, 1991), it can be concluded that, as fengabine 200 mg and 400 mg has no significant effect on the test battery when compared to placebo, it has very low potential for behavioural toxicity in elderly patients.

The problems of testing drug effects in the elderly are highlighted in this investigation. In the word recognition test there was great inter-individual variation which makes for difficulties in assessing a drug effect *per se*. There also appears to be some effects of practice which suggests that pre-study training needs to be intensified and/or this test may not be reliable for assessing drug effects in elderly volunteers.

Pharmacokinetic tests demonstrated that fengabine was well absorbed and extensively metabolised, although there was variation in subject's capacity to metabolise the drug. On day 1 peak fengabine concentrations of 448 ng ml⁻¹ and 615 ng ml⁻¹ were recorded for 200 mg and 400 mg doses respectively. The corresponding concentrations on day 7 were 152 ng ml⁻¹ and 239 ng ml⁻¹. These recordings suggest that fengabine may induce its own metabolism, reflecting previous findings where this drug was shown to increase gamma glutamyl transferase levels (Chabannes *et al.*, 1986).

Although the clinical development of fengabine has ceased there is little evidence to suggest that the drug has any noticeable behavioural toxicity. This low behavioural toxicity augurs well for the safe clinical use of similar GABA mimetic substances, particularly in ambulant patients where freedom from iatrogenic cognitive lapses and psychomotor impairment is essential for the safe completion of everyday tasks.

The support received from Synthelabo Recherche (LERS) is gratefully acknowledged.

References

- Ascalone, V. & Dal Bo, L. (1987). Determination of amitriptyline, chlorimipramine and their demethylated metabolites in plasma by normal phase and UV detection. In *Development in analytical methods in pharmaceutical biomedical and forensic sciences*, eds Piemonte, G., Tagliaro, F., Marigo, M. & Frigerio, A. pp 223–239. New York: Plenum Publishing Corporation.
- Ascalone, V., Dal Bo, L., Deschamps, N. & Guinebault, P. (1989). Determination of the gabaergic antidepressant drug fengabine and some of its metabolites in plasma by capillary gas chromatography with electron capture detection. *Chromatogr.*, **490**, 81–90.
- Bartholini, G., Scatton, B., Zivkovic, B. & Lloyd, K. G. (1978). On the mode of action of SL 76002, a new GABA receptor agonist. In *GABA neurotransmitters*, eds Krogsgard-Larsen, P., Scheel-Kruger, J. & Kofod, H., pp. 326–339. Copenhagen: Munksgaard.
- Bellantuono, C., Reggi, V., Tognoni, G. & Garattini, S. (1980). Benzodiazepines: clinical pharmacology and therapeutic use. *Drugs*, **19**, 195–218.
- Blackwell, B. & Simon, J. S. (1986). Second generation antidepressants. *Drugs of Today*, **22**, 611–633.
- Castleden, C. M., George, C. F., Hallett, C. & Marcer, D. (1977). Increased sensitivity to nitrazepam in old age. *Br. med. J.*, **1**, 10–12.
- Chabannes, J. P., Baro, P., Lambert, P. A., Decade, P. & Musch, B. (1986). Antidepressant activity of fengabine (SL 79229): Results from an open pilot study. In *L.E.R.S. Volume 4*, eds Bartholini, G., Lloyd, K. G. & Morselli, P. L., pp 139–146. New York: Raven Press.
- Crome, P. & Dawling, S. (1988). Pharmacokinetics of non-MAOI antidepressants in the elderly. In *Antidepressants and the elderly*, ed. Ghose, K. Beckenham: Croom Helm.
- Depoortere, H. & Riou-Merle, F. (1986). Pharmacological profiles of probagide and fengabine compared with classical antidepressants. In *L.E.R.S. Volume 4*, eds Bartholini, G., Lloyd, K. G. & Morselli, P. L. pp. 97–99. New York: Raven Press.
- Greenblatt, D. J., Sellers, E. M. & Shader, R. I. (1982). Drug disposition in old age. *New Engl. J. Med.*, **306**, 1081–1087.
- Hanks, G. W. (1984). The effect of amitriptyline and nomifensine on critical flicker fusion threshold in an elderly population. In *Nomifensine: A pharmacological and clinical profile*. RSM ICSS No. 70, eds Rees, L. W. & Priest, R. G. pp 71–76. Oxford: Oxford University Press.
- Hindmarch, I. (1975). A 1,4 benzodiazepine, temazepam: its

- effects on some psychological parameters of sleep and behaviour. *Arzneim-Forsch. (Drug Res.)*, **25**, 1836–1839.
- Hindmarch, I. (1982). Critical flicker fusion frequency (CFF). The effects of psychotropic compounds. *Pharmacopsychiat.*, **15**, Suppl. 1, 44–48.
- Hindmarch, I. (1987). Antidepressant drugs and cognitive function. In *Quo Vadis: diagnosis and treatment of depression*, eds Biziere, S., Garattini, S. & Simon, P. Paris: Medsi/McGraw.
- Hindmarch, I. & Gudgeon, A. C. (1980). The effects of clobazam and lorazepam on aspects of psychomotor performance and car handling ability. *Br. J. clin. Pharmacol.*, **10**, 145–150.
- Hindmarch, I. & Parrott, A. C. (1978). The effect of a subchronic administration of three dose levels of a 1,5-benzodiazepine derivative, clobazam, on subjective assessments of sleep and aspects of psychomotor performance the morning following night-time medication. *Arzneim.-Forsch. (Drug Res.)*, **28(II)**, 11, 2169–2172.
- Hindmarch, I. & Subhan, Z. (1986). The effects of antidepressants, taken in conjunction with alcohol, on information processing and psychomotor performance related to car driving ability. In *Drugs and driving*, eds O'Hanlon, J. F. & de Gier, J. J., pp. 231–240. London: Taylor and Francis.
- Hindmarch, I., Barwell, F. & Alford, C. (1990a). Behavioural toxicity of antidepressants. In *Antidepressants: Thirty years on*, eds Leonard, B. & Spencer, P. London: CNS Publishers.
- Hindmarch, I., Harrison, C. & Shillingford, C. A. (1988). An investigation of the effects of lofepramine, nomifensine, amitriptyline and placebo on aspects of memory and psychomotor performance related to car driving. *Int. clin. Psychopharmacol.*, **4**, 157–165.
- Hindmarch, I., Kerr, J. S. & Sherwood, N. (1990b). Psychopharmacological aspects of psychoactive substances. In *Addiction controversies*, ed. Warburton, D. New York: Harwood Academic.
- Hindmarch, I., Kerr, J. S. & Sherwood, N. (1991). The effects of alcohol and other drugs on psychomotor performance and cognitive function. *Alc. and Alc.*, **26**, 71–79.
- Hindmarch, I., Subhan, Z. & Stoker, M. J. (1983). The effects of zimeldine and amitriptyline on car driving and psychomotor performance. *Acta Psychiat. Scand.*, **68(suppl. 308)**, 141–146.
- Lloyd, K. G., Zivkovic, B., Scatton, B., Morselli, P. L. & Bartholini, G. (1989). The GABAergic hypothesis of depression. *Prog. Neuropsychopharmacol. Biol. Psychiat.*, **13(3–4)**, 341–351.
- Morselli, P. L., Garreau, M. & L'Heritier, C. (1991). An overview of fengabine versus tricyclics in depression. *Biol. Psychiat.*, Abstracts of the 5th World Congress of Biological Psychiatry, **29**, 11S.
- Neilsen, N. P., Cesana, B., Zizolfi, S., Ascalone, V., Priore, P. & Morselli, P. L. (1990). The effects of fengabine, a new GABAergic agent, in depressed outpatients: a double blind study versus clomipramine. *Acta Psychiat. Scand.*, **82**, 366–371.
- Parrott, A. C. & Hindmarch, I. (1978). Factor analysis of a sleep evaluation questionnaire. *Psychol. Med.*, **8**, 325–329.
- Parrott, A. C. & Hindmarch, I. (1980). The Leeds Sleep Evaluation Questionnaire in psychological investigations – a review. *Psychopharmacol.*, **71**, 173–179.
- Scatton, B., Lloyd, K. G., Zivkovic, B., Dennis, T., Claustre, Y., Dedek, J., Arbilla, S. T., Langer, S. Z. & Bartholini, G. (1987). *J. Pharmac. exp. Ther.*, **241**, 251–257.
- Sternberg, S. (1969). Memory scanning: memory processes revealed by reaction time experiments. *Am. Sci.*, **57**, 421–457.
- Sternberg, S. (1975). Memory scanning: new findings and controversies. *Quart. J. exp. Psychol.*, **27**, 1–32.
- Widlocher, D. (1983a). Psychomotor retardation: Clinical, theoretical and psychometric aspects. *Psychiat. Clin. N. Am.*, **6**, 27–39.
- Widlocher, D. (1983b). *La Ralentissement Dépressif*. Paris: Presses Universitaires de France.
- Woodworth, R. S. & Scholsberg, H. (1958). *Experimental psychology*. London: Methuen.
- Zivkovic, B., Lloyd, K. G., Scatton, B., Sanger, D. J., Depoortere, H., Dedek, J., Arbilla, S., Langer, S. Z. & Bartholini, G. (1986). Pharmacological and neurochemical spectra of fengabine (SL 79229), a new antidepressant agent. In *L.E.R.S. Volume 4*, eds Bartholini, G., Lloyd, K. G. & Morselli, P. L., pp. 85–95. New York: Raven Press.

(Received 29 October 1991,
accepted 17 August 1992)