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DROWSINESS, IMPAIRED PERFORMANCE AND TRICYCLIC ANTIDEPRESSANT DRUGS

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1 The effects of amitriptyline, nortriptyline, protriptyline, and a chemically related potential antidepressant, BW247, on performance tests and subjective ratings were studied.

2 Two groups of twelve healthy subjects received drugs and lactose dummy in identical capsules at weekly intervals according to a balanced design, under double-blind conditions, and with standardized tests and environment.

3 Amitriptyline produced the most marked effects, with significant ($P < 0.05$) impairment in auditory vigilance after 6.25 mg. Auditory reaction time, tapping rate, arithmetic, and digit symbol substitutions were impaired by amitriptyline 12.5 and 25 mg and all doses produced increased ratings of mental sedation. The effects began 1.5 h after drug and lasted approximately 5 h.

4 Nortriptyline produced fewer effects which were later in onset. Tapping at 1.8 h and auditory vigilance at 3.5 to 4.5 h were impaired by nortriptyline 25 mg whereas reaction time was prolonged by both doses at 5 h. No change in rating of mental sedation occurred.

5 No significant change in performance or subjective ratings followed protriptyline 10 mg or BW247, 12.5 and 25 mg.

6 The findings are discussed in relation to the presence of secondary and tertiary amines on the side chain of the compounds, and their relative abilities to block neuronal uptake of noradrenaline and 5-hydroxytryptamine.

Introduction

Drowsiness is a frequently reported side effect of the tricyclic antidepressants. Studies in rats led Bickel & Brodie (1964) to suggest that the sedative properties of antidepressants are confined to those whose side chain terminates in a tertiary amine group, while demethylation to the secondary amine is accompanied by loss of the sedative action but an increase in antidepressant potency. This may also be true in man (Bickel & Brodie, 1964; Caille, Sauriol, Albert, Mockle & Panisset, 1972).

Reports from clinical practice indicate that amitriptyline, a tertiary amine, causes drowsiness (Daneman, 1965; Forrest, Affleck, Gibb & Priest, 1964). Nortriptyline, a secondary amine and also the major metabolite of amitriptyline in man (Hucker, 1962) may produce rather less drowsiness (Priest, 1976), but Overo, Gram & Hansen (1975) reported pronounced sedation in healthy volunteers 2–4 days after receiving a single dose of nortriptyline 58 mg i.v. infused over 70 min. Protriptyline, another antidepressant of the secondary amine type, has been variously reported to cause some drowsiness (Lewis & Silverstone, 1970; Priest, 1976), no effect on alertness up to 40 mg/day (Daneman, 1965) or even some stimulation (Gilbert, 1967) in depressed or schizophrenic patients. However, the number of patients reporting either drowsiness or excitation in any one group of subjects is small and the effect of protriptyline on arousal is certainly not clear.

These clinical reports show enormous variations in drug dosage, method of administration and the type of subject used, and objective controlled comparisons of drowsiness and performance in man following different antidepressants are lacking. Using an experimental design which has previously proved useful for assessing drowsiness after histamine antagonists (Peck, Fowle & Bye, 1975) we studied the antidepressants amitriptyline, nortriptyline and protriptyline in normal healthy volunteers to assess their relative effects on performance and subjective drowsiness. In addition, the effects of a potential antidepressant, 3-methylamino-1,1 diphenylprop-1-ene (BW 247) are reported. This is a secondary amine closely related in structure to the tricyclic antidepressants (Figure 1) which blocks the uptake of biogenic amines into rat cerebral tissue (Salama, Insalaco & Maxwell, 1971). It lacks the anticholinergic properties seen with the tricyclic antidepressants.

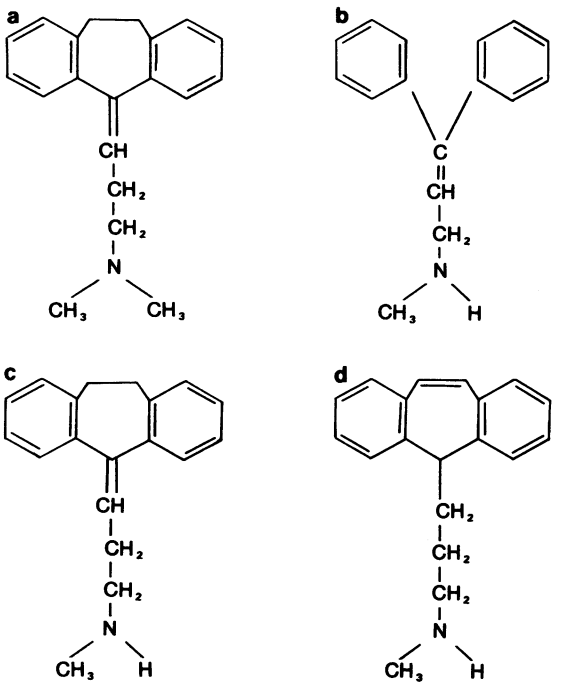

Figure 1 Structural formulae of a) amitriptyline, b) BW 247, c) nortriptyline and d) protriptyline.

Methods

Subjects

Two separate trials were performed. In the first, twelve male volunteers aged 22–35 years participated. A further twelve, eight men and four women, aged 21–48 years participated in the second. Volunteers were recruited from the staff of the Wellcome Research Laboratories. They were transported to and from the laboratory by car one day a week for 6 weeks. No coffee, tea or cigarettes were allowed after 22.00 h on the pre-trial day or during the trial day until completion of the tests.

Tests

The tests consisted of:

(1) An auditory vigilance test, lasting 1 h, in which subjects were presented via headphones with tape recorded short tones 0.5 s in duration occurring every 2 s and set in white noise. The signals to be detected were 40 tones 0.4 s in duration occurring randomly, but with 10 in each 15 min of the test. Subjects recorded their detections by pressing buttons (Wilkinson, 1968).

(2) A short term memory test lasting 15 min in which 90 series of 8 digits were recorded by the subject. The number of individual errors and the number of lines containing an error were counted.

(3) An auditory reaction time test lasting 15 min in which the subject pressed a microswitch as rapidly as possible in response to tones presented via headphones, and which occurred at intervals of 5 to 9 s with a mean of 7 s.

(4) An arithmetic test consisting of simple additions of five pairs of digits. The number of sums completed and the number of errors made were counted.

(5) A digit symbol substitution test lasting 90 s (Wechsler, 1955).

(6) A tapping test lasting 60 s using a microswitch.

Subjective effects were measured using visual analogue scales (Lader & Norris, 1969) in which the subject records his mental state by marking a series of 100 mm lines indicating dimensions of mental and physical state.

Procedure

Subjects were studied in the same groups of 4 on Tuesdays, Wednesdays or Thursdays at weekly intervals for 6 consecutive weeks. They arrived in the laboratory at 08.30 h and were given a standardized light breakfast. At 09.00 h the subjects entered a soundproof room held at 70°F and divided into four cubicles. They then began a 2 h session consisting of the following:

Trial 1 (1) Vigilance test, (2) tapping test, (3) digit symbol substitution, (4) reaction time, (5) visual analogue scales, (6) salivation measured over 75 s in response to sucking an acid drop for 15 s, and collecting in a measuring cylinder, (7) visual near point, measured using a black cross on white card sliding down a metre rule, (8) pupil size recorded photographically with a fixed focus camera, (9) heart rate, systolic and diastolic blood pressure in the erect and supine positions, measured at the radial pulse and using a sphygmomanometer respectively.

Trial 2 (1) Vigilance, (2) short term memory, (3) reaction time, (4) arithmetic test, (5) digit symbol substitution, (6) tapping, (7) visual analogue scales.

Following the first 2 h session treatments were administered at 11.00 h in both Trials. Subjects were given a standardized snack meal at 11.30 h. The test schedule began again at 11.45 h in Trial 1, and 12.00 h in Trial 2. The schedule was repeated once more after a 45 min break in Trial 1 and 30 min break in Trial 2.

Drugs

Drugs were prepared in identical gelatin capsules. Each subject received each treatment at weekly

intervals according to two balanced 6 x 6 Latin square designs for each trial, with double-blind conditions. In Trial 1 the following preparations were used: amitriptyline 6.25, 12.5 and 25 mg; BW 247 12.5 and 25 mg and lactose dummy. In Trial 2 each subject received: amitriptyline 12.5 and 25 mg; nortriptyline 12.5 and 25 mg; protriptyline 10 mg and lactose dummy. All active drugs were in the form of the hydrochloride salt but doses are expressed as the base.

Analysis of results

All measured variables from both trials were analysed by analysis of variance. Each test session was analysed separately only when there was shown to be a significant treatment x session interaction overall. Means differing by $P<0.05$ were accepted as significantly different. Analysis of covariance was used to examine any effect of treatments on the change from pre to post treatment values for vigilance and reaction time. Subjective rating scores were analysed both as raw scores and after arc-sin transformation (Aitken, 1969). One subject in Trial 1 failed to appreciate the principle of the test and marked the lines always at the ends. This was not observed until after the start of the trial, and we therefore did not have the complete set of twelve subjects for analysis of variance. The results were therefore analysed by a Fisher's exact probability test for the eleven subjects who completed their lines correctly.

Results

These are shown in Figures 2 and 3 and the significance of differences in Table 1. There were no differences in any measured variable before lactose compared with values before any of the drug treatments.

Auditory vigilance

In Trial 1 there were no significant treatment differences in the number of correct signal detections made or false reports 0.75–1.75 h post-drug. By 3.5–4.5 h post-drug all doses of amitriptyline significantly reduced the number of signals detected. No effect followed BW 247.

In Trial 2 the number of correct signal detections made 1–2 h post-drug were reduced, following both amitriptyline 12.5 and 25 mg compared with lactose. No other treatment produced an effect on vigilance which differed from that following lactose at this time. During the second test session, 3.5–4.5 h post-drug, the effects of both doses of amitriptyline were still apparent. Further, nortriptyline 25 mg then also reduced the number of signals detected. Nortriptyline 12.5 mg and protriptyline 10 mg produced no significant effect in this test. At no time was the number of false reports affected by different treatments.

Analysis of the number of correct detections in each 15 min period revealed that the number of signals detected in the fourth quarter of the second test in Trial 1 were significantly reduced by amitriptyline

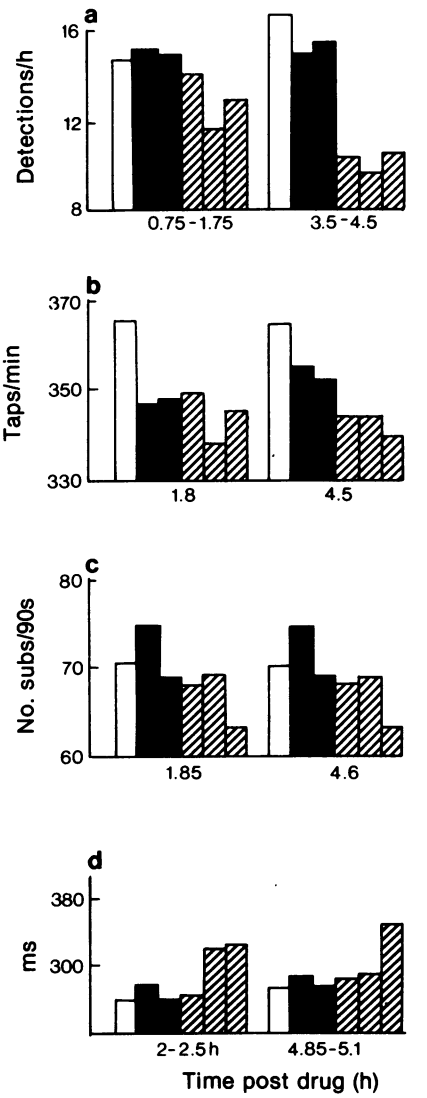

Figure 2 Columns show mean values in the four performance tests (a, vigilance; b, tapping; c, digit symbol substitution and d, reaction time) for twelve subjects obtained in Trial 1. The different treatments are indicated by: column 1 (□) lactose dummy; columns 2 and 3 (■) BW 247 12.5 and 25 mg respectively; columns 4, 5 and 6 (▨) amitriptyline 6.25, 12.5 and 25 mg respectively. Significance of differences in the means are shown in Table 1.

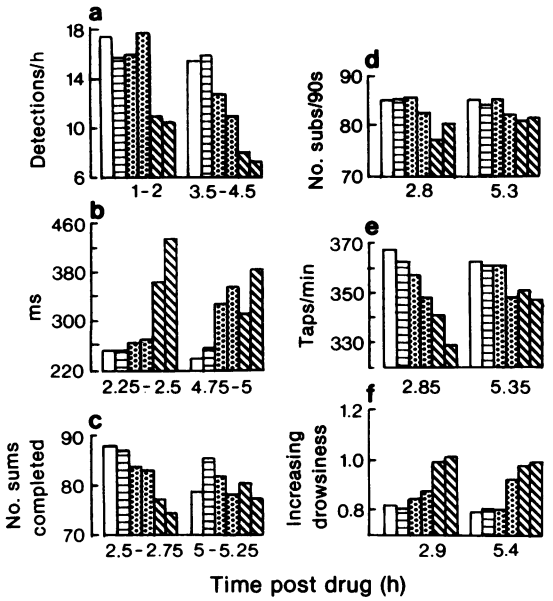

Figure 3 Columns show mean values for five performance tests (a, vigilance; b, reaction time; c, arithmetic test; d, digit symbol substitution and e, tapping) and subjective effects for twelve subjects obtained in Trial 2. Subjective effects (f) are shown as the mental sedation score derived from the scales alert-drowsy, clear headed-muzzy, quickwitted-mentally slow, and attentive-dreamy. Raw values were converted by arc-sin transformation and the ordinate indicates radians. The different treatments are indicated by: column 1 (□) lactose dummy; column 2 (▤) protriptyline 10 mg; columns 3 and 4 (▦) nortriptyline 12.5 and 25 mg respectively; columns 5 and 6 (▩) amitriptyline 12.5 and 25 mg respectively. Significance of differences are given in Table 1.

12.5 mg. In Trial 2 the drug effects were apparent in the last two quarters of the second test.

The only additional finding revealed by analysis of covariance was a reduction in detections 3.5 to 4.5 h after nortriptyline 12.5 mg.

Auditory reaction time

In Trial 1 reaction times were increased at 2–2.25 h after amitriptyline 12.5 mg and 25 mg. By 4.85–5.1 h these effects were no longer significant although amitriptyline 25 mg showed a trend towards increased reaction times. No effects followed BW 247.

In Trial 2 reaction times were increased 2.25–2.50 h and 4.75–5.0 h after both doses of amitriptyline but less so 4.75–5.0 h post-drug. Again the effect of nortriptyline appeared later, when both doses prolonged reaction times during the second post-drug session but had no effect in the first. Protriptyline 10 mg had no effect. Analysis of covariance failed to reveal any additional changes ascribable to treatment.

Short term memory test

At no time during Trial 2 was short term memory significantly impaired by antidepressants compared with lactose.

Arithmetic test

In Trial 2 the number of sums completed in this test was reduced 2.5 h after amitriptyline 12.5 and 25 mg but was unaffected by either dose of nortriptyline or protriptyline. There were no effects after any of the treatments 5 h post-drug.

Digit symbol substitution

Performance in this test was unaffected throughout Trial 1. (Significant impairment occurred after amitriptyline 25 mg when both sessions were analysed together, but no treatment x session interaction occurred.)

The number of completed substitutions in Trial 2 was reduced 2.8 h after amitriptyline 25 mg and at both times after amitriptyline 12.5 mg. No other treatment impaired performance in this test.

Tapping test

There was no significant variation in tapping rates throughout Trial 1.

In Trial 2 during the first post-drug session only, tapping rates were significantly reduced when subjects received amitriptyline 12.5 and 25 mg and also nortriptyline 25 mg. There were no effects 5.3 h post-drug.

Subjective effects

The results of analysis of the visual analogue scales are summarized in Figure 3 and Tables 1 and 2.

In Trial 2 2.9 h after amitriptyline 12.5 and 25 mg the subjective ratings differed from lactose in those dimensions which indicated mental sedation (Lader & Norris, 1969). By the second session after amitriptyline this effect had largely disappeared although on the alert-drowsy scale the effect was still significant. The subjects were also more calm and relaxed after amitriptyline than after lactose.

By contrast, although on several dimensions a trend towards drowsiness was apparent after nortriptyline, the effects were never significant in either session, with the exception that subjects rated themselves as more relaxed after both doses at 5.4 h. There were no significant effects after protriptyline.

Table 1 Significance of differences in performance and subjective ratings between active drug treatment and lactose

Test	*Time after drug (h)*	*Treatment (mg) Trial 1*					*Time after drug (h)*	*Treatment (mg) Trial 2*				
		AMI (6.25)	*AMI (12.5)*	*AMI (25)*	*BW (12.5)*	*BW (25)*		*AMI (12.5)*	*AMI (25)*	*NOR (12.5)*	*NOR (25)*	*PRO (10)*
Vigilance	0.75–1.75	NS	NS	NS	NS	NS	1–2	0.01	0.01	NS	NS	NS
(Detections/h)	3.5–4.5	0.05	0.01	0.01	NS	NS	3.5–4.5	0.01	0.01	NS	0.05	NS
Reaction time	2–2.25	NS	0.05	0.05	NS	NS	2.25–2.5	0.01	0.01	NS	NS	NS
(ms)	4.85–5.1	NS	NS	NS	NS	NS	4.75–5	0.05	0.01	0.05	0.01	NS
Arithmetic	—	—	—	—	—	—	2.5–2.75	0.05	0.01	NS	NS	NS
/no. of sums)	—	—	—	—	—	—	5–5.25	NS	NS	NS	NS	NS
Digit-symbol	1.85	NS	NS	NS	NS	NS	2.8	0.01	0.01	NS	NS	NS
substitution/90s	4.6	NS	NS	NS	NS	NS	5.3	0.05	NS	NS	NS	NS
Tapping	1.8	NS	NS	NS	NS	NS	2.85	0.01	0.01	NS	0.01	NS
(Taps/min)	4.5	NS	NS	NS	NS	NS	5.35	NS	NS	NS	NS	NS
Subjective lines	—	—	—	—	—	—	2.9	0.01	0.01	NS	NS	NS
Mental sedation	—	—	—	—	—	—	5.4	NS	NS	NS	NS	NS

Mean values in test performance and subjective ratings (mental sedation with arc-sin transformation) at different times after treatments are shown in Figures 2 and 3. The statistical significance of any differences are indicated above: 0.01 and 0.05 indicate $P < 0.01$ and $P < 0.05$ respectively; NS indicates $P > 0.05$. Treatment abbreviations are: AMI, amitriptyline; BW, BW 247; NOR, nortriptyline; PRO, protriptyline.

Analysis of the raw scores of mental sedation gave results identical with those after arc-sin transformation with one exception. Amitriptyline 12.5 mg produced an effect at 5.4 h.

As previously stated, one subject in Trial 1 failed to appreciate the use of visual analogue scales. His data were, therefore, excluded and the change in mental sedation from pre-treatment to post-treatment analysed for the remaining 11 subjects. It can be seen from Table 2 that significant mental sedation followed all doses of amitriptyline at all times except 4.7 h after amitriptyline 12.5 mg. No changes followed BW 247.

Autonomic effects

In Trial 1 salivary secretion, visual near point, heart rate and systolic and diastolic blood pressure in the supine and erect positions and pupil size were recorded. No treatment effects were seen on any of these measures compared with lactose.

Discussion

These results show that amitriptyline in doses equal to and lower than those used clinically impair human performance in a series of objective behavioural tests, and this impairment is associated with drowsiness. By contrast, nortriptyline causes only slight impairment in performance unassociated with subjective drowsiness, while protriptyline and BW 247 produce neither objective nor subjective effects.

The effects of amitriptyline occurred earlier and with lower doses than nortriptyline. With the exception of short-term memory, performance was impaired in all of the Trial 2 tests after both amitriptyline 12.5 and 25 mg, and some effects were still apparent 3.5–5.5 h after treatment. In Trial 1 reaction times were prolonged in the first session after amitriptyline 12.5 mg and 25 mg. There were no effects 0.75–1.75 h after amitriptyline in the vigilance test but 3.5–4.5 h after treatment performance in this test was impaired by all three doses of amitriptyline given. This difference in results between the two trials appears to be due to the 15 min time difference in starting the two sessions, i.e. the effects of amitriptyline begin 1.5 h after administration, as shown by analysing the results in 15 min periods.

Nortriptyline impaired performance much less often and was later in onset than amitriptyline. Reaction time and vigilance test was impaired 3.5–5 h after nortriptyline. The exception to this slower onset of action of nortriptyline was the fall in tapping rate seen in the first session after nortriptyline 25 mg.

These results are consistent with clinical reports suggesting that amitriptyline, a tertiary amine, produces considerable drowsiness, nortriptyline a secondary amine rather less, and that protriptyline, another secondary amine, has little or no sedative action. For example, Daneman (1965) reported that twenty-three of fifty depressed patients receiving amitriptyline 25 mg 2–6 times/day complained of drowsiness. Forrest *et al.* (1964) found that four of ten patients receiving 25–50 mg three times daily also complained of drowsiness. Eight of fifteen patients receiving nortriptyline 25 mg twice daily for 4 weeks experienced drowsiness at the end of the first week only (Priest, 1976). However, the importance of observing a control group on inactive treatment was demonstrated by Asberg, Gronholm, Sjöqvist & Tuck (1970) who found that although 76% of thirty-one depressive patients receiving nortriptyline three times a day experienced some drowsiness during the first week of administration, 68% of the placebo group also suffered drowsiness. The secondary amine, BW 247, related to the tricyclic antidepressants, was found to

Table 2 Subjective changes in Trial 1

Impairment compared with predrug values	*Lac*	*Treatment (mg)* AMI (6.25)	AMI (12.5)	AMI (25)	BW (12.5)	BW (25)
1.9 h post drug						
More impaired	7	11	11	11	6	5
Less impaired	4	0	0	0	5	6
Value of *P*		0.045	0.045	0.045	0.500	0.335
4.7 h post drug						
More impaired	5	10	9	11	6	5
Less impaired	6	1	2	0	5	6
Value of *P*		0.032	0.091	0.006	0.500	0.665

Scores derived by summation of individual scores from lines indicating mental sedation taken after treatments were compared with pre-treatment scores. The dimensions summed were, alert-drowsy, attentive-dreamy, clear headed-muzzy, and quick witted-mentally slow. The number of subjects improving or worsening were counted and proportions after active drugs compared with those after lactose by Fisher's exact probability test. Scores from one subject who failed to appreciate the test could not be analysed and have been omitted.

have no sedative action in the present study. These results are consistent with the suggestion of Bickel & Brodie (1964) that the tertiary amines are sedatives while this property is not present in the secondary amines. However, the results with nortriptyline show that sedative properties may not completely disappear in all secondary amines.

Sulser, Watts & Brodie (1962) have proposed that demethylation of tertiary amines leads to loss of their sedative actions. In addition they suggest that it is necessary for the occurrence of the antidepressant properties. This has also been explained in terms of the relative abilities of tricyclic compounds to inhibit neuronal uptake of biogenic amines in the central nervous system. Using various models to study reuptake mechanisms tertiary amines have been shown to be more active in blocking 5HT uptake than secondary amines (Todrick & Tait, 1969; Lidbrink, Jonsson & Fuxe, 1971), while the secondary amines preferentially inhibit noradrenaline uptake (Siwers, Freyschuss, Hamberger, Tuck, Malmfors & Sjöqvist, 1970; Lidbrink *et al.*, 1971). Maxwell, Keenan, Chaplin, Roth & Exkhardt (1969) and Salama *et al.* (1971) have shown that BW 247 is forty times more potent in blocking the uptake of noradrenaline into rat cortical slices than its primary and tertiary derivatives. In this test nortriptyline is the most potent blocker of noradrenaline uptake of the compounds studied in this report. BW 247 is more potent than protriptyline, with amitriptyline the least potent. Sedation cannot therefore be related to blockade of noradrenaline uptake. Similarly blockade of 5-hydroxytryptamine uptake cannot be implicated in the mechanisms of sedation. Using synaptosmal preparations from rat hypothalamus, Ferris (1972, personal communication) found that protriptyline and nortriptyline were the weakest blockers of uptake. Amitriptyline was more potent, but BW 247 was the most potent, being some ten times more active than protriptyline and nortriptyline. The mechanism underlying production of drowsiness by these compounds remains to be discovered.

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