EFFECT OF BUTRIPTYLINE ON SUBJECTIVE FEELINGS AND SLEEP

Butriptyline ($\pm 10,11$ -Dihydro-N,N, β -trimethyl-5H-dibenzo [a,d]cycloheptene-5-propylamine) has been reported to relieve depression (Grivois, 1971), to suppress rapid eye movement (REM) sleep in rats (Jaramillo & Greenberg, 1974) and to have little effect on the re-uptake of brain noradrenaline or brain 5-HT (Pugsley & Lippmann, 1974). The present study examines the effect of butriptyline on subjective feelings and sleep in eight normal volunteers, two men and six women, aged 52-62 years. Butriptyline (75 mg nocte) was given for 3 weeks, preceded and followed by 1 week of placebo.

Subjective evaluation of mood, concentration, quality of sleep and morning vigilance were made daily by means of self-rating analogue scales (Oswald, Lewis, Dunleavy, Březinová & Briggs, 1971) and did not show any significant differences among the experimental conditions. There was a trend ($P < 0.1$) to depressed mood and impaired concentration on drug, similar to but much weaker than the unfavourable changes reported by normal subject on other antidepressants such as imipramine or viloxazine (Oswald, Březinová & Dunleavy, 1972; Hartmann & Cravens, 1973; Březinová, Adam, Chapman, Oswald & Thomson, unpublished observations).

Nocturnal sleep was recorded by electrophysiological techniques on the 4th and 6th baseline

nights, 1st and 3rd drug nights (early drug phase), 19th and 21st drug nights (late drug phase) and on the 1st, 2nd, 3rd, 5th and 7th nights of withdrawal. The records were scored blind according to international criteria (Rechtschaffen & Kales, 1968) and the raw data processed by computer. Nonparametric tests were used for statistical evaluation, namely, Friedman's two-way analysis of variance, testing the overall differences among all four conditions, and Wilcoxon's matched-pairs signed-ranks test for the differences between separate pairs of conditions (Siegel, 1956) with the level of significance set at 0.017 following the Dunn-Bonferroni method (Miller, 1966). The main results are shown in Table 1.

Significant changes in EEG sleep characteristics suggested a mild sedative effect of the drug. The total sleep duration increased on drug, and decreased on withdrawal, by about 20 min in each case, compared with the baseline, the overall differences being significant ($P < 0.01$). Similar changes were observed in the amount of stage 2: an increase on drug and a decrease on withdrawal ($P < 0.01$). The differences in the amount of slow wave sleep, stages 3 + 4, were not significant. The total amount of intervening wakefulness and drowsiness (stages 0 + 1) accumulated during the night showed a slight decrease during the late drug phase and a marked increase on withdrawal, the

Table 1 Mean $\pm$ s.d. effect of butriptyline (75 mg nightly) on sleep

	Baseline	Early drug	Late drug	Withdrawal	χ^2	P <
Total sleep time (min)	466 $\pm$ 43	487 $\pm$ 23	485 $\pm$ 31	447 $\pm$ 34	11.6	0.01
Sleep onset latency (min)	26 $\pm$ 22	18 $\pm$ 12	24 $\pm$ 24	28 $\pm$ 12	5.7	NS
REM sleep latency (min)	74 $\pm$ 22	145 $\pm$ 28**	100 $\pm$ 29	85 $\pm$ 18	16.4	0.001
Intervening st 0 + 1 total min	58 $\pm$ 40	58 $\pm$ 30	50 $\pm$ 29	84 $\pm$ 31	8.6	0.05
Intervening st 0 + 1 in first 3 h of sleep	13 $\pm$ 8	29 $\pm$ 8*	22 $\pm$ 6	27 $\pm$ 4**	11.0	0.02
Shifts to st 0 + 1 in first 3 h of sleep	10 $\pm$ 4	16 $\pm$ 7	15 $\pm$ 7	16 $\pm$ 6**	10.9	0.02
Stage 2 (total min)	238 $\pm$ 33	280 $\pm$ 31	268 $\pm$ 35**	234 $\pm$ 14	15.0	0.01
Stage 3 + 4 (total min)	92 $\pm$ 34	87 $\pm$ 32	88 $\pm$ 24	73 $\pm$ 23*	5.9	NS
Stage REM (total min)	107 $\pm$ 28	82 $\pm$ 14**	93 $\pm$ 19	104 $\pm$ 16	16.4	0.001
Mean duration in min of single episodes of st 0 + 1	2.1 $\pm$ 0.9	1.5 $\pm$ 0.4	1.4 $\pm$ 0.5	2.7 $\pm$ 1.2	12.3	0.01

χ^2 : Overall comparison by Friedman's test.

** Difference from baseline significant in Wilcoxon one-tail test at $P < 0.005$ ($T = 0$).

* Difference from baseline significant in Wilcoxon one-tail test at $P < 0.01$ ($T = 1$ or 2).

Figure 1 Effect of butriptyline (75 mg nocte) on the amount of intervening wakefulness and drowsiness in the first 3 h of sleep. Means of eight normal subjects for each recorded night show sleep is more broken on the drug and early during withdrawal.

The horizontal axis represents the time scale of the experiment in weeks. The vertical axis shows the 8 subjects' mean number of min of intervening wakefulness and drowsiness in the first 3 h of sleep on the recorded nights.

The open columns represent recorded nights with placebo, the black columns recorded nights on drug.

overall differences being significant ($P < 0.05$). The increased amount of intervening stages 0 + 1 on withdrawal was accompanied by a significant increase in the number of shifts to those stages in the first 3 h of sleep ($P < 0.005$).

Other changes in sleep patterns indicated a stimulant effect of the drug, especially during the early drug phase and manifest in the first part of the night. The amount of intervening stages 0 + 1 in the first 3 h of sleep significantly increased during the early drug phase when compared with baseline ($P < 0.01$), partially returned to baseline values during the late drug phase and showed a new significant increase on withdrawal (Figure 1). The number of shifts to stages 0 + 1 in the first 3 h and in the first 6 h of sleep were higher both during the drug phase and after withdrawal than during the baseline phase and the overall differences were significant ($P < 0.02$). The difference between the baseline and the early drug was significant for the number of shifts to stages 0 + 1 in the first 6 h of sleep ($P < 0.01$) and approached significance ($P < 0.03$) for the number of shifts in the first 3 h of sleep. The increase in the number of shifts to stages 0 + 1 on drug was accompanied by a shorter average duration of single episodes of those stages whereas a similar increase in the shifts on withdrawal was characterized by a longer average duration of the episodes.

REM sleep duration was significantly decreased during the drug period (Figure 2). The amount of

Figure 2 Butriptyline reduces the duration of REM sleep. Means of eight subjects across 2 or 5 nights. The horizontal axis represents the successive hours of accumulated sleep. The vertical axis shows the mean cumulative min of REM sleep per h of sleep. (○ = baseline; ● = early drug; ■ = late drug; □ = withdrawal.)

stage REM in the first 6 h of sleep averaged 71 min for baseline, 46 min for early drug, 59 min for late drug and 75 min for withdrawal ($P < 0.01$). REM sleep during the early drug phase was decreased by 35% of the baseline value ($P < 0.005$). Partial adaptation was observed and by the time the late drug phase was reached the amount of REM sleep had returned towards the baseline values. There were indications of a REM sleep rebound early in the withdrawal week, the maximum value being found on the third withdrawal night, but this represented only an increase of 10% above baseline and did not reach significance. The latency to the first REM period significantly increased on drug ($P < 0.005$). The degree of change of REM sleep duration on butriptyline was smaller than that with the standard tricyclic drug imipramine, and was comparable to the effect of doxepin (Dunleavy, Brezinová, Oswald, MacLean & Tinker, 1972). There was an even greater contrast, however, with the lack of any effect from trimipramine, a drug similar in being only a weak 5-HT uptake inhibitor, or iprindole, another potent 5-HT uptake inhibitor without effect on REM sleep (Dunleavy *et al.*, 1972). Thus butriptyline provides another example of how the duration of REM sleep cannot be readily linked to changes in brain amines.

In conclusion, butriptyline produces mild sedation and promotes sleep, but it is also possible to detect a sleep-disturbing action of a type found with other tricyclic drugs. Compared with other related drugs butriptyline causes less unpleasant subjective effects.

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THE EFFECT OF ETHANOL ON RESIDUAL PLASMA METHAQUALONE CONCENTRATIONS AND BEHAVIOUR IN VOLUNTEERS WHO HAVE TAKEN MANDRAX

It has been demonstrated that hypnotics with long half lives impair performance in both simple and complex tasks several hours after their therapeutic effect has ceased (Malpas, Rowan, Joyce & Scott, 1970; Borland & Nicholson, 1975; Bond & Lader, 1975). We have undertaken a preliminary study to investigate the possibility that ethanol might interact with residual concentrations of Mandrax present 24, 48 and 72 h after a single dose and so produce even greater impairment of performance on behavioural tests than either alcohol or drug alone. Since recent reports have shown that ethanol may modify drug concentrations in body fluids (Mould, Curry & Binns, 1972; Rubin, Gang, Misra & Leiber, 1970) and earlier studies (Swaby, 1973; Williams, 1975) have indicated that it interacts with methaqualone residues to modify performance, plasma levels of the drug were measured on each evening of the study to establish any possible relationship between behavioural changes and differences in drug concentrations.

Twelve healthy volunteers, six male and six female, aged 21-39 years took part in the trial. They normally drank alcohol only in moderation and were receiving no other current medication. During the course of the study they were requested to abstain from alcohol for 10 h prior to taking the hypnotic until the tests were complete on the third evening each week. The subjects were allocated at random under double blind conditions to each of the following three treatments which were arranged in a fully balanced design over three consecutive weeks.

- A Two Mandrax tablets (methaqualone 250 mg, diphenhydramine hydrochloride 25 mg) to be taken at 22 h 30 min on day 1 and a weight related dose of flavoured ethanol mixture (0.5 g ethanol/kg) at 17 h 30 min on each of the following three evenings.
- B Two Mandrax placebo tablets and ethanol as in A.