The effect of acute administration of (*meta* trifluoro methyl-phenyl)-1-(benzoyl oxy) ethyl amino-2-propane (780 SE) and fenfluramine on human sleep

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In contrast to other amphetamine derivatives, fenfluramine (40 mg) and 780 SE (300 mg) had no effect on the rapid eye movement (REM) phase of sleep. Like other amphetamines they disturbed sleep, increasing the number of shifts to stage 1 (drowsiness) and stage W (arousal).

Rechtschaffen & Maron (1964) and Baekeland (1967) have demonstrated that dextroamphetamine reduces the amount of rapid eye movement (REM) sleep in the night independently of general sleep disturbance. A comparison of several amphetamine derivatives has demonstrated that fenfluramine 40 mg, while still disturbing sleep, does not alter REM sleep either in amount or distribution (Lewis, 1969), confirming the finding of Oswald, Jones & Mannerheim (1968). All other derivatives tested were found to affect REM sleep. Oswald (1969), however, suggested that(*meta*-trifluoromethylphenyl)-1-(benzoyl oxy) ethyl amino-2-propane (780 SE) in a dose equivalent to 215 mg amphetamine altered the distribution of REM sleep in the night though the percentage of REM sleep remained normal. The dose of 780 SE used by Oswald (450 mg) probably exceeded that likely to be used clinically.

This study compares the effects of 300 mg 780 SE and 40 mg fenfluramine on nocturnal sleep.

Methods.—Seven normal male volunteers (age range 21–24 yr) acted as subjects. They reported to the laboratory one night a week in the late evening when silver disc electrodes were attached above and below the outer canthi for eye movement recording, and to the scalp for e.e.g. recording. Electrodes under the chin recorded submental muscle tone.

The drugs (780 SE, 300 mg and placebo) were given 30 min before retiring. The order of administration was balanced for 2 drug and 2 placebo nights for each subject. There was a first (adaptation) night which was discarded. Recording was continuous from approximately 23.30 h to 07.45 h.

The records were analysed page by page for wakefulness (W), the four non-REM stages of sleep and REM sleep according to international criteria (Rechtschaffen & Kales, 1968). They were also scored for

TABLE 1

	Means and S.D.			Differences between pairs of treatments		
	(1) Placebo	(2) 780 SE	(3) Fenfluramine	(1) *v.* (2)	(1) *v.* (3)	(2) *v.* (3)
Total sleep time (min)	438·5 (12·1)	422·9 (23·1)	436·9 (21·1)	N.S.	N.S.	N.S.
% Stage 1	6·0 (2·2)	10·0 (3·9)	8·7 (3·7)	0·01	0·01	0·05
% Stage 2	41·7 (5·8)	46·8 (5·0)	49·5 (5·6)	N.S.	N.S.	N.S.
% Stages 3+4	28·5 (5·7)	19·1 (4·2)	22·2 (2·1)	0·01	N.S.	N.S.
% REM sleep	23·3 (3·4)	22·0 (4·0)	18·9 (4·9)	N.S.	N.S.	N.S.
Shifts to stages 1 or W per h of sleep	3·1 (0·7)	4·3 (0·9)	3·9 (2·0)	0·05	N.S.	N.S.
Delay to first REM (min)*	68·0 (6·88)	78·0 (11·25)	151·8 (13·8)	N.S.	0·01	N.S.
Stage 1 in first 3 h sleep (min)*	6·7 (4·1)	17·9 (6·6)	12·5 (9·7)	0·001	0·05	N.S.

* Median and semi-interquartile range given for these two parameters since the distributions are not normal.

sleep disturbance; that is the number of shifts from any stage of sleep to stage 1 (drowsiness) or stage W (arousal). Details of this and other parameters have been given elsewhere (Lewis, 1969).

The subjects used here were seven of those used in a previous study of amphetamine derivatives (Lewis, 1969), and so it was possible to compare present results with those obtained earlier. In particular, comparison was made between 780 SE and fenfluramine (40 mg).

The results were analysed using a two-way analysis of variance (Winer, 1962), except for the delay to the first REM period and the amount of stage 1 in the first 3 h of sleep, which were analysed by the Friedmann non-parametric analysis of variance (Wilcoxon & Wilcox, 1964).

Results.—The effects of 780 SE on the whole night are summarized in Table 1. As can be seen 780 SE considerably altered sleep in that it increased the amount of stage 1 (drowsiness) and the number of shifts to stages 1 or W. In other words it produced a disturbed sleep and this disturbance was greater than that induced by fenfluramine. The increased amount of stage 1 was associated with a reduced amount of stage 3+4. Neither 780 SE nor fenfluramine had an effect on the percentage of REM sleep, though fenfluramine increased the delay to the first REM period. There was an insignificant interaction between 780 SE and amount of REM sleep per hour of sleep during the first 7 h of sleep.

In the first 3 h of sleep, 780 SE and fenfluramine increased the amount of stage 1, with 780 SE administration resulting in a greater increase. No other change was significant.

Discussion.—Oswald (1969) suggested that 780 SE in a dose of 450 mg led to a suppression of REM sleep at the beginning of the night and that in the last 2 h of sleep there was a REM sleep increase, resulting in an apparently normal overnight REM sleep. No such compensatory REM sleep increase was found here. 780 SE, which like fenfluramine is a trifluoromethylphenyl derivative of amphetamine, appears also to have no REM suppressant effect in the dose (300 mg) used. However, Oswald's (1969) data would suggest that dose is important. The same may be true of fenfluramine, since a study of the sleep of three patients following overdose (400, 600 and 800 mg) of fenfluramine (Riley, Corson, Haider & Oswald, 1969) demonstrated REM sleep suppression with slight subsequent rebound.

Amphetamine is well known for its sleep inhibiting properties. Both 780 SE and fenfluramine retain this sleep disturbing property when the dose of 780 SE (300 mg) is equivalent to about 150 mg amphetamine on a molecular weight basis. Such a dose of amphetamine would result in acute insomnia. In this study, no subjective effects were reported.

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