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Effects of Fluvoxamine and Dothiepin on Psychomotor Abilities in Healthy Volunteers

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FAIRWEATHER, D. B., J. ASHFORD AND I. HINDMARCH. *Effects of fluvoxamine and dothiepin on psychomotor abilities in healthy volunteers.* PHARMACOL BIOCHEM BEHAV 53(2) 265–269, 1996.—We gave 12 healthy male volunteers single doses of 50 mg fluvoxamine, 100 mg fluvoxamine, 75 mg dothiepin, and placebo in a double-blind crossover study. Subjects completed a test battery that was sensitive to the behaviourally toxic effects of psychoactive drugs prior to dosing, and then at 1, 2, 3, 4, and 6 h after dose. The test battery included tasks of choice reaction time, tracking, critical flicker fusion threshold, and memory scanning. Subjective feelings were assessed using the line analogue rating scales and the Milford–Epworth sleepiness scale. Daytime activity was recorded by means of wrist actigraphy. The results show that the positive internal control (dothiepin) had a sedative effect in that it impaired performance in the majority of the tests and also reduced daytime activity. Both doses of fluvoxamine remained relatively neutral throughout and did not impair psychomotor performance or cognitive ability in any of the tests. These results indicate that fluvoxamine may be a safe and efficacious antidepressant for outpatients who wish to carry on with the tasks of everyday life without being sedated.

Fluvoxamine Dothiepin Psychomotor performance Daytime activity

THE RANGE of antidepressants available today allows the physician to choose the most appropriate treatment for patients. It is widely accepted that the majority of antidepressants are equipotent in terms of clinical efficacy; therefore, another major criterion in the selection of a medication is the extent to which a particular compound produces unwanted side-effects. Among the possible side-effects of a psychoactive drug are impairments of cognition and performance, which only serve to exacerbate the problem rather than remedy it. The tricyclic antidepressants (TCA's) are the most widely prescribed drugs in the treatment of depressive disorders, and the sedative side-effects associated with them are well documented (8,13). Impairment of cognition and psychomotor ability, including dose-dependent impairment (18), has also been reported with the TCA's [e.g., (4,5)].

Any compound that has the potential to disrupt the integrity of psychological aspects of performance is known to be behaviourally toxic. A significant level of behavioural toxicity will prevent drug-induced improvement of cognitive and psychomotor behaviour and so be countertherapeutic. Furthermore, any sedation, tiredness, and fatigue associated with antidepressant medication might well increase the risk of drug-related accidents, especially in ambulant patients.

Increased appreciation of the role of serotonin in depression has led to the development of highly selective inhibitors of serotonin reuptake (SSRI's). These novel compounds are much more selective than the older TCA's and provide effective antidepressant activity without the sedating, anticholinergic, or cardiotoxic reactions characteristic of the older drugs. The nonsedating properties of the SSRI's represent a significant benefit over the older TCA's in the context of daytime functioning, the risk of accidents, and overall quality of life (1).

Among the SSRI's, fluvoxamine appears to be a compound that is as efficacious as reference antidepressants but much safer in terms of toxicity, overdose, and suicide than the TCA's (20). Fluvoxamine also appears to have a favourable adverse effect profile compared with the older TCA's (21), and may prove to be advantageous in the treatment of depression in patients who wish to carry on with the tasks of everyday life without increasing the risk of accidents.

It was therefore proposed to study the psychomotor and

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cognitive effects of fluvoxamine and the tricyclic dothiepin using a standard, validated psychometric test battery.

METHODS

Subjects

A total of 12 healthy male volunteers, aged 21–50 years, were entered into the study. All subjects were in good physical and mental health and had no history of significant disease or mental illness. None of the subjects was taking any concomitant medication likely to interfere with the study measures. Written informed consent was obtained from all subjects and also the consent of their general practitioners. The study was approved by the Ethics Committees of the South West Surrey Health Authority and the University of Surrey.

Design

The study was a randomised, double-blind, placebo-controlled, four-way, cross-over design in which each subject acted as his own control. Treatment sequence was balanced for residual effects using a Latin square design. The treatments were 50 mg fluvoxamine, 100 mg fluvoxamine, 75 mg dothiepin, and placebo, all supplied as identical capsules. Alcohol, nicotine, and caffeine were prohibited on study days. Each treatment day was separated by a 1-week washout period.

Procedure

Prior to the study all subjects were medically examined and familiarised with the study procedures. They were also trained on the battery of psychometric tests to preclude any learning effects. On each of the test days, subjects attended the study centre where a breath alcohol reading was taken. Subjects were then given a wrist actigraph to be worn on the nondominant arm. Following this, pretreatment baseline recordings were made on each of the tests (described subsequently). Treatments were then administered, and further testing was carried out at 1, 2, 3, 4, and 6 h after dose. The Milford–Epworth Sleepiness scale (MESS) was completed at 6 h after dose only.

Subjects were then taken home and required to return after a 1-week washout period. The same procedure was followed on each of the study days, and a medical examination was carried out after the last study day. Compliance was verified by the investigator who observed capsule ingestion. The assessments were as follows.

Critical flicker fusion threshold (CFF). We used CFF as a means of measuring the ability to distinguish discrete sensory data (6). The test device was composed of four light-emitting diodes held in foveal fixation at 1 m from the subject. The lights flickered on and off at a constantly increasing or decreasing rate, and subjects were required to discriminate flicker from fusion. Individual thresholds were determined by the psychophysical method of limits on three ascending and three descending scales. The mean of these values was then recorded.

Choice reaction time (CRT). We used CRT as a sensitive measure of drug-induced changes in sensorimotor performance (9,12). From a central starting position, subjects were required to extinguish one of the six red lights, illuminated at random, by touching the appropriate response button. Using this arrangement it was possible to measure three components of reaction time: the total reaction time (TRT) from stimulus onset to completion of response; the movement time (MRT) between the start and response buttons; and the processing or recognition time (RRT), obtained from subtracting MRT from TRT. The mean reaction time for 20 stimulus presentations was recorded.

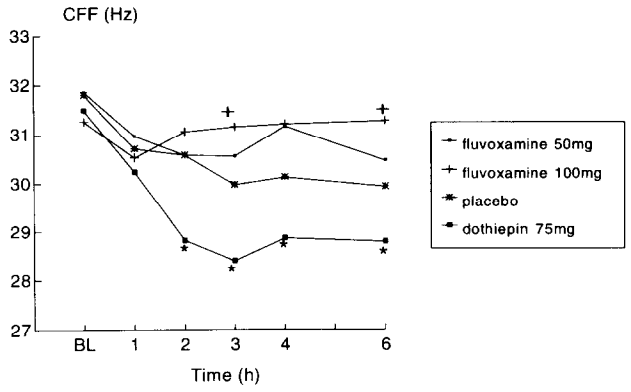
Sternberg memory scanning task (STM). High-speed scanning and retrieval from short-term memory were assessed using a reaction time technique pioneered by Sternberg (19). Subjects were required to memorise a series of one to four digits (the stimulus set) presented sequentially. They were then presented with a series of individual probe digits and were required to respond to the probes by using a two-button yes/no choice response box. We made 24 such presentations during each assessment. Accuracy and response times were measured.

Compensatory tracking test (CTT). This interactive task of psychomotor function (14) entailed tracking a moving arrow on a VDU screen using a joystick. The response measure was the mean deviation from the track program over the 1-min trial period, with lower scores indicative of more accurate tracking. A peripheral awareness task was included in which the subject responded to a stimulus presented in the periphery of vision while simultaneously attending to the tracking test. The mean reaction time to 10 of these stimuli over the trial period was taken as the response measure for this component of the divided attention task.

Subjective sedation. Subjective ratings of drug effects were obtained from a series of 10-cm line analogue rating scales (LARS). The mean scores of ratings of "tiredness," "drowsiness," and "alertness" (which were included among a number of distractor scales) were taken as a measurement of perceived sedation (11).

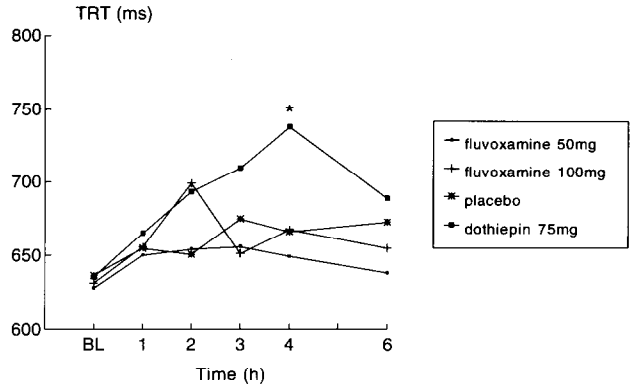
MESS. Using 10-cm line analogue rating scales, subjects were required to rate the likelihood of their falling asleep in a number of everyday situations. The overall mean score represents the level of sleepiness during the day. This rating scale was adapted from the MESS (15,16).

Wrist actigraphy. Subjects were required to wear wrist actigraphs (AMI AMA-32 Motionloggers) on their nondominant wrist for the duration of each test day. These small wristwatch-size devices contain a piezoelectric transducer that detects motion and generates a signal voltage. In zero crossing mode the signal voltage is compared with a reference voltage for a change in state. The device records the number of changes in state per epoch (30 s). This equates to an activity frequency measure. Data are downloaded from the actigraph



*P<0.005, +P<0.05

FIG. 1. The effects of fluvoxamine and dothiepin on CFF (Hz).



* P<0.00005

FIG. 2. The effects of fluvoxamine and dothiepin on TRT (ms).

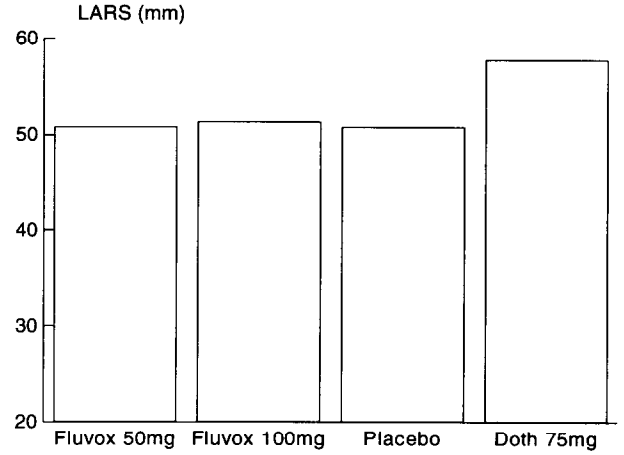


FIG. 3. The effects of fluvoxamine and dothiepin on sedation (LARS, mm).

onto a dedicated PC, and the data are analysed using ACTION software. The computer-generated result gives a measure of mean daytime activity.

Statistical Analysis

The data were analysed using repeated analyses of variance (ANOVA). If there was an overall significant treatment effect ($p < 0.05$), differences between means were evaluated post-hoc using the Newman-Keuls test.

RESULTS

All subjects completed the study and no serious adverse events were recorded.

For CFF, overall analysis revealed that 50 mg fluvoxamine, 100 mg fluvoxamine, and placebo were statistically indistinguishable. There was, however, a treatment effect [$F(3, 33) = 14.87$, $p < 0.00001$], where dothiepin was shown to produce significantly different results from placebo and both doses of fluvoxamine. Posthoc analysis revealed that dothiepin results were significantly impaired (seen as a decrease in CFF threshold) compared with placebo at 2, 3, 4, and 6 h after dose ($p < 0.005$). The higher dose of fluvoxamine slightly increased the threshold at 3 and 6 h after dose ($p < 0.05$) (Fig. 1).

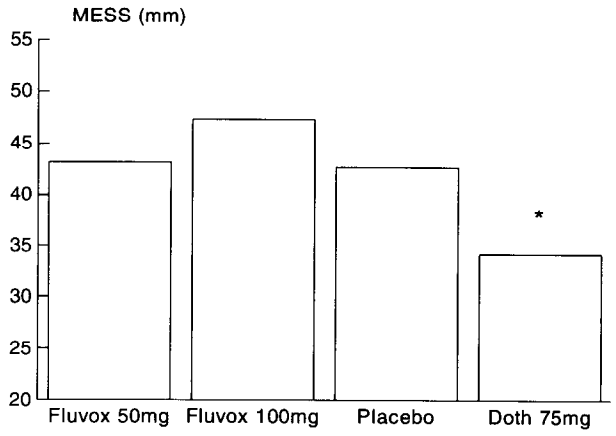
ANOVA revealed a treatment effect in the RRT component of the CRT task ($F = 5.71$, $p < 0.005$). Dothiepin produced a significantly higher RRT than placebo ($p < 0.05$) at 4 h after dose, whereas fluvoxamine had no effect. Dothiepin also impaired MRT ($p < 0.05$) and TRT ($p < 0.00005$) at 4 h after dose (Fig. 2). Fluvoxamine 100 mg produced significantly faster MRT scores ($p < 0.05$) than placebo at the 2-h time point.

Fluvoxamine and dothiepin were not significantly different from placebo in the results of the CTT or STM tests. For LARS, a significant treatment effect was revealed where $F = 3.08$, $p < 0.05$. Posthoc analysis showed that dothiepin produced significantly higher ratings of sedation than both doses of fluvoxamine ($p < 0.05$), and although there was a trend for dothiepin to be more sedative than placebo, this was not significant (Fig. 3). In the MESS scores (Fig. 4), posthoc analysis of the treatment effect ($F = 9.44$, $p < 0.0005$) revealed dothiepin to be significantly more sedative than placebo ($p < 0.005$).

The actigraph data (Fig. 5) revealed dothiepin to be more sedative in that the mean activity over the whole recording period was less with dothiepin than with placebo, although this difference failed to reach significance ($p = 0.055$). Mean daytime activity with fluvoxamine was similar to that of placebo. (A more detailed analysis of the actigraph data will be published separately.)

DISCUSSION

In addition to being clinically effective and well tolerated, it is essential that antidepressants should not cause sedation or impair psychomotor and cognitive function. Compounds that induce these detrimental effects can result in poor compliance leading to relapse. Furthermore, the risk of drug-related accident in ambulant patients is greatly increased. The tricyclic antidepressants are among those most widely used treatments for depression even though they are associated with objectively determined sedation (4) and behavioural toxicity (9). Evidence suggests that some of the SSRI's are relatively free from these adverse effects (7,10,12,17).



* P<0.005

FIG. 4. The effects of fluvoxamine and dothiepin on sedation (MESS, mm).

The present study investigated the effects of dothiepin and two doses of fluvoxamine in healthy volunteers using a standard, validated test battery. A consistent pattern of results was found across the dependent variables. Dothiepin produced a reduction in alertness and decrements in performance, whereas fluvoxamine generally produced performance at around placebo level or better; these effects were particularly apparent on CFF. A similar pattern was observed in the CRT task, where dothiepin slowed reaction time and fluvoxamine was no different from placebo.

In addition to objective tests of performance and sedation, it is important that a subjective assessment be obtained, i.e., patients' reactions as to how they feel. Dothiepin produced a significant increase in subjects' self-ratings of perceived sedation compared to both placebo and fluvoxamine (as measured by LARS and MESS). The pattern throughout was for dothiepin to be more sedative, and this was also apparent in daytime activity recordings using wrist actigraphs.

As the detrimental effects of dothiepin have been shown previously and the tests used are valid and reliable indicators of drug effects (12), it can be implied that because fluvoxamine had no impairing effect on the test battery when compared with placebo, it has very low potential for behavioural toxicity.

It has been suggested that tolerance develops to the impairing effects of the sedating TCA's on CFF and that studies in healthy volunteers bear no relationship to the effects seen in patients. In a double-blind, repeated-dosing, 6-week patient study (2), CFF scores were below baseline for the duration of treatment with the TCA amitriptyline (75 mg), despite alleviation of the depression. CFF scores improved with the SSRI fluoxetine (20 mg), and the difference between the two drugs was significant at every test point over the 6-week period. Furthermore, the findings of a recent study (3) showed that patients who had been given a stable medication for 3 mo had improved CFF and CRT scores with SSRI's (fluoxetine and sertraline) compared with to TCA's (amitriptyline, dothiepin, clomipramine, imipramine, and trimipramine). The conclusions of these patient studies reflect many of the patterns found in acute dose healthy volunteer studies where, in contrast to the SSRI's, some of the older TCA's have been shown to induce detrimental effects on cognitive and psychomotor abilities [e.g., (5,7,10,17)].

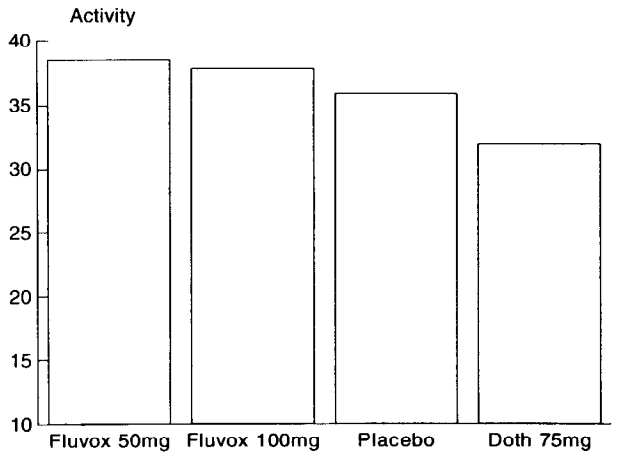


FIG. 5. The effects of fluvoxamine and dothiepin on daytime activity (actigraphy).

Although many of the antidepressants available today are equipotent in alleviating depression. they differ in respect to their side-effect profiles; therefore, it is important to evaluate the potential of drug-induced behavioural toxicity. This is of particular relevance in those outpatients who drive motor vehicles or work in risk-prone domestic or industrial environments. Like some of the other SSRIs (e.g., sertraline, paroxetine, and fluoxetine), there is no evidence from this study to suggest that fluvoxamine, at a clinically effective dose, has any intrinsic sedative activity likely to interfere with the performance of the activities of everyday living. Newer antidepressants such as fluvoxamine, which have the potential to reduce depression without disrupting the integrity of the patient's cognitive processes, have an important role in the pharmacotherapy of depressive disorders.

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