Original Article

Study of the Effect of Nortriptyline and Fluvoxamine on Psychomotor Functions in Healthy Volunteers

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ABSTRACT

Background: Today, many antidepressants are available, but they often cause adverse effects, particularly psychomotor and cognitive. It leads to patient maladjustment and may impair psychomotor performance. Fluvoxamine is a newer antidepressant and hence the present study was planned to investigate its effect on psychomotor functions and compare with nortriptyline and record their adverse reactions. **Materials and Methods:** A total of 26 healthy volunteers were included in this double-blind, placebocontrolled, crossover study. Single oral doses of fluvoxamine 50 mg, nortriptyline 50 mg and placebo were administered following a Latin square design. The objective parameters-six digit cancellation test, digit symbol substitution test, critical flicker fusion test, arithmetic ability test, hand steadiness test and subjective parameters such as visual analogue scale 1, 2, 3 were tested at 0, 2 and 4 h. The side-effects were also investigated. **Results:** Nortriptyline impaired all subjective and objective psychomotor functions while fluvoxamine did not show any significant effect on objective tests. However, on subjective parameters, there was a significant effect. The side-effects observed were dryness of mouth with the nortriptyline and nausea and headache with fluvoxamine. **Conclusion:** Fluvoxamine is a better antidepressant drug in comparison with nortriptyline as it causes a less impairment of psychomotor functions.

Key words: *Fluvoxamine, nortriptyline, psychomotor function*

INTRODUCTION

Mood disorders appear to afflict at least 12% of women and 8% of men[1]. Major depression or unipolar depression is the most common psychiatric disorder. Mental illnesses were earlier not well understood. But, these days, with advanced technology, brain receptors have been mapped.

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In 1957, Kuhn reported that imipramine has antidepressant properties. This was followed by other tricyclics such as amitriptyline, nortriptyline, doxepine, etc. and, later on, the selective serotonin reuptake inhibitor, i.e. fluvoxamine, fluoxetine, sertraline, etc.

However, to date, the mechanism of action of these antidepressant drugs is yet to be precisely known. Today, many antidepressants are available but they often cause adverse effects, particularly psychomotor and cognitive. This leads to patient maladjustment and may impair psychomotor performance, which plays important role in driving and operating complex machinery. Therefore, it is desirable to develop antidepressant drugs with a minimal effect on these functions so that the patient's productivity or social adjustment are not hampered.

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Fluvoxamine is a newer antidepressant and hence the present study was planned to investigate its effect on psychomotor functions and compare with nortriptyline and record their adverse reactions.

MATERIALS AND METHODS

A total of 26 healthy volunteers, 20 males and six females, of age group -30 years with informed consent were included in this double-blind, placebocontrolled, crossover study. Subjects who were dependent on alcohol, tobacco or other drugs were excluded. A single oral dose of fluvoxamine 50 mg, nortriptyline 50 mg and placebo was administered following a Latin square design. The parameters were tested at 0, 2 and 4 h. Before the study volunteers received training till a performance plateau was reached.

Tests for psychomotor functions: A sensory component

Test for perception

Six-digit cancellation test (6DCT):[2] Volunteers were required to cancel as many target digits as possible in a sheet consisting of 1,200 randomized digits in 3 min.

Test for recognition and recoding

Digit symbol substitution test (DSST):[3] Volunteers were required to insert the corresponding symbol in the space above each digit in a sheet consisting of 200 randomized digits in 2 min.

Test for central integration

Critical flicker fusion test (CFFT):[4] It is a reliable psychometric test as there is no learning curve effect.[5] The apparatus consists of a viewing tube at the end of which a red circle of light flickers at the rate of 550 cycles/s. The Critical Fusion Frequency was determined by increasing the frequency from 5 Hz till a steady light source was seen and the Critical Flicker Frequency by decreasing the frequency from 50 Hz till flickering was seen.

Test for central processing

Arithmetic ability test (AA):[6] The subjects had to solve simple mathematical problems, i.e. addition, subtraction, multiplication and division (five of each) within 2 min.

Motor component

Test for steadiness[7]

This was tested by steadiness tester, which consists of holes of different size sand subjects had to insert stylus into the hole without touching its sides.

Subjective component

Visual analogue scale (VAS)[8]

The volunteers were asked to indicate the state of their current feeling by marking on a 100 mm horizontal line. The opposite mood-related adjectives at each end were as follows:

1. Wide awake - extreme sleepy
2. Alert - dull
3. Active - tired

Side-effects

Volunteers marked their subjectively felt side effects on a sheet.

Statistical analysis of data

The sample size of 26 was calculated by the institutional statistician. The tests used were ANOVA followed by *post-hoc* Newman-Keuls multiple comparison test.

RESULTS AND DISCUSSION

In the study, nortriptyline 50 mg dose decreased the substitution of symbols score on DSST and the cancellation of digits score on 6DCT [Table 1]. It

Table 1: Effects of fluvoxamine and nortriptyline at 0, 2 and 4 h

Test	Drug	Mean±SEM			Mean difference	
		0 h	2 h	4 h	2 h	4 h
6DCT	Placebo	204.4±5.01	205.3±5.00	205.7±5.09	0.90	1.30
	Fluvoxamine	196.9±5.37	199.2±5.62	201.8±5.57	2.30	4.90
	Nortriptyline	199.7±5.62	202.0±5.87	180.3±6.11	2.30	-19.40*
DSST	Placebo	162.2±3.45	163.2±3.49	164.8±3.34	1.00	2.60
	Fluvoxamine	161.4±3.54	161.3±3.47	162.0±2.98	-0.10	0.60
	Nortriptyline	158.1±4.02	159.7±4.02	126.6±3.72	1.60	-31.50*
CFFT	Placebo	39.08±0.31	39.06±0.32	39.12±0.28	-0.02	0.04
	Fluvoxamine	38.79±0.41	39.12±0.41	39.08±0.38	0.33	0.29
	Nortriptyline	39.25±0.33	39.46±0.26	36.75±0.40	0.21	-2.50*
AA	Placebo	16.69±0.66	16.08±0.55	16.27±0.61	-0.61	-0.42
	Fluvoxamine	14.65±0.86	14.92±0.70	14.69±0.81	0.27	0.04
	Nortriptyline	15.12±0.71	15.04±0.75	7.07±0.44	-0.08	-8.04*

*$P<0.05$

reduced the CFFT threshold and AA score suggestive of impairment of central integrative capacity and central processing ability respectively [Table 1] It increased errors in the hand steadiness test, suggestive of motor impairment [Table 2].These findings of nortriptyline on objective tests are also reflected in the subjective assessment of VAS-1, VAS-2 and VAS-3 with a significant shift of the scale toward drowsiness, tiredness and dullness [Table 2]. Nortriptyline when compared with fluvoxamine and placebo had shown significant impairment on objective [Table 3] and subjective tests at 4 h [Table 4]. Thus, in the present study nortriptyline at the dose of 50 mg significantly affected the psychomotor functions. Tricyclics like nortriptyline cause adverse effects of drowsiness and psychomotor impairment due to their antihistaminic, antimuscarinic and α_1-antagonist action.[9]. The findings are in arrangement with studies of Ogura, *et al*.,[10] Bye *et al*.[11] and Seppala, *et al*.[12]

It is seen from the studies of Curran and Lader[13] Fairweather, *et al*.[14] Fleishaker and Hulst[15] that fluvoxamine 50 mg had no significant effect on objective tests except the study of van Harten[16] in which performance was impaired.

In our study, fluvoxamine in the dose of 50 mg did not show any significant effect on objective tests such as 6DCT, DSST, CFFT, AA test [Table 1] and hand steadiness test [Table 2]. However, on subjective parameters such as VAS-1, VAS-2 and VAS-3, there was a significant effect indicating a shift of the scale toward drowsiness, tiredness and dullness [Table 2]. Also, nortriptyline in comparison with fluvoxamine impaired psychometric tests significantly [Tables 3 and 4].

In a recent study of the receptor binding of a wide range of antidepressants in human post-mortem brain, fluvoxamine was among the least-potent compounds at α_1, α_2, H_1 and muscarinic receptor sites. This may account for its lack of sedation and consequently lack of impairment of psychomotor function.[17] Thus, the findings of effect of fluvoxamine on various

Table 2: Effects of fluvoxamine and nortriptyline at 0, 2 and 4 h

Test	Drug	Mean±SEM			Mean difference	
		0 h	2 h	4 h	2 h	4 h
HST	Placebo	682.7±76.21	710.5±101.8	717.4±116.1	27.80	34.70
	Fluvoxamine	678.2±41.76	713.2±61.26	647.5±57.57	35.00	-30.70
	Nortriptyline	658.0±55.82	653.1±100.7	1257.0±77.70	-4.90	599*
VAS-1	Placebo	64.12±2.08	62.69±2.70	56.38±2.71	-1.43	-7.74
	Fluvoxamine	66.69±1.65	59.46±2.42	54.81±2.69	-7.23	-11.88*
	Nortriptyline	66.46±1.85	64.58±2.68	29.23±1.41	-1.88	-37.23**
VAS-2	Placebo	66.73±2.17	61.31±2.27	61.08±3.03	-5.42	-5.65
	Fluvoxamine	69.81±1.98	61.00±2.60	55.85±2.49	-8.81*	-13.96**
	Nortriptyline	70.73±1.85	68.23±2.99	24.88±1.79	-2.50	-45.85**
VAS-3	Placebo	64.58±2.11	60.04±2.34	58.00±3.06	-4.54	-6.58
	Fluvoxamine	63.50±2.29	59.38±2.29	54.81±2.26	-4.12	-8.69*
	Nortriptyline	64.65±1.89	60.81±2.77	25.42±1.73	-3.84	-39.23**

*$P<0.05$; **$P<0.01$

Table 3: Interdrug comparison of mean difference at 2 and 4 h

Test	Drug	Mean difference	
		2 h	4 h
6DCT	Placebo vs. fluvoxamine	-1.40	-3.60
	Placebo vs. nortriptyline	-1.40	-20.70*
	Fluvoxamine vs. nortriptyline	0	-24.30*
DSST	Placebo vs. fluvoxamine	-1.10	-2.00
	Placebo vs. nortriptyline	-0.60	-34.10*
	Fluvoxamine vs. nortriptyline	-1.70	-32.10*
CFFT	Placebo vs. fluvoxamine	-0.35	-0.25
	Placebo vs. nortriptyline	-0.23	-2.54**
	Fluvoxamine vs. nortriptyline	-0.12	-2.79**
AA	Placebo vs. fluvoxamine	-0.88	-0.46
	Placebo vs. nortriptyline	-0.53	-7.62*
	Fluvoxamine vs. nortriptyline	-0.35	-8.08*

*$P<0.05$; **$P<0.001$

Table 4: Interdrug comparison of mean difference at 2 and 4 h

Test	Drug	Mean difference	
		2 h	4 h
HST	Placebo vs. fluvoxamine	-7.20	-65.40
	Placebo vs. nortriptyline	-32.70	563.30*
	Fluvoxamine vs. nortriptyline	-39.90	629.70*
VAS-1	Placebo vs. fluvoxamine	-5.80	-4.14
	Placebo vs. nortriptyline	-0.45	-29.49*
	Fluvoxamine vs. nortriptyline	-5.34	-25.35*
VAS-2	Placebo vs. fluvoxamine	-3.39	-8.31
	Placebo vs. nortriptyline	-2.92	-40.20*
	Fluvoxamine vs. nortriptyline	-6.31	-31.89*
VAS-3	Placebo vs. fluvoxamine	-0.42	-2.11
	Placebo vs. nortriptyline	-0.70	-32.65*
	Fluvoxamine vs. nortriptyline	-0.28	-30.54*

*$P<0.001$

Table 5: Side-effects reported by the volunteers

Side-effects	Placebo	Fluvoxamine	Nortriptyline
Dry mouth	–	4 (15.38)	14 (53.84)
Nausea	–	8 (30.76)	–
Headache	–	6 (23.07)	–

Figures in parentheses indicates percentage

psychometric tests in our study substantiate those of the other workers. Further, there is limitation of analogue system as words may fail to describe the exactness of the subjective experience.[8]

The volunteers complained dryness of mouth with nortriptyline due to anticholinergic action and nausea headache with fluvoxamine [Table 5]. The cause for nausea, vomiting with fluvoxamine is increased synaptic availability of serotonin which stimulates $5HT_3$ receptors. These side-effects are expected and also reported by others.[9,17]

CONCLUSION

Nortriptyline significantly depresses the objective and subjective psychometric performance in comparison with placebo and fluvoxamine. There was no evidence of impairment of psychometric tests by fluvoxamine in our study. However, it has impaired the subjective test. Dryness of mouth is the reported adverse effect of nortriptyline, whereas nausea and headache are the adverse effects of fluvoxamine. Hence, fluvoxamine can be a better alternative to nortriptyline as it causes minimal psychomotor impairment.

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