Original Article

Psychopharmacological effects of tianeptine and nortriptyline in human volunteers

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Abstract

Background: Antidepressant drugs cause psychomotor impairment during treatment of depression and these psychomotor skills play important role in driving and other activities. Tianeptine is a novel antidepressant with different mechanism of action. Hence, the present study was planned to investigate its effect on psychomotor functions and compare with nortriptyline and to record the adverse drug reactions.

Methods: In a randomised, double blind placebo-controlled crossover study, single oral dose of nortriptyline and tianeptine was administered in 26 healthy volunteers. The objective psychometric tests included were: six digit cancellation test, digit symbol substitution test, critical flicker fusion test, arithmetic ability test, hand steadiness test and subjective parameters were visual analogue scale 1 and 2. The adverse drug reactions were also recorded. The tests were administered at 0, 2 & 4 hours post dose.

Results: Nortriptyline significantly impaired objective as well as subjective psychometric tests whereas tianeptine did not demonstrate any significant effects on both parameters. Dryness of mouth with nortriptyline and headache with tianeptine were the major side-effects.

Conclusion: Tianeptine 12.5mg single dose does not impair psychomotor performance.

Key words: Depression; antidepressive agents; psychomotor performance.

Introduction

Depression is one of the commonest psychiatric disorders. There has been lot of development in the treatment of depression beginning with tricyclic antidepressants (TCA) to the recent selective serotonin reuptake inhibitors (SSRI). Most of the antidepressants are of equal clinical efficacy but differ in causing behavioural toxicity. Behavioural toxicity is defined as the extent to which a drug disrupts those abilities necessary for the safe performance of cognitive and psychomotor tasks of everyday life [1]. Psychomotor skills play important role in driving and operating complex machinery and their impairment may result in various accidents. Hence, it is desirable to develop antidepressant drugs with minimal effect on these functions so that the patients' productivity and social adjustment is not hampered.

Tianeptine is a novel antidepressant drug which in contrast to other antidepressants facilitates the reuptake of serotonin (5-HT) and hence the present study was planned to investigate its psychopharmacological effects and compare with nortriptyline.

Methods

A total of 26 apparently healthy volunteers (in good physical and psychological health and not on any medication), 20 males and 6 females, of age group 18 to 30 years willing to participate and providing informed written consent, were included for the study. A detailed medical examination was also conducted before the study. None of the subjects was dependent on alcohol, tobacco or other drugs. The study was approved by the institutional ethics committee and carried out in the Department of Pharmacology.

A double blind, placebo-controlled, cross-over

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study was performed. Nortriptyline was used as positive internal control to impair performance on psychomotor test and to establish validity of test battery. Randomised allocation was peformed, drugs were prepared in identical gelatin capsules and were given in oral form as single dose. Drugs used were tianeptine 12.5mg, nortriptyline 50mg and placebo (vitamin C). Drugs were coded or blinding was done by an individual who was not involved in the study; neither the investigator nor the participants. The code was sealed and was opened on completion of the study. Drugs were given to the subjects following a Latin square design. Each volunteer acted as his own control and each volunteer got each formulation by making cross over. The washout period of one week was given between two drugs.

Before beginning of the study, the subjects were explained about the experimental procedures and the psychomotor function tests. The volunteers received training till a performance plateau was reached with the battery of psychomotor tests in order to preclude any learning curve effect. Instructions were given to the volunteers 2 days prior to the day on which the study was to be carried out. The volunteers were asked to refrain from smoking, drinking alcohol or taking any medication one day prior to the study. On the day of study, the control parameter was tested between 10-10.30 a.m. The test drug was given along with one glass of water at 11 a.m. Thereafter, the various parameters were tested 2 hr and 4 hr after drug administration. Instructions were given to the volunteers not to eat anything except drinking water between the breakfasts till the study was completed. They could perform their routine task except mechanical work or driving vehicle. The volunteers had their lunch after the study was over. They were escorted to their residence by the investigator.

The following tests were used to assess psychomotor functions.

Objective parameters

1. Six Digit Cancellation Test (6DCT) [2]: This test was used to assess the perception part of sensory component. Volunteers were given a sheet consisting of 1200 randomised digits arranged in 40 columns and were asked to cancel as many target digits as possible in three minutes.

2. Digit Symbol Substitution Test (DSST) [3]: This test was used to assess recoding and recognition of sensory information. Volunteers were required to insert the corresponding symbol in the space above each digit in a sheet consisting of 200 randomised digits in two minutes.

3. Critical Flicker Fusion test (CFFT) [4]: CFFT is regarded as the assessment of choice for investigating the change in overall integrative activity of the CNS produced by psychoactive drugs. It is a reliable psychometric test as there is no learning curve effect [5]. The apparatus consisted of a viewing tube at the end of which a red circle of light flickered at the rate of 5-50 cycles / sec. The 'Critical Fusion Frequency' was determined by increasing the frequency from 5Hz till a steady light source was seen and 'Critical Flicker Frequency' by decreasing the frequency from 50Hz till flickering was seen. Three readings of each were taken and the score was the mean of 6 readings.

4. Arithmetic Ability Test (AA) [6]: Central processing was assessed by arithmetic ability test in which the volunteers were asked to solve simple mathematical problems i.e. addition, subtraction, multiplication and division (five of each) within two minutes time.

5. Test for Steadiness [7]: The steadiness tester assessed the motor component. It consisted of holes of different sizes and subjects had to insert stylus into the hole without touching its sides.

Subjective parameters

Visual Analogue Scale (VAS) [8]: VAS was used to assess drug effects on mood. The subjects were asked to indicate the state of their current feeling by marking on a 100mm horizontal line. The semantic opposites were wide awake/extreme sleepy and alert/ dull.

Side effects: Volunteers marked their subjectively felt side effects on a sheet.

Statistical analysis: At the level of significance α=5% and power 95%, the sample size required was calculated to be 26. The data was analysed by ANOVA followed by post- hoc Newman- Keuls

multiple comparison test.

Results

Nortriptyline 50mg dose decreased the cancellation of digits score on 6DCT, substitution of symbols score on DSST, the CFFT threshold and arithmetic ability scores at 4 hours ($p<0.05$) (Table 1). It increased the errors in hand steadiness test ($p<0.05$) suggestive of motor impairment (Table 2). These findings of nortriptyline on objective tests are also reflected in the subjective assessment of visual analogue scale VAS-1 and VAS-2 with a significant shift ($p<0.01$) of the scale towards drowsiness, and dullness (Table 2). Tianeptine in the dose of 12.5mg did not show any significant effect on objective tests such as

Table 1- Effects of Nortriptyline, tianeptine and placebo at 0 hours, 2 hours and 4 hours

Test	Drug	Mean±S.E.M		
		0 Hour	*2 Hours*	*4 Hours*
6 DCT	Nortriptyline	199.7±5.62	202.0±5.87	180.3±6.11*
	Tianeptine	190.5±6.14	192.23±6.92	193.46±6.69
	Placebo	204.4±5.01	205.3±5.00	205.7±5.09
DSST	Nortriptyline	158.1±4.02	159.7±4.02	126.6±3.72*
	Tianeptine	153.8±3.53	156.2±3.90	157.7±3.75
	Placebo	162.2±3.45	163.2±3.49	164.8±3.34
CFFT	Nortriptyline	39.25±0.33	39.46±0. 26	36.75±0.40*
	Tianeptine	39.19±0.32	38.96±0.36	39.04±0.32
	Placebo	39.08±0.31	39.06±0.32	39.12±0.28
AA	Nortriptyline	15.12±0.71	15.04±0.75	7.07±0.44*
	Tianeptine	16.38±0.75	16.15±0.57	17.27±0.75
	Placebo	16.69±0.66	16.08±0.55	16.27±0.61

*p<0.05

Table 2- Effects of nortriptyline and tianeptine at 0 hours, 2 hours and 4 hours

Test	Drug	Mean±S.E.M		
		0 Hour	*2 Hours*	*4 Hours*
HST	Nortriptyline	658.0±55.82	653.1+100.7	1257.0+77.70*
	Tianeptine	649.6±55.06	688.4±71.92	631.5+56.59
	Placebo	682.7±76.21	710.5±101.8	717.4+116.1
VAS-1	Nortriptyline	66.46±1.85	64.58±2.68	29. 23+1.41*
	Tianeptine	63.04±1.34	62.35±1.88	56.85+2.46
	Placebo	64.12±2.08	62.69±2.70	56.38+2.71
VAS-2	Nortriptyline	70.73±1.85	68.23±2.99	24.88+1.79**
	Tianeptine	67.54±1.91	64.42±2.61	61.31+2.52
	Placebo	66.73±2.17	61.31±2.27	61.08+3.03

*p<0.05, **p<0.01

6DCT, DSST, CFFT, AA test and HST (Table 1 & 2) at 2hrs and 4hrs. On subjective tests, it has not shown any significant effect on VAS-1 & VAS-2 (Table 2). Nortriptyline when compared with tianeptine and placebo had shown significant impairment on objective test: 6DCT, DSST, AA, HST ($p<0.05$) and CFFT ($p<0.001$) and subjective tests ($p<0.05$) at 4 hours. However, tianeptine did not significantly differ in subjective as well as objective psychometric tests compared to placebo.

Aprroximately 15% of volunteers complained of dryness of mouth with tianeptine compared to 54% with nortriptyline. While 23% of volunteers suffered from headache after tianeptine, none reported headache after nortriptyline.

Discussion

Effective pharmacotherapy of depression started with the advent of tricyclic antidepressants, imipramine being a prototype of this class. Relatively newer generation of tricyclic antidepressants such as nortriptyline had low incidence of side effects. SSRI produced fewer autonomic adverse effects associated with the tricyclic antidepressants. This was followed by serotonin reuptake enhancer, tianeptine, for management of depression.

Despite advent of newer effective antidepressant agents, adverse effects still remain a concern. Antidepressant drugs even today compromise the quality of life of the patients by impairing psychomotor skills. The present study was carried out to assess the effect of nortriptyline and tianeptine on psychomotor functions. The study was conducted in healthy volunteers. Patients of depression may have already underlying psychomotor impairment and it would be difficult to differentiate whether the psychomotor impairment is due to the antidepressant drug or due to the disease condition [9]. According to Wittenborn, the assessment of psychomotor effects of medication in patients is difficult and can be misleading. In patients under treatment symptomatic improvement can yield an improved score on psychomotor test which is not necessarily a consequence of an enhancement of psychomotor behaviour per se [10]. Cognitive impact of antidepressants in depressive patients appears to be the same as in healthy volunteers on single dose administration [11].

Psychomotor performance results from the coordination of sensory and motor system through the integrative and organisational process of brain and central nervous system. The processing of sensory information is influenced by personality, memory, and individual motivation, while the overall function of the integrative mechanism is governed by the state of arousal of the central nervous system. Complex feedback and adaptive systems complete the process by which environmental stimuli produce appropriate, coordinated behavioural responses. Detection, perception and recognition of a stimulus are, three levels of information processing, which together account for the majority of the sensory activity of the organism. Change in the level of activity of the sensory input brought about by the administration of a drug can have a disruptive effect on total psychomotor performance and reduce the responsiveness of an individual to changes in his environment. The perceptual processing of sensory information can be readily assessed by using a letter or number cancellation task, providing the motor components are not too great. Recognising sensory information involves the matching of the perceptual figuration with a pre-existing or stored stimulus pattern. The identification of current information and matching with previously stored, is obviously a function of sensory recoding and processing systems. Recoding and recognition of sensory information is well illustrated in the performance of digit symbol substitution test. Central processing is a major component of central nervous system's activity. The most reliable and certainly the easiest way of measuring cognitive 'processing' ability are by an arithmetic or number handling task [3].

In this study per se effect of the drugs was noted as well as inter-drug comparison of psychomotor effects was done. In the present study nortriptyline was used as positive internal control to impair performance on psychomotor test and to establish validity of test battery. So, nortriptyline in the dose of 50mg significantly impaired psychomotor functions. Nortriptyline caused adverse effects of drowsiness and psychomotor impairment due to its anti-histaminic, anti-muscarinic and α1 antagonist action [12]. The findings are in agreement with other studies [13,14,15].

Tianeptine is a newly introduced antidepressant and it acts by a novel mechanism i.e. it promotes reuptake of serotonin. In stress conditions,

serotonin which is released from neuronal store activates hypothalamo-pituitary adrenal (HPA) axis and the antidepressant activity of tianeptine is due to blockade of stress induced activation of HPA axis. It does not bind or has low affinity for α1, α2, ß-adrenergic receptor, GABA, glutamate, dopamine D2, benzodiazepine, muscarinic, nicotinic, adenosine A1 and A2 receptors [16].

Ridout and Hindmarch found no significant effect on psychometric tests such as break reaction time (BRT), choice reaction time (CRT), CFFT line analogue rating scale and wrist actigraphy with single dose of tianeptine 12.5mg and 37.5mg at -1, 1, 2, 4 and 5 hours post dose [17]. Toon et al. reported improvement of attention with tianeptine 37.5mg per day given for 4 days and of mood when it was given with oxazepam 30mg per day [18]. Saletu found early improvement in thymopsychic (mood, effect, wakefulness) and noopsychic (attention, memory) parameters during the 8 hours test period after single 25mg dose of tianeptine [19]. Thus, the findings of effect of tianeptine on various psychometric tests in our study substantiate those of the other workers. The side effects observed in the study are expected and also reported in literature [12,18].

Most often depression is associated with cognitive and psychomotor impairment. This cognitive dysfunction may be more debilitating sequelae of the illness causing reduced quality of life, poor compliance and risk of accidents. Hence while prescribing antidepressant drugs, psychomotor effects and side effect profile should be kept in mind.

Key Points

- Nortriptyline significantly depresses the objective and subjective psychometric performance in comparison to placebo and tianeptine.
- There was no evidence of impairment of psychometric tests by tianeptine in the present study.
- Dryness of mouth is the reported adverse effect of nortriptyline whereas; headache and dryness of mouth are observed with tianeptine.
- Tianeptine is a better alternative to nortriptyline as it causes minimal psychomotor impairment.

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