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Acute Effects of Citalopram and Imipramine on Psychomotor Performance in Healthy Volunteers: A Comparative Study

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Abstract:

Aim: To evaluate and compare the acute effects of citalopram and imipramine on psychomotor performance in healthy volunteers.

Methods: 30 healthy male participants (20-35 yrs) received single oral doses of citalopram (20 mg), imipramine (50 mg) and placebo in a double blind, cross over study. A battery of objective (critical flicker fusion, digit letter substitution, six letter cancellation, arithmetic ability, digit span and hand steadiness) and subjective (visual analogue scales) tests of psychomotor functions were performed at 0, 1.5 and 3 hrs.

Results: Imipramine (tricyclic antidepressant) caused significant ($p < 0.001$) impairment of psychomotor functions at 3 hrs. In contrast, citalopram (selective serotonin reuptake inhibitor) did not produce detrimental effect on the objective and subjective assessment of psychomotor functions, but showed positive effects on critical flicker fusion threshold ($p < 0.05$ at 1.5 hr and $p < 0.001$ at 3 hrs), on digit letter substitution score ($p < 0.001$ at 3 hrs) and on six letter cancellation score ($p < 0.01$ at 3 hrs).

Conclusion: Imipramine possesses detrimental effect on psychomotor performance of the recipients. In contrast, citalopram do not impair psychomotor performance and may improve it.

Key words: *antidepressants, citalopram, imipramine, psychomotor performance*

INTRODUCTION

Behavioral toxicity is a side effect of many drugs and can be defined as the extent to which a drug disrupts those abilities necessary for performance of the psychomotor and cognitive tasks of everyday life [1].

Psychomotor performance results from the coordination of sensory and motor system through the intergrative and organizational process of brain and central nervous system. Central, sensory and motor components of psychomotor performance can be evaluated by standard validated battery of psychomotor r function tests [2].

Several psychotropic drugs may adversely affect work performance that depends on psychomotor activities. Measuring the effects of a drug on psychomotor and cognitive ability is important to obtain an objective assessment of its psychotropic actions & to identify potential interference with every day activities such as driving, operating machinery & performing daily routine tasks [2].

Tricyclic antidepressants (TCAs) like imipramine, amitriptyline and clomipramine apart from inhibiting reuptake of serotonin (5-HT) & norepinephrine, also antagonize α_1 adrenergic, H_1 histaminic and muscarinic cholinergic receptors, and thus compromise the quality of life of the patients by causing psychomotor impairment, somnolence, and tremors etc. [3].

Increased understanding of neurotransmitter & receptor interactions led to the development of newer antidepressants with more selective activity like selective serotonin reuptake inhibitors (SSRIs).

Citalopram is a newer SSRI. It would be interesting t o see whether citalopram has any central effects that could interfere with the psychomotor functions and thus with the patients ability to perform skilled works or daily routine activities.

MATERIAL & METHODS

Subjects: 30 healthy male participants of the age group of 20-35 yrs, willing to participate were included in the study. Each subject completed a brief medical history and underwent a complete physical examination before inclusion in the study. All the participants were explained the general aim of the study and the risk of possible untoward side effects. All the participants gave their written informed consent.

Drugs: Single oral doses of citalopram (20mg), imipramine (50mg) and placebo were administered in identical capsules to the participants.

Experimental design: A double blind, placebo controlled cross over study was carried out in the Department of Pharmacology, Government Medical College, Nagpur. The study protocol was approved by institutional ethics committee.

Participants underwent training sessions with the battery of psychomotor function tests to preclude

any learning curve effect. Participants were divided into five groups. Each group consists of six participants, received medication in a double blind Latin square design. Washout period of one week was given between two interventions. On the study day, participants were asked to have breakfast at 8 a.m. and report to laboratory at 10 a.m. After 15 minutes of acclimatization period, the control parameters were tested between 10.15 a.m. to 10.45 a.m. The test drug was given along with a glass of water at 11 a.m. Thereafter, the psychomotor functions were tested 1.5 & 3 hrs post drug. It took 15 min for a participant to complete a series of tests.

Participants were not allowed to eat any food during study time, however drinking water was allowed. They were not allowed to move out of laboratory till completion of the study. Participants were strictly instructed to avoid mechanical work or driving vehicle. Participants were instructed to refrain from smoking, drinking alcohol or taking any medication one week prior and during the study period.

Tests for psychomotor functions:

A. Objective assessment

1. Critical flicker fusion test (CFFT) [4]**:** Critical flicker fusion (CFF) threshold is the assessment of choice for investigating the change in overall integrative activity of the central nervous system (CNS) produced by psychoactive drugs. The critical flicker frequency may be defined as the fastest rate at which a flickering source of light appears to be flickering as opposed to being steady or as the point at which a flickering light gives rise to the subjective sensation of a steady light.

The CFF threshold was assessed by CFF apparatus. The apparatus is basically a viewing tube, at the end of which a green/red circle of light capable of flickering at the rate of 5-50 cycles/sec, is projected on to a non reflecting surface. Green light with 100% brightness was selected. The participants were allowed adaptation to a least flickering frequency for 1 min. After this period of accommodation the frequency was progressively increased or decreased until the subject reported a change in his perception of flicker (i.e. from fusion to flicker and from flicker to fusion). Six such readings were taken (three with increasing frequency & three with decreasing frequency). The mean of the six observed CFF frequency (hertz) was noted.

2. Digit letter substitution test (DLST) [5]: This test assesses recognition capacity of brain. Participants were provided a working sheet consisting of 144 digits arranged randomly in nine rows. Participants were required to substitute as many digits with letters from the key as possible within 2 minutes. The letters in the key and the digits in the working section were changed randomly to avoid the effect of memory on repeated testing. Scoring was done on the basis of number of correct substitution.

3. Six letter cancellation test (6 LCT) [6]**:** This test assesses perceptual processing of sensory information. Participants were provided a working sheet, consisting of 260 randomized letters arranged in 20 rows. Participants had to cancel as many target letters from key, as possible within 90 seconds. The six letters in the key were changed randomly to avoid the effect of memory or practice during repeated administration of test. Scoring was done on the basis of number of correct cancellations.

4. Arithmetic ability test (AAT) [7]: This is a test for assessing central processing capacity. There were four problems of mathematical calculation i.e. addition, substraction, multiplication & division, randomly distributed in 4 rows and 5 columns. Participants were asked to solve the problems either row wise or column wise in two minutes. Two points were awarded for each correct division and multiplication, whereas one point each for correct addition and substraction. Total score was calculated.

5. Digit span test (DST) [8]: It is a useful measure for estimating drug effect on short term memory. After hearing a nine digit sequence, participants were asked to write down it after 10 seconds, in the sequence dictated. The digits 1 to 9 were used randomly without repetition in one sequence. Such five different sequences were repeated at each testing. Marking was done depending upon the placement of correct digit in the same sequence that was dictated.

6. Hand steadiness test (HST) [9]: It is a sensitive test for evaluating the effect of drug on fine motor activity. Hand steadiness was tested by steadiness tester – a device with a series of holes (Whipple's holes) of varying size (9 holes with diameter ranging from 4 mm to 19 mm), a stylus and a digital counter. The

participant was asked to insert the whole metallic portion of stylus into the target hole without touching the sides of the hole starting from the largest hole and moving towards the smaller ones at uniform speed. The error (E) recorded by the digital counter i.e. number of times the stylus touched the side of the holes was noted. Stop watch was used to record the time (T) to finish the task. Performance index was calculated as a product of T and E. The average of three such readings was calculated.

B. Subjective assessment

7. Visual analogue scales [10]: Psychoactive drugs can act upon the mood, feelings and status of awareness of recipients. The analogue scales are used to rate the subjective mood or feelings and are useful in detecting sedative drug effects. Two visual analogue scales with opposite mood adjectives (extremely sleepy--- wide awake and tired --- active) were used. The participants were asked to appropriately mark on the scale depending upon their current state of feelings.

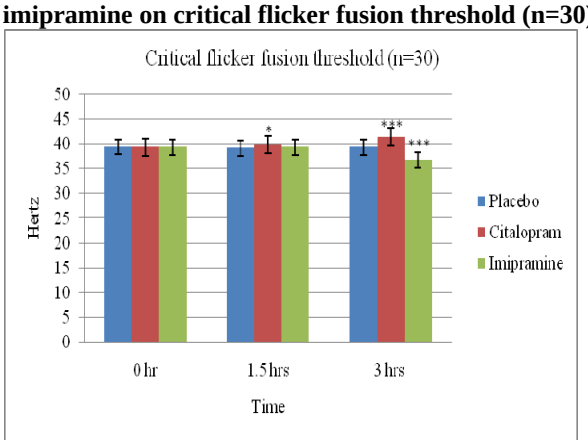
Statistical analysis: At the level of significance α = 5% and power 95%, the sample size of 30 was calculated. Within group analysis was done by one way ANOVA (analysis of variance) with repeated measure, followed by posthoc Tukey Kramer test. Between groups analysis was performed by one way ANOVA followed by posthoc Tukey Kramer test. All statistical tests were performed at 5% significance level.

RESULTS & DISCUSSION

Effective pharmacotherapy of depression started with the advent of tricyclic antidepressants. However adverse effects including psychomotor impairment were a concern. Newer antidepressants with more selective actions like SSRIs were developed later on. Citalopram is a SSRI and there are very few studies on the effects of this drug on psychomotor performance. The present study is on the effects of citalopram on psychomotor functions in healthy volunteers. It is a double blind, crossover study. In this study per se effects of the drugs were noted as well as inter drug comparison of psychomotor effects was done. Both a negative (placebo) and a positive control (imipramine) were used to assess both the sensitivity of the tests used and the effects of citalopram.

At baseline, mean ± SD values of critical flicker fusion (CFF) threshold were similar with placebo (39.38 ± 1.7 Hz), imipramine (39.3 ± 1.4 Hz) and citalopram (39.3 ± 1.6 Hz). In the present study imipramine 50 mg significantly reduced critical flicker fusion (CFF) threshold ($p<0.001$) at 3 hrs (Figure 1), which is suggestive of impairment of overall integrative capacity of brain. This finding is in accord with the previous study in which significant reduction in CFF threshold was found with 50 mg imipramine [11].

Figure 1: Effect of placebo, citalopram and imipramine on critical flicker fusion threshold (n=30)



Values in mean ± S.D., * $p < 0.05$, *** $p < 0.001$ (one way analysis of variance with repeated measure followed by Tukey Kramer test)

Detrimental effect of imipramine on CFF threshold was also found when compared with citalopram ($p<0.05$ at 1.5 hrs & $p<0.001$ at 3 hrs) and placebo ($p<0.001$ at 3 hrs) (Table 1). Imipramine, apart from inhibiting reuptake of 5-HT and NE also antagonize histaminic H1 and muscarinic receptors which is responsible for sedation and psychomotor impairment.

Citalopram significantly increased CFF threshold at 1.5 hrs ($p<0.05$) and 3 hrs ($p<0.001$) (Figure 1). Increase in CFF threshold was also observed with citalopram when compared with placebo at 1.5 hrs ($p<0.01$) and 3 hrs ($p<0.001$) (Table 1). Psychopharmacological studies have demonstrated an enhancement of sustained attention and improved control of motor responses to sensory stimuli as well as improved efficiency of information processing with enhancement of serotonergic function [12].

It is suggested that SSRIs affect cognition and psychomotor performance differentially depending upon their relative potency and selectivity for 5-HT (serotonin) uptake inhibition [13]. It is reported that SSRIs that had positive effects have higher potencies for serotonin uptake

Table 1: Mean difference at 1.5 hrs and 3 hrs (Between groups analysis)

Interventions	*Mean difference at 1.5 hrs*	*Mean difference at 3 hrs*
CFF threshold		
Placebo vs Imipramine	-0.26003 ± 0.0142	-2.4736 ± 0.348***
Placebo vs Citalopram	0.8434 ± 0.0006**	2.09330 ± 0.6642***
Citalopram vs Imipramine	-0.58337 ± 0.0136*	-4.567 ± 0.3154***
Digit letter substitution test		
Placebo vs Imipramine	-3.2337 ± 1.021	-26.563 ± 13.832***
Placebo vs Citalopram	1.6663 ± 1.617	5.767 ± 9.96
Citalopram vs Imipramine	-4.90 ± 2.638*	-32.33 ± 3.88***
Six letter cancellation test		
Placebo vs Imipramine	-0.9 ± 0.424	-10.567 ± 0.490***
Placebo vs Citalopram	0.0667 ± 1.391	2.633 ± 4.573**
Citalopram vs Imipramine	-0.833 ± 1.967	-13.2 ± 0.083***
Arithmetic ability test		
Placebo vs Imipramine	-0.8337 ± 0.244	-6.5337 ± 0.710***
Placebo vs Citalopram	-0.6667 ± 0.46	-0.333 3± 0.485
Citalopram vs Imipramine	-0.20 ± 0.216	-6.867 ± 0.225***
Digit span test		
Placebo vs Imipramine	-5.167 ± 2.769	-19.6333 ± 5.046***
Placebo vs Citalopram	-1.7663 ± 2.058	2.9667 ± 2.665
Citalopram vs Imipramine	-6.933 ± 0.711**	-22.567 ± 2.383***
Hand steadiness test		
Placebo vs Imipramine	2 ± 30.26	186.333 ± 48.86***
Placebo vs Citalopram	-7.667 ± 7.90	6.333 ± 8.49
Citalopram vs Imipramine	5.667 ± 38.16	180 ± 57.35***
Visual analogue scale 1		
Placebo vs Imipramine	-6.70 ± 2.93	-35.136 ± 1.118***
Placebo vs Citalopram	-2.80 ± 2.658	1.5663 ± 0.224
Citalopram vs Imipramine	-3.9 ± 5.588	-36.703 ± 1.342***
Visual analogue scale 2		
Placebo vs Imipramine	-1.333 ± 1.65	-34.503 ± 01.20***
Placebo vs Citalopram	-1.133 ± 4.116	-4.577 ± 9.56
Citalopram vs Imipramine	-0.3 ± 5.677	-39.07 ± 2.76***

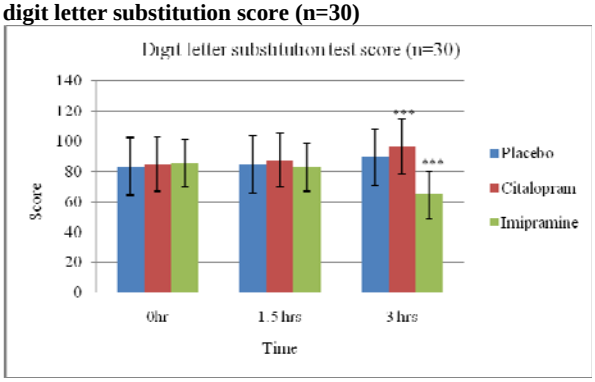
* p < 0.05, ** p < 0.01, *** p < 0.001 (one way analysis of variance followed by posthoc Tukey Kramers test

inhibition (sertraline, 0.19 nM; paroxetine,0.29 nM; citalopram, 1.8nM) than those that had neutral effects (fluvoxamine, 3.8nM; fluoxetine, 6.8 nM) [12,13]. Moreover, citalopram has low affinity for H1 histaminic, dopamine D2, benzodiazepine and muscarinic receptors. Results of the present study suggest that imipramine impair information processing and overall intergrative capacity, whereas citalopram improves it.

In the present study, imipramine showed significant reduction in digit letter substitution test (DLST) score at 3 hrs ($p<0.001$) (Figure 2), which confirms the findings of previous studies [14, 15]. Decrement in DLST scores was also observed in comparison with citalopram ($p<0.05$ at 1.5 hrs, $p<0.001$ at 3 hrs) and placebo ($p<0.001$ at 3 hrs) (Table 1). These results suggest that imipramine also has the potential to affect recognition and recoding capacity.

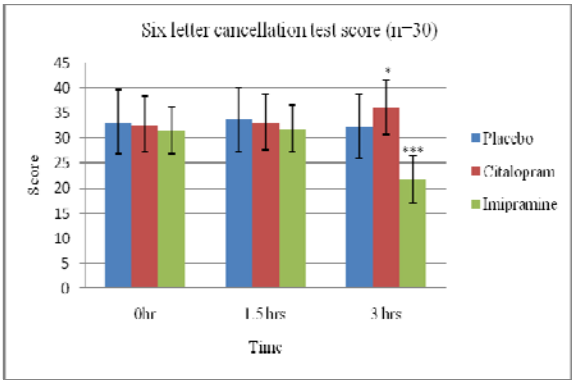
Whereas citalopram showed significant ($p<0.001$) increase in DLST score at 3 hrs. A trend toward increment in score was also observed at 3 hrs when compared with placebo but could not reach statistically significant level (Figure 2, Table 1). In a similar type of study, significant increase in symbol copying was found following a single dose of citalopram 20 mg [16]. Our findings suggest that citalopram can improve recognition and recoding capacity of brain due to enhanced serotonergic neurotransmission.

Figure 2: Effect of placebo, citalopram and imipramine on digit letter substitution score (n=30)



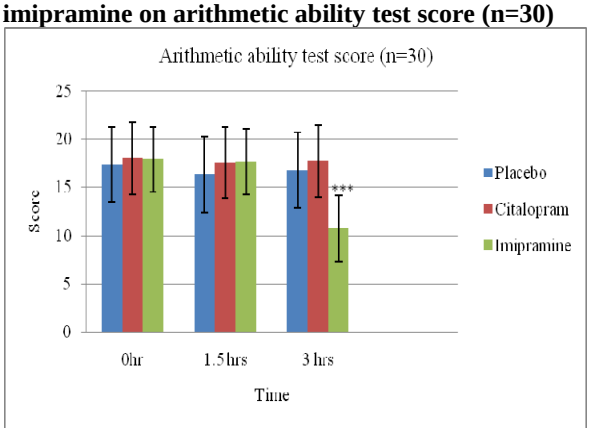
Values in mean ± S.D., *** p < 0.001 (one way analysis of variance with repeated measure followed by Tukey Kramer test)

Figure 3: Effect of placebo, citalopram and imipramine on six letter cancellation test score (n=30)



Values in mean ± S.D., * p < 0.05, *** p < 0.001 (one way analysis of variance with repeated measure followed by Tukey Kramer test)

Figure 4: Effect of placebo, citalopram and imipramine on arithmetic ability test score (n=30)



Values in mean ± S.D., *** p < 0.001 (one way analysis of variance with repeated measure followed by Tukey Kramer test)

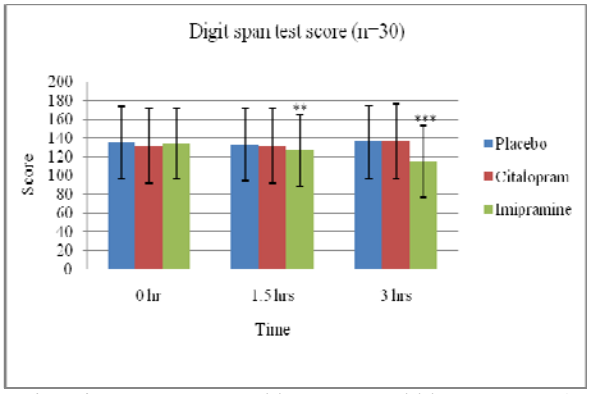
Imipramine significantly (p<0.001) reduced scores of six letter cancellation test (SLCT) and arithmetic ability test at 3 hrs independently and in comparison with placebo and citalopram, suggesting impairment of sensory and central processing mechanism of perception respectively (Figure 3 and 4, Table 1). A previous study had also found reduction in numerical ability with imipramine [14]. On the contrary, citalopram showed significant (p<0.01) improvement in SLCT scores in comparison with placebo at 3 hrs, (Figure 3, Table 1) which is suggestive of improvement in sensory processing mechanism due to increased 5-HT (serotonin) neurotransmission. Improvement in CFF threshold, DLST and SLCT scores observed with citalopram correlate with its peak plasma concentration [17]. However citalopram did not produce significant effect on arithmetic ability test score suggesting its lack of effect on central processing mechanism and non sedative property.

In the present study, imipramine significantly reduced digit span test (DST) score at 1.5 hrs (p<0.01) and 3 hrs (p<0.001) (Figure 5). These reductions in score were also significant when compared with placebo at 3 hrs (p<0.001) and citalopram at 1.5 hrs (p<0.01) and 3 hrs (p<0.001) (Table 1). The central cholinergic system plays an important role in the memory function and imipramine has antimuscarinic activity. This could be the reason for impairment of memory with imipramine. Although impairment of memory has been reported with 150 mg imipramine, the present study found memory impairment with 50 mg. This difference in doses producing detrimental effect on memory can be explained by a research study which found no linear correlation between plasma levels of tricyclics and psychomotor performance [13].

Citalopram and placebo did not produce detrimental effect on DST score (Figure 5). Citalopram is highly selective in its activity and has low affinity for muscarinic receptors, which could be the reason for its lack of detrimental effect on memory.

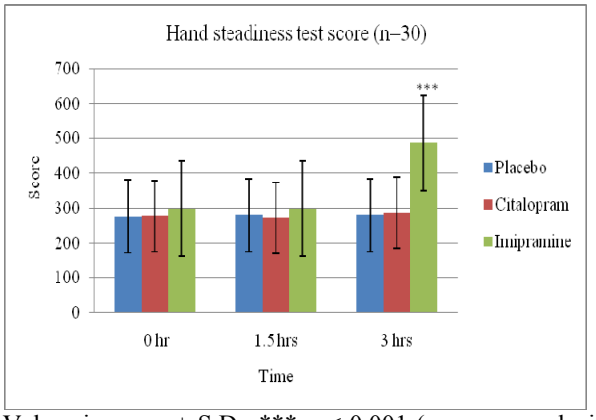
Imipramine has been reported to impair the tasks involving sonsorimotor coordination [18]. The present study found significant (p<0.001) increase in errors during hand steadiness test with imipramine independently as well as in comparison with citalopram and placebo, at 3 hrs (Figure 6, Table 1).

Figure 5: Effect of placebo, citalopram and imipramine on digit span test score (n=30)



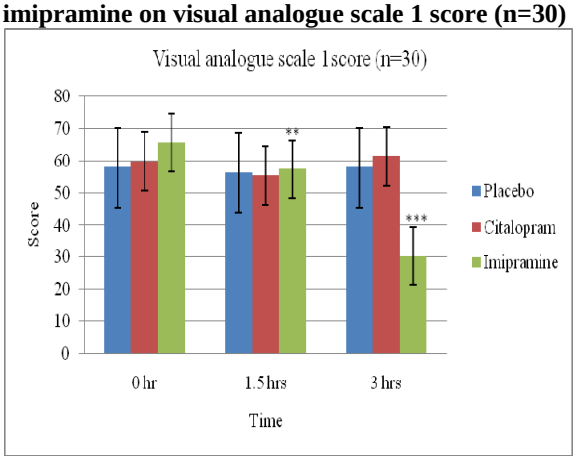
Values in mean ± S.D., ** p < 0.01, *** p < 0.001 (one way analysis of variance with repeated measure followed by Tukey Kramer test)

Figure 6: Effect of placebo, citalopram and imipramine on hand steadiness test score (n=30)



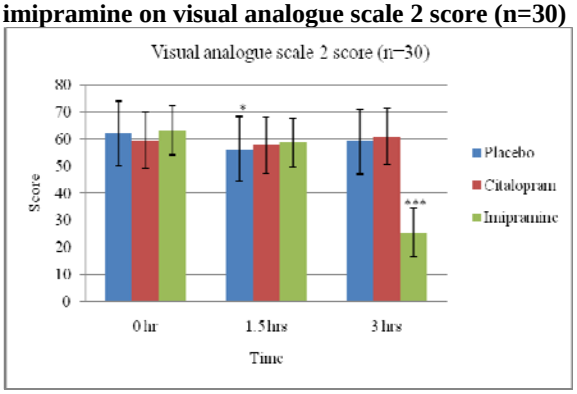
Values in mean ± S.D., *** p < 0.001 (one way analysis of variance with repeated measure followed by Tukey Kramer test)

Figure 7: Effect of placebo, citalopram and imipramine on visual analogue scale 1 score (n=30)



Values in mean ± S.D., ** p < 0.01, *** p < 0.001 (one way analysis of variance with repeated measure followed by Tukey Kramer test)

Figure 8: Effect of placebo, citalopram and imipramine on visual analogue scale 2 score (n=30)



Values in mean ± S.D., * p < 0.05, *** p < 0.001 (one way analysis of variance with repeated measure followed by Tukey Kramer test)

Psychomotor performance is the result of coordination of sensory and motor system through intergrative and organizational process of the brain and central nervous system [2]. As imipramine has shown detrimental effects on sensory (DLST and SLCT) and central processing (AAT) mechanism, this could also be the reason for impairment of fine motor performance with imipramine during hand steadiness test. The results with citalopram and placebo were not significant suggesting lack of adverse effect of citalopram on fine motor activity.

A significant shift in visual analogue scale 1 towards sleepiness was observed with imipramine at 1.5 hrs ($p<0.01$) and 3 hrs ($p<0.001$) (Figure 7). A shift in visual analogue scale 2 towards tiredness was observed with imipramine which was non significant at 1.5 hrs but reached to statistically significant level at 3 hrs ($p<0.001$) (Figure 8). Group analysis also found significant ($p<0.001$) change in mean difference with imipramine at 3 hrs when compared to citalopram and placebo (Table 1). A trend towards increased awakeness and activity (visual analogue scale 1 and 2 respectively) was observed with citalopram at 3 hrs but could not reach statistically significant level. A shift in scale towards tiredness was also observed with placebo at 1.5 hrs ($p<0.05$) but this became non significant at 3 hrs (Figure 8).

Most of the detrimental effects of imipramine were found at 3 hrs in the present study which correlates with its peak plasma concentration [19]. Majority of the patients who received imipramine complained of drowsiness which is also reflected in subjective visual analogue scales. Single dose of citalopram did not induce psychomotor impairment when compared with placebo. Subjective findings with citalopram correlated with the objective assessment.

Measuring the acute effects of a drug on psychomotor performance in healthy subjects is a validated method for evaluating sedative nature of the drug. However, it should be noted that the results of our acute experiment may not be directly applicable to patients who are treated chronically over periods of months and years when the development of adaptive changes in the receptors and neuroeffector systems can be anticipated.

Although citalopram has shown improvement in overall integrative and sensory processing mechanism of psychomotor performance, it requires similar evaluation in depressive patients to establish its beneficial effect on psychomotor performance.

CONCLUSION

The present study conducted on healthy volunteers found that imipramine, which is a prototype of tricyclic antidepressants, possesses detrimental effects on psychomotor performance of the recipients. In contrast, citalopram (a very selective SSRI) lacks the potential to impair psychomotor performance.

In addition to lowering the risk of psychomotor impairment, citalopram could be a useful antidepressant to that subset of depressive patients whose psychomotor performance is already compromised. This is subject to further confirmation from similar study in patients with major depression.

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