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Original Article

Effects of Tolperisone on Psychomotor Performance and Vigilance Functions on Normal Healthy Volunteers

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ABSTRACT

Background: Tolperisone is a central muscle relaxant drug that principally used for treatment of multiple neurological disorders that causing muscle spasticity also, it indicated for various rheumatologic disorders due to relative analgesic effect. Aims: the aim of present study was estimation the effects of tolperisone on the psychomotor performance on normal healthy volunteers. **Subjects and Methods**: Twenty two medical college students (15 males and 6 females) with age ranged from 22-23 years was randomly selected are enrolled in this study. The enrolled subjects were encouraged to practice on psychomotor performance tester prior the conductance of the study to reach a good expertise level with this device. Then assessment of psychomotor reaction time performances and assessment of psychomotor vigilance performances before and after tolperisone single dose 50 mg. **Results**: Tolperisone single dose leads to insignificant effect on total reaction time, recognition reaction time p >0.05, but it prolog the movement reaction time from 320.54±44.63 to 347.16±29.67 ms significantly p=0.034. Moreover, tolperisone in the present study revealed insignificant effect on vigilance parameters p >0.05. **Conclusion**: Central muscle relaxant effect of tolperison on normal healthy volunteers produced prolongation in motor reaction time without central depressant effect on vigilance and arousal capability.

Keywords: Tolperisone, vigilance, psychomotor performance

1. INTRODUCTION

Tolperisone is a central muscle relaxant drug that is principally used for treatment of multiple neurological disorders that causing muscle spasticity also, it indicated for various rheumatologic disorders due to relative analgesic effect.[1] Animal model study demonstrated that tolperisone leads to significant desirable muscle relaxant effects without

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significant central nervous system depressant effect compared to other central muscle relaxant agents like benzodiazepine and baclofen.[2] Tolperisone and related agents have a potent local anesthetic effect due to membrane stabilizing property on the afferent and peripheral neurons that inhibits propagation of action potential of both C and A nerve fibers.[3]

The main mechanisms of tolperisone are inhibition of voltage gated sodium and calcium channels causing reduction in sodium and calcium neuronal currents, additionally it may inhibit voltage gated potassium channels at higher dose causing inhibition of spinal reflex actions.[4] Previous electrophysiological study revealed that tolperisone inhibits voltage gated channels at cerebral, cerebellar, dorsal root ganglion neurons with potential modulation on cortical synaptic neurons.[5]

Moreover, toperisone is regarded as a potent inhibitor for monosynaptic and weak inhibitor for polysynaptic reflexes with dose-dependent inhibition of flexor reflexes via suppression of noradrenergeic-descending and reticulo-spinal tracts at spinal cord leading to the reduction in pain transmission .[6]

Furthermore, it preferentially blocks voltage gated sodium channels type (Nav1.2, Nav1.3, Nav1.7, and Nav1.8) at somato-sensory and prefrontal cortex causing a reduction in cortico-spinal reaction time .[7]

Since, human psychomotor performance depending on the audio-visual stimuli and individual performance that is interconnected at different spinal and supra-spinal levels for speed and accurateness of central cognitive capacity.[8] Indeed, psychomotor performance is mainly articulated by stimulus action, receptor activation, afferent conduction, spinal transmission and then data processing at cortical level [9] , thus slowing at any of these steps due to voltage gated channel inhibition by tolperisone may affect the speed of human psychomotor performance, therefore the aim of present study was estimation the effects of tolperisone on the psychomotor performance on normal healthy volunteers.

2. MATERIALS AND METHODS

This study was done in Department of Clinical Pharmacology and Therapeutic, College of Medicine, Al-Mustansiriyia University, Baghdad-Iraq 2016. This study was approved by professional scientific committee in College of Medicine, Al-Mustansiriyia University. Verbal consent was obtained from all enrolled participants. Twenty one medical college students (15 males and 6 females) with age ranged from 22-23 years was randomly selected were enrolled in this study. The enrolled subjects were encouraged to practice on psychomotor performance tester prior the conductance of the study to reach a good expertise level with this device.

Any volunteers with eyeglasses, current medications, somatic or psychiatric disorders were excluded from this study.

Assessment of psychomotor reaction time performances

Each volunteer sit in a comfortable position about 75-100cm from the tester at well-lighted room, then index finger was putted in an urgent position for pressing any illuminated red light on the flat panel as soon as possible, when the testing began the red light will appeared on the panel and the volunteer will press it rapidly, this trial was repeated five time, the mean of five readings will appears on the digital screen.

Leeds battery psychomotor tester measures the followings:

- Total reaction time (TRT): is the total time in milliseconds from starting the stimuli to the end of the response.
- Recognition reaction time (RRT): is the total time in milliseconds for recognition the stimuli.
- Movement reaction time (MRT): is the total time in milliseconds from the end of recognition of stimuli to the end of motor action.

Assessment of psychomotor vigilance performances

Each volunteer sit in a comfortable position about 75-100cm from the tester at dim-lighted room, then thumb finger was putted in an urgent position for pressing the key when the four illuminated red light at the top vertical panel to be fused or flickered .

When the illuminated red light changed from flickering to steady light it represent Critical Fusion Frequency Threshold ($CFFT^A$) or ascending frequency, but when the illuminated red light changed from steady light to flickering light it represent Critical Flicker Frequency Threshold ($CFFT^D$) or descending frequency these was measured in Hz after taken the mean of five consecutive readings .

Better $CFFT^A$ results are > 30 Hz, better $CFFT^D$ results are <30 Hz. The summation of $CFFT^A$ and $CFFT^D$ dividing by two represent Critical Flicker-Fusion Frequency Threshold (CFFFT).[10]

$CFFT^A$, $CFFT^D$ and CFFFT reflect subject arousal activity while TRT, RRT and MRT reflects subjects cognitive processing activity.[11]

Psychomotor reaction time and vigilance performances were measured before and after two hours from taken single dose of tolperisone 50mg (tolpres DUNG-ltd).

All measured procedures were done at morning 9.00 am.

Statistical analysis

Data presented as mean± SD the paired t- test was used to detect the significance of differences before and after single dose of tolperisone regarding *p* value less than 0.05 as significance.

3. RESULTS

Tolperisone single dose leads to insignificant effect on total reaction time and recognition reaction time $p > 0.05$, but it prolog the movement reaction time from 320.54±44.63 to 347.16±29.67 ms significantly $p=0.034$. Moreover, tolperisone in the present study revealed insignificant effect on vigilance parameters p >0.05 table (1).

Table 1: effects of tolperisone on psychomotor reaction time and vigilance on normal healthy volunteers

Variables	Before (n=21)	After (n=21)	t	95% CI	*P*
TRT (ms)	675.66±33.76	673.72±34.88	-	-23.3488-	0.85
RRT(ms)	354.12±23.99	344.56±22.74	0.183	19.4688	0.19
MRT(ms)	320.54±44.63	347.16±29.67	-	-24.1384-	0.034*
CFFT^{A} (Hz)	33.65±6.83	33.88±6.99	1.325	5.0184	0.91
CFFT^{D}(Hz)	29.44±7.33	29.88±6.45	2.191	1.9839-	0.83
CFFFT(Hz)	31.45±6.11	31.88±6.33	0.108	49.2561	0.82
			0.207	-4.0802-	
			0.224	4.5402	
				-3.8662-	
				4.7462	
				-3.4501-	
				4.3101	

*p <0.05, data expressed as mean± SD, TRT: Total reaction time; RRT: Recognition reaction time; MRT: Movement reaction time; CFFT^{A}: Critical Fusion Frequency Threshold; CFFT^{D}: Critical Flicker Frequency Threshold; CFFFT: Critical Flicker-Fusion Frequency Threshold.

4. DISCUSSION

The present study demonstrated that tolperisone did not affects central cognitive and vigilance function in normal healthy volunteers as revealed by Dulin *et al*, study which demonstrated that tolperison single or repeated doses did not affect sedation scores and reaction times.[12]

Single dose of tolperisone (50mg) impairs movement reaction time via prolongation of motor reaction time compared to the baseline value as supported by Kocsis *et al* study that revealed tolperisone inhibits spinal monosynaptic and polysynaptic reflexes causing reduction in spinal processing for afferent and efferent stimuli which *per se* reflecting the prolongation in movement reaction time .[13]

Moreover, the present study revealed that tolperison does not impaired vigilance in normal healthy volunteers via preservation of critical flicker fusion frequency threshold values at post-treatment era; this finding is compatible with Stamenoya *et al*., that disclosed non-deteriorating effect of tolperison on cognitive function ifunction even in higher doses in stroke patients .[14]

Additionally, tolperisone may be regarded as neuroprotective agent via blocking voltage gated sodium channel, voltage gated calcium channel and NMDA antagonist that causing significant reduction in neuronal excitotoxicity through selective inhibition of voltage gated sodium channel in over-stimulated neurons,[15] this neuroprotective effects was not demonstrated in the present study may due to small sample size, short duration and/or small drug dose. Furthermore, Al-kuraishy *et al*., demonstrated that single dose of dextromethorphan which is NMDA antagonist with significant sodium and calcium channel blockers led to significant improvement in psychomotor performances [16], but this effects was not showed in the present study regarding the effects of tolperisone.

The minimal central effects of tolperisone on normal healthy volunteers may be explained through selective inhibition of tolperisone on hyper-excitable and depolarized neurons at spinal and cortical levels as in spasticity, [17]thus, tolperisone unlike other central muscle relaxants that acted via inhibition of presynaptic neurotransmitter release with impairment of psychomotor performances it acts through channel inhibition without motor reaction time and psychomotor deteriorations .[18]

The limitations of the present study are small sample size, short duration of study and excluding the gender differences thus; the possibility of significant effects cannot be ruled up in broad scale study. Moreover, Na^{+}-channel activity was not estimated under the effect of tolperisone.

But this study may be regarded the first study that demonstrated a peripheral deteriorating effect of tolperisone in normal healthy volunteers without central depressant effect.

5. CONCLUSION

central muscle relaxant effect of tolperison on normal healthy volunteers produced prolongation in motor reaction time without central depressant effect on vigilance and arousal capability.

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