Original Article

Central Beneficial Effects of Trimetazidine on Psychomotor Performance in Normal Healthy Volunteers

Hayder M. Al-Kuraishy, Ali I. Al-Gareeb

From the Department of Pharmacology, Toxicology and Medicine, College of Medicine, Al-Mustansiriyah University, Baghdad, Iraq

Abstract

Background: Trimetazidine is a fatty oxidation inhibitor, leading to shifting of energy substrate from fatty acid oxidation toward glucose oxidation that leads to the reduction of oxygen requirement. The aims of the present study were to elucidate the effects of trimetazidine on psychomotor performance and vigilance on normal healthy volunteers. **Materials and Methods:** A total of 234 subjects (age 22–25 years) were recruited in this study. The volunteers were randomizing into two groups with 117 volunteers in each group. Group I received an inert starch capsule served as a control, and Group II received trimetazidine tablet 15 mg/day. The duration of therapy was 5 days. Test procedure was done at 9.00 a.m. on the psychomotor tester. Before the drug administration, prescore values were recorded and then after 5 days of therapy, the postscore values were recorded. **Results:** The placebo did not demonstrate a significant effect on all psychomotor performances and flicker-fusion elements ($P > 0.05$). Trimetazidine therapy produced a highly significant effect on all components of psychomotor performances and flicker-fusion parameters ($P < 0.001$) compared with pretreatment era. **Conclusion:** We conclude that trimetazidine improves psychomotor performance and vigilance in normal healthy volunteers through advancing total reaction time and critical flicker-fusion frequency.

Keywords: *Critical flicker-fusion frequency, psychomotor performance, trimetazidine*

Introduction

Trimetazidine (1 (2-3-4 trimethoxybenzyl) piperazine dihydrochloride) is a fatty oxidation inhibitor, blocks β-oxidation long-chain 3-ketoacyl coenzyme A thiolase (the final enzyme in β-oxidation). It leads to the shifting of energy substrate from fatty acid oxidation to the glucose oxidation leading to reduction of oxygen requirement since fatty acid oxidation required more oxygen than glucose oxidation.[1]

Through optimizing the oxygen demands, trimetazidine is mainly used as anti-ischemic agent and improves heart function since it does not affect blood pressure or heart rate.[2] Moreover, trimetazidine inhibited oxidative damage in the mitochondrial membrane that put forth an important cytoprotective and acts as metabolic modulators in ischemic heart disease, gastrointestinal disorders, renal damage, and hepatic ischemia.[3]

In addition, trimetazidine exerts a neuroprotective effect during cerebral ischemia, antinociceptive, and potential antidepressant effects.[4]

Trimetazidine also inhibits lipopolysaccharide-induced brain inflammation in animal model study via upregulation of antioxidant enzymes, provoke axonal regeneration, and myelination and prevents drug-induced hippocampal oxidative damage and experimental brain atrophy.[5,6]

In vivo studies demonstrated that trimetazidine improves brain glucose uptake and prevent cerebral ischemic-reperfusion injury.[7]

They are many approaches that can be utilized to estimate cognitive functions, one of these approaches is done by measuring psychomotor performance.[8] Improvement of psychomotor performances as a result of utilizing nootropic agents has been documented in previous studies while brain depressants like barbiturate, benzodiazepines, sleep medicine, and first generation antihistamine has been shown to influnce psychomotor performance adversely.[9,10]

Our hypothesis was because of trimetazidine improving brain glucose uptake with significant antioxidant effects thus,

How to cite this article: Al-Kuraishy HM, Al-Gareeb AI. Central Beneficial Effects of Trimetazidine on Psychomotor Performance in Normal Healthy Volunteers. Adv Biomed Res 2017;6:69.

Received: September, 2015. **Accepted:** February, 2016.

Address for correspondence:
Dr. Hayder M. Al-Kuraishy, Department of Pharmacology, Toxicology and Medicine, College of Medicine, Al-Mustansiriyah University, P.O. Box 14132, Baghdad, Iraq. E-mail: hayderm36@yahoo.com

Access this article online

Website: www.advbiores.net

DOI: 10.4103/2277-9175.190994

Quick Response Code:

trimetazidine, may accelerate psychomotor performances and because of these facts, therefore the aims of the present study were to elucidate the effects of trimetazidine on psychomotor performance and vigilance in normal healthy volunteers.

Materials and Methods

This study was carried out at the Department of Clinical Pharmacology, College of Medicine, Al-Mustansiriyah University in Baghdad, Iraq, from May to June 2015. The research was permitted and approved by the Scientific Committee. Informed consent was obtained from all volunteers before starting of the study. The volunteers were in normal health with no history of psychiatric disorders, nonsmoker, nonalcoholic, and the subjects with any disease, even eyeglasses or history of drug intake, were excluded from this study. A total of 234 subjects (age 22–25 years and 120:114 M: F ratio) were recruited in this study.

Before entrance to the experimental research, we advised the volunteers to abstained chocolate, cola drinking, and any caffeinated beverage; all volunteers were familiar with test measures. The research volunteers were randomized into two groups according to a block permuted randomization, with 117 volunteers in each group. Group I received an inert starch capsule served as a control, and Group II received trimetazidine tablet 15 mg/day (vastarel, Servier Phlilippin Inc.). The duration of therapy was 5 days. Test procedure was done at 9.00 a.m. on the psychomotor tester (Zak GmbH.H-D-8346 Simbach/Inn, Germany). Before the drug administration, prescore values were recorded and then after 5 days of therapy, the postscore values were recorded.

Psychomotor estimation was obtained from the following:[11]

- Total reaction time (TRT): Time required (ms) from starting the stimulus to the end of the performance
- Recognition reaction time (RRT): Time required (ms) from starting the stimulus at the beginning of the reaction
- Movement reaction time (MRT): Time required (ms) from starting of motor action to the end of the performance.

TRT and RRT were recorded directly from psychomotor tester whereas MRT was calculated by subtracting RRT from TRT (MRT = TRT − RRT).

- Critical flicker frequency descends (CFFd): Measure time in minutes required for light perception from steady (constant) to flicker (waving) state
- Critical-fusion frequency ascends (CFFa): Measure time in minutes required for light perception from flicker (waving) to steady (constant) state.

Critical flicker-fusion frequency (CFFF) = Flicker frequency + fusion frequency/2.

CFFF measures central sensorimotor integration. RRT measures cortical arousal and vigilance status.

Statistical analysis

Statistical estimation was achieved by paired *t*-test; results are accessible as mean ± standard error. A value of $P < 0.05$ was considered statistically significant.

Results

The placebo did not demonstrate significant effects on all psychomotor performances and flicker-fusion elements ($P > 0.05$) [Table 1].

Trimetazidine therapy produced a highly significant effect on all components of psychomotor performances and flicker-fusion parameters ($P < 0.001$) compared with pretreatment era. Trimetazidine reduced TRT from 761.05 ± 8.02 ms to 666.57 ± 8.45 ms, RRT from 381.66 ± 5.54 ms to 354.40 ± 5.31 ms, MRT from 379.39 ± 3.95 ms to 312.17 ± 6.63 ms, critical fusion frequency (CFFa) from 33.39 ± 0.12 Hz to 34.30 ± 0.13 Hz, critical flicker frequency (CFFd) from 30.76 ± 0.15 Hz to 27.99 ± 0.11 Hz, and CFFF from 32.07 ± 0.11 Hz to 31.14 ± 0.09 Hz [Table 2].

Trimetazidine produced significant effects on psychomotor performance and CFFF regardless of gender, since results of the present study showed insignificant effects between enrolled males and females ($P > 0.05$) on all psychometric parameters, except on MRT there is mild significant differences between males and females ($P = 0.086$) [Table 3].

Discussion

Trimetazidine leads to significant acceleration of psychomotor performance measures compared to placebo after a short period of therapy; additionally it improved CFFF significantly. These findings were supported by Hassanzadeh *et al*.'s (2015) experimental study that demonstrated a stimulant and neuroprotective effect of trimetazidine even in healthy subjects,[5] also Erbas *et al*. demonstrated modulation of rearing and stereotype behavior due to trimetazidine therapy mediated by mesolimbic dopaminergic effects.[12]

Thus, the present study revealed potential effects of trimetazidine in advancing the psychomotor performance in normal, healthy volunteers indicating a positive vigilance effect of trimetazidine in stimulation of arousal pathways also, trimetazidine accelerates CFFF that pointed out to the provoking effects of trimetazidine on sensorimotor integration; since CFFF evaluates cortical activity and central perceptional process of sensorimotor integration while TRT, MRT, and RRT reflect the cerebral arousal activity.[13] Therefore, trimetazidine accelerates brain activity and peripheral sensorimotor reaction through amplifications of these potential measures.

Trimetazidine improves brain activity via neuronal cell protection against intracellular acidosis and preserves brain

Table 1: Placebo effects on psychomotor performance and critical flicker- fusion frequency in normal healthy volunteers

parameters	Before	After	*t*	95% CI	*P*
TRT (ms)	754.39±7.99	746.04±8.05	0.745	−13.85-30.55	0.458
RRT (ms)	376.22±5.63	372.17±5.56	0.518	−11.44-19.55	0.606
MRT (ms)	378.17±3.96	373.87±4.09	0.797	−6.38-14.97	0.427
CFFa (Hz)	33.38±0.12	33.34±0.12	0.230	−0.324-0.410	0.818
CFFd (Hz)	30.77±0.15	30.83±0.15	0.306	−0.446-0.327	0.760
CFFF (Hz)	32.08±0.11	32.08±0.10	-0.058	−0.3005-0.283	0.954

Results are expressed as mean±SE, *P*>0.05; TRT: Total reaction time, RRT: Recognition reaction time, MRT: Movement reaction time, CFFa: Critical-fusion frequency ascending, CFFd: Critical-flicker frequency descending, CFFF: Critical-flicker fusion frequency

Table 2: Trimetazidine effects on psychomotor performances and critical flicker-fusion frequency in normal healthy volunteers

Parameters	Before	After	*t*	95% CI	*P*
TRT (ms)	761.05±8.02	666.57±8.45	9.438	74.65-114.31	<0.0001*
RRT (ms)	381.66±5.54	354.40±5.31	3.660	12.50-42.02	0.0005*
MRT (ms)	379.39±3.95	312.17±6.63	10.261	54.24-80.19	<0.0001*
CFFa (Hz)	33.39±0.12	34.30±0.13	−5.802	−1.25-0.560	<0.0001*
CFFd (Hz)	30.76±0.15	27.99±0.11	15.367	2.40-3.139	<0.0001*
CFFF (Hz)	32.07±0.11	31.14±0.09	6.553	0.6503-1.209	<0.0001*

Results are expressed as mean±SE, *P*>0.05, TRT: total reaction time, RRT: Recognition reaction time, MRT: Movement reaction time, CFFa: Critical-fusion frequency ascending, CFFd: Critical-flicker frequency descending, CFFF: Critical-flicker fusion frequency, *$P<0.001$

Table 3: Gender differences of trimetazidine effects on psychomotor performances and critical flicker- fusion frequency in normal healthy volunteers

Gender	TRT (ms)		RRT (ms)		MRT (ms)		CFFF (Hz)	
	Before	After	Before	After	Before	After	Before	After
Male (*n*=60)	750.18±11.26	662.1±11.75	377.95±7.93	354.63±7.42	372.23±5.70	307.46±9.31	32.10±0.14	31.20±0.14
Female (*n*=57)	772.5±11.33	671.28±12.25	385.57±7.77	354.15±7.68	386.92±5.34	317.12±9.49	32.05±0.16	31.08±0.13
P value	0.789	0.905	0.654	0.723	0.036*	0.385	0.575	0.174

Results are expressed as mean±SE,*$P<0.05$, TRT: Total reaction time, RRT: Recognition reaction time, MRT: Movement reaction time, CFFF: Critical-flicker fusion frequency

mitochondrial membrane, inhibition of lipid peroxidation, regulation of Na/Ca channel, and acceleration of glucose uptake.[14] Moreover, it augments the central Adenosine triphosphate (ATP) level leading to the increasing in the neuronal activity which explained the central stimulating effects of trimetazidine in advancing the psychomotor performance.[15] In addition, trimetazidine regarded as potent modulator of glutaminergic neurotransmission, it antagonized α-amino-3-hydroxy-5-methyl-4-isox azolepropionic acid (AMPA) and kainite, but not at Methylenedioxyamphetamine (MDA) receptors, since MDA antagonist dextromethorphan improves psychomotor in normal healthy volunteers;[16] this gives an idea that trimetazidine may improve psychomotor performance through glutaminergic neurotransmission.

Oxidative stress deteriorates the cognitive function and psychomotor performances, thus it was suggested that antioxidant effects of α-lipoid acid, *Ginkgo biloba*, and piracetam improve working memory and psychomotor performance,[17,18] and because of trimetazidine regarded as a novel antioxidant, it accelerates all measures of psychomotor performance in normal healthy volunteers. Recently, angiotensin receptor blockers improve psychomotor performance through antioxidant effect, augmentation of endogenous antioxidant enzymes, and significant reduction of lipid peroxidations.[19]

Furthermore, neuronal excitation augments brain energy consumption mainly from glucose metabolism and because of the end product of glucose metabolism is acetyl-coenzyme A, which is responsible for synthesis of brain acetylcholine, which *per se* explain the exciting effects of trimetazidine, since, cholinomimetic agents improve positive score in psychometric assessment.[20,21]

In addition, trimetazidine activates brain p38 mitogen-activated protein kinase, which is responsible for preservation of neuronal electrical potential of central and peripheral neurons,[22] which explain the improvement in movement reaction time of psychomotor performances.

Regarding gender differences in the effects of trimetazidine on the psychomotor performances and CFFF, trimetazidine showed insignificant difference and there are higher

variations in critical flicker frequency than the critical fusion frequency also, female volunteers showed a lower score of CFFF than male subjects, these changes may explain by variations in psychometric studies.[23,24]

Conclusion

We conclude that trimetazidine improves psychomotor performance and vigilance in normal healthy volunteers through advancing total reaction time and CFFF.

Acknowledgment

We would like to thank Professor, Dr. Sadiq Alhamash, Dean, College of Medicine, Al-Mustansiriyah University for his great support.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Sandhiya S, Dkhar SA, Pillai AA, George M, Jayaraman B, Chandrasekaran A. Comparison of ranolazine and trimetazidine on glycemic status in diabetic patients with coronary artery disease – A randomized controlled trial. J Clin Diagn Res 2015;9:OC01-5.
2. Peng S, Zhao M, Wan J, Fang Q, Fang D, Li K. The efficacy of trimetazidine on stable angina pectoris: A meta-analysis of randomized clinical trials. Int J Cardiol 2014;177:780-5.
3. Zhang F, Huang B, Zhao Y, Tang S, Xu H, Wang L, *et al.* BNC Protects H9c2 Cardiomyoblasts from H 2 O 2 -Induced Oxidative Injury through ERK1/2 signaling pathway. Evid Based Complement Alternat Med 2013;2013:802784.
4. Iqbal S, Baziany A, Hussain M, James S, Wright S, Hemmings S, *et al.* Trimetazidine as a potential neuroprotectant in transient global ischemia in gerbils: A behavioral and histological study. Brain Res 2002;928:1-7.
5. Hassanzadeh G, Hosseini A, Pasbakhsh P, Akbari M, Ghaffarpour M, Takzare N, *et al.* Trimetazidine prevents oxidative changes induced in a rat model of sporadic type of Alzheimer's disease. Acta Med Iran 2015;53:17-24.
6. Dhote V, Balaraman R. Anti-oxidant activity mediated neuroprotective potential of trimetazidine on focal cerebral ischaemia-reperfusion injury in rats. Clin Exp Pharmacol Physiol 2008;35:630-7.
7. Nowak P, Zagzil T, Konecki J, Szczerbak G, Szkilnik R, Niwinski J, *et al.* Trimetazidine increases [3H] glucose uptake in rat brain. Pharmacol Rep 2006;58:559-61.
8. Hoffman LA, Sklar AL, Nixon SJ. The effects of acute alcohol on psychomotor, set-shifting, and working memory performance in older men and women. Alcohol 2015;49:185-91.
9. Müller U, Rowe JB, Rittman T, Lewis C, Robbins TW, Sahakian BJ. Effects of modafinil on non-verbal cognition, task enjoyment and creative thinking in healthy volunteers. Neuropharmacology 2013;64:490-5.
10. Faraji J, Soltanpour N, Jafari SY, Moeeini R, Pakdel S, Moharreri A, *et al.* Stress inhibits psychomotor performance differently in simple and complex open field environments. Horm Behav 2014;65:66-75.
11. Al-Kuraishy HM, Al-Gareeb AI. Advanced central effects of yohimbine on the cognitive function, psychomotor performance task and working memory: A randomized controlled clinical trial study. Br J Pharm Res 2015;5:328-35.
12. Erbas O, Akseki HS, Eliküçük B, Taskiran D. Antipsychotic-like effect of trimetazidine in a rodent model. ScientificWorldJournal 2013;2013:686304.
13. Mewborn C, Duda B, Lindbergh C, Terry D, Puente A, Bovier E, *et al*. A-09processing speed and critical flicker fusion as mediators of age and cognition. Arch Clin Neuropsychol 2014;29:506-7.
14. Mironova OP, Zarubina IV, Krivoruchko BI, Smirnov AV. Antioxidant effects of amtizol and trimetazidine in brain ischemia. Patol Fiziol Eksp Ter; 2001:13-6.
15. Jain S, Bharal N, Mediratta PK, Sharma KK. Trimetazidine exerts protection against increasing current electroshock seizure test in mice. Seizure 2010;19:300-2.
16. Al-Kuraishy HM, Al-Gareeb AI, Ashor AW. Effect of a single dose of dextromethorphan on psychomotor performance and working memory capacity. Indian J Psychol Med 2012;34:140-3.
17. Al-Kuraishy HM, Al-Gareeb AI, Albuhadilly AK, ALmgoter BM. Modulation effects of piracetam and *Ginkgo biloba* on the cognitive and working memory functions: Psychometric Study. Curr Psychopharmacol 2014;3:87-92.
18. Al-Kuraishy HM, Al-Gareeb AI. Co-administration effects of α-lipoic acid and nucleo CMP on arousal and sensory cortical activity. J Young Pharm 2016;8:12-7.
19. Arora E, Khajuria V, Tandon VR, Sharma A, Choudhary N. Comparative evaluation of aliskiren, ramipril, and losartan on psychomotor performance in healthy volunteers: A preliminary report. Perspect Clin Res 2014;5:190-4.
20. Magistretti PJ, Allaman I. A cellular perspective on brain energy metabolism and functional imaging. Neuron 2015;86:883-901.
21. Gauthier S, Lopez OL, Waldemar G, Jones RW, Cummings J, Zhang R, *et al.* Effects of donepezil on activities of daily living: Integrated analysis of patient data from studies in mild, moderate and severe Alzheimer's disease. Int Psychogeriatr 2010;22:973-83.
22. Khan M, Meduru S, Mostafa M, Khan S, Hideg K, Kuppusamy P. Trimetazidine, administered at the onset of reperfusion, ameliorates myocardial dysfunction and injury by activation of p38 mitogen-activated protein kinase and Akt signaling. J Pharmacol Exp Ther 2010;333:421-9.
23. Bernardi L, Costa VP, Shiroma LO. Flicker perimetry in healthy subjects: Influence of age and gender, learning effect and short-term fluctuation. Arq Bras Oftalmol 2007;70:91-9.
24. Ilamkar KR. Psychomotor retardation, attention deficit and executive dysfunctional in young non-hospitalised un-medicated non-psychotic unipolar depression patients. J Clin Diagn Res 2014;8:124-6.