Piracetam (2-Oxo-Pyrrolidone) Advance and Modulate Central Processing Reaction Time in Normal Healthy Volunteers: Randomized Experimental Study; Single Blind Clinical Trail

Corresponding Author:
Dr. Hayder M Alkuraishy,
Lecturer, Pharmacology, College of Medicine - Iraq

Submitting Author:
Dr. Hayder M Alkuraishy,
Lecturer, Pharmacology, College of Medicine - Iraq

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Author(s): Alkuraishy HM, Mahdi AH, Ashoor AW

Abstract

The present study was designed to show the effect of piracetam (2-Oxo-Pyrrolidone) on simple reaction time. This study involved 30 healthy volunteers which were recruited from medical college students (20 males and 10 females). The reaction time was measured by ruler dropper test method, and by this method we can determine the nerve time, movement time &processing time. This study showed that piracetam significantly improves the processing time of reaction time, which reflects the stimulatory and enhancement effect on cognitive function and vigilance.

Introduction

Simple reaction time determine, the time a subject matter takes to react to single stimulus i.e. one response or one stimulus or many stimuli with one response.(1)

Simple reaction time was used as far as back as the 19th century. Donders (1868) hypothesized that the reaction time could be used to estimate the speed of cognitive procedure, also simple reaction time provided an momentum to the information processing analysis for mental processing study. (2,3) Also difference in the simple reaction time is due to processing time (3).

Furthermore; some authors categorized reaction time into simple or complex, the complex is the time between changeable stimulus and a correspondingly variable response (4,5). The simple reaction time composed of Processing time : is the time for the responder to perceive that a signal has occurred and to make a decision a response, this depend on sensation of stimulus (time takes to detect the sensory input from an object) this quicker for auditory signals and also earlier for signals with high intensity.(6)

Subsequent to that, the sensation and awareness occurred for the stimulus, programming and response selection strong-minded which is the time necessary to decide which of any response making.(7) Movement time : is the time needed for muscle movement which depend on nerve conduction velocity. Therefore, the reaction time depend on three important measures which are processing time (pt), nerve time (nt) and dynamic time (dt). (6) Also, the physiological basis for simple reaction time depends on monoaminergic, cholinergic, serotonergic and aspartanergic system in different parts of central nervous system particularly the prefrontal cortex(8,10).

Selective noradrenalin inhibitor are significantly improved the ability of attention and speed of cognitive function (10) also; dopaminergic system closely associated with intentional performance, also the dopaminergic neurons modulate involuntary attention shifting to mission –disrespectful events and may disrupt the subsequent re-orienting effort to relevant task after distraction(12,13,14) Moreover, many agents and drugs poignant the simple reaction time these are:

Non-sedative antihistamine like fexofenadine and loratidin are not created any deleterious effect on cognition and reaction function(15). CNS stimulant drugs improve the cognition, psychomotor test and reaction time and Nicotine and caffeine recover attention and reduce the effects of depression on reaction time through the upgrading of vigilance(16).

Piracetam (2-oxo-pyrrolidone) is a nootropic drug structurally linked to GABA. It has been used clinically to treat a extensive variety of diseases and circumstances, mainly in treatment of organic brain syndrome, myoclonus, memory mutilation, post-concussional syndrome, dizziness, alcohol withdrawal and cerebrovascular insufficiency.

Piracetam is cerebral homeostatic regularize, neuroprotectant, cerebral metabolic enhancer and brain integrative agent. It enhances brain energy; synaptic membrane, receptor structure and plasticity. It has various effects on glutamate neurotransmission on micromolar levels moreover; piracetam potentiates potassium-induced release of glutamate from hippocampal nerves. Piracetam is between the toxicologically safest drugs ever urbanized even in mega doses. Piracetam has been shown to progress
cognitive performance in animal model system, also it is reported to be used extensively as a sign of humanizing cognitive purpose in children with Down syndrome (17,18) treatment of young and aged rats with piracetam appreciably augmented membrane fluidity in some brain area, this supporter that some of the pharmacological properties of piracetam can be explained by its effect on membrane fluidity, in addition piracetam was devoid of effect on the performance of young animals but dose vulnerably decline the choice reaction time, this propose that piracetam dose not effect short term memory but may make possible choice behavior (19) Piracetam improves the function of the neurotransmitter acetylcholine via muscarinic cholinergic receptors which are implicated in memory processes. Furthermore, Piracetam may have an effect on NMDA glutamate receptors which are involved with learning and memory processes. Piracetam may exert its global effect on brain neurotransmission via modulation of ion channels (i.e., Na+, K+). Also it increase oxygen consumption in the brain, apparently in connection to ATP metabolism, and increases the activity of adenylyl kinas in rat brain., but may acts through potentiating of previously in attendance transmission and that evidence point in the direction of modulated influx of Ca influx through non –L-type voltage dependant calcium channel or decrease in potassium efflux (20) So the aim of this study is to obtain the effects of piracetam on the simple reaction time in normal healthy volunteers.

Methods

This study was carried in department of pharmacology and medicine, college of medicine, Al-Mustansiriya University during April 2011. The subjects of this study were medical college students, 30 volunteers (20 males and 10 females) were conventional to enroll and complete single blind random clinically study 3 male right handed 2 female are the other are left handed. The simple reaction time was determined by ruler dropper test (21).

The key of this test is to find the time requisite for subject to grasp a dropped object (12 inch rules). This test give an idea of subject awareness, recognition and movement time to a simple solitary stimulus. The subject braced his hand on edge of desk so that finger over the edge ready to grasp the ruler as it is dropped, then the researcher hold the rules such that its zero centimeter mark is even with the center of subject finger, at some random time, dropped, so the distance that rules fell is recorded, from this distance the simple reaction time can be designed.

\[ \text{Rt} = \sqrt{\frac{2SF}{A}} \]

\( \text{Rt} = \) simple reaction time \( \text{Sf} = \) the average distance that the ruler drop \( \text{A=} \) is the acceleration gravity (980 cm/sec\(^2\)) Because of (rt) is a sum of of \( dt+nt +pt \) \( [(dt)= \) dynamic time \( , (nt) = \) nerve time \( ,(pt)= \) processing time] 

So R= \( dt+nt+pt \)

The \( (nt) \) represent the nerve signals travel at speed of 30,000 cm/sec under the distance from brain to finger so nt= distance / rate ,while the \( (dt) \) can be founded by timing 25 complete pinch (open & close) then dividing the time by 50 since each open and close in two action \( ,(pt) \) is calculated by subtracted the sum of \( (dt)\)and \( (nt) \) from \( (rt) ,so \) in this study, in order to avoid experimental bias \( (nt)&(rt) \) were calculated .Each volunteer, do this procedure ,then each volunteer take 800mg piracetam in opaque formulated gelatinous capsule and after two hour, the procedure repeated to show the differences in ruler dropper test before and after piracetam 800mg tablet, then that data grouped as mean± SD and use paired t test with p value regarding p value as

Results

The characteristics of the study designed in table (I) Table (II) shows the simple reaction time which was assessed by ruler drop test, is 292.25msec. Only 4.30 msec represent the time of impulse conduction. There are inconsequential differences between males and females in simple reaction time or its components, also left handed subjects react more relaxing than right handed but the effect does not reach the level of significance (p>0.05) table III.

Effect of piracetam on simple reaction time:

The simple reaction time reduced from 292.25 ±31.21 to 190.21 ± 12.14 (p0.05 table (V). Therefore, piracetam produced significant improvements in total simple reaction time, mainly through the processing time (pt) (figure 1) The processing time highly decreased from 99.85 ± 7.94 to 22.71 ± 3.31 p

Discussion

In this study there is assurance that piracetam improved the reaction time and processing time of total reaction, reflecting the stimulatory effect of piracetam on brain. Simultaneously as mentioned in the introduction, there were unrestricted number of variables which influence the validity and reliability of psychometric test regarding the reaction time, so
there was intra individual variation, all these affect the results of study.\textsuperscript{(23)} The gender affect all the reaction time baseline data as well as cognitive function but does not reach the level of significance due to sample size, but other studies showed non-significant differences in intellectual activity and reaction times between males and females.\textsuperscript{(23)}

Additionally, dominant hand plays a role in principles of simple reaction time, but in this revision base line data and after treatment with piracetam there was significant difference or enhancement regarding the dominant hand, but other study speculated that when deeper dispensation is required there is tendency to revert to the dominant limb.\textsuperscript{(24)} Motor reaction which varied with length of the distance between the brain and hand (hand–brain distance) showed trivial differences,\textsuperscript{(25)} but piracetam not affected by hand brain distances.\textsuperscript{(26)} This supported by study that show there is significant association between hand brain distance and reaction time.\textsuperscript{(27)} Adjoin to this, preceding studies which showed that short hand brain distance provided rapid reaction times.\textsuperscript{(28)}

In regarding to the main components of total reaction time dynamic time regarded as standard, but there was variation in nerve time and processing time.\textsuperscript{(29)} The mechanism of action of piracetam is not known, although it is hypothesized to act on ion channels or ion carriers thus leading to non-specific increased in the neuronal excitability, while explaining its lack of agonistic or inhibitory effects on synaptic action. Piracetam has been found to increase blood flow and oxygen consumption in parts of the brain but this may be a side-effect of increased brain activity rather than a primary effect or mechanism of action for the drug.\textsuperscript{(30)}

Piracetam remarkably improve the simple reaction time and cognitive function primarily from first to last reduction in processing time which is the chief part of cognitive purpose, this effect may explain the stimulatory effects of piracetam on basal forebrain neuron, because basal forebrain neuron plays a role in scheming both cognitive and non-cognitive aspect of simple reaction time.\textsuperscript{(31)}

Moreover, piracetam improves cognitive performance of schizophrenics as it does with non-schizophrenics, but does not improve or worsen the chronic schizophrenia disease state.\textsuperscript{(32)}

Piracetam, be active at more than one site of brain concerning the cholinergic system, dopaminergic system and glutaminergic system. Therefore, Agents act as agonist on cholinergic system like physostigmin or dopaminergic agonist like ropirinol produced beneficial improvement in total reaction time.\textsuperscript{(33)} As a result, the beneficial sound effects of piracetam on the mental activity and cognitive function correlated to its effect on nitric oxide release, since the nitric oxide generate neuron excitatory effects on forebrain neurons, but the ability of piracetam to release nitric oxide was not determined in this study.

Antidegenerative and anti-apoptotic effects on nitric oxide may explain the progression of post-traumatic syndrome by piracetam, also piracetam improve the cerebral blood flow and reverses the hypoperfusion productively in patients with minor traumatic brain injury as compared to the control group and taken in concurrence with the symptomatic improvement, these findings can be measured particularly significant. Piracetam has been shown to reverse perfusion abnormalities in cases of stroke and dementia.\textsuperscript{(34)}

Several meta-reviews of literature on piracetam indicate that piracetam increases performance on a variety of cognitive tasks among dyslexic children, though this may reflect its enhancement of cross-hemispheric communication and of cognitive function in general, rather than a specific improvement in whatever causes dyslexia. Piracetam also seems to inhibit brain damage caused by a variety of factors including hypoxia and excessive alcohol consumption.\textsuperscript{(35)} Piracetam has been studied in an extensive number of clinical experiments, and has shown positive results in the treatment of post-stroke aphasia, epilepsy, cognitive decline following heart and brain surgery, dementia, myoclonus also piracetam appears to increase communication between the two hemispheres of the brain, and increases activity of the corpus callosum.\textsuperscript{(36)}

Cognitive dysfunction has been shown to be linked with reduced cholinergic transmission and the facilitation of central cholinergic transmission will improve memory and chronic piracetam therapy showed significant reduction of brain acetylcholinesterase activity thereby probably facilitating cholinergic transmission and improving memory of animals. Thus the memory improving activity of piracetam may be attributed to its anti-acetylcholinesterase property.\textsuperscript{(37)} Moreover, it is assumed that piracetam provides the neuron with better protection against oxidative stress by normalizing membrane-associated cell activity.\textsuperscript{(38)}

One attractive study suggests that piracetam might increase the number of cholinergic receptors in the brain. Older mice were given piracetam for two weeks and then the mass of muscarinic cholinergic receptors in their frontal cortices was measured. The researchers establish that these elder mice had 30–40% superior density of these receptors than
Piracetam, dissimilar many other drugs, appears to have a regenerative consequence on the nervous system. The antioxidant effect of vinpocetine and piracetam appear at low doses in contrast, the higher doses were associated with an increase in oxidative stress, though both drugs offered significant protection against GSH depletion induced by ethidium bromide also in spinal cord ischemia–reperfusion injury in the rabbit, piracetam has been reported to suppress malondialdehyde, increase glutathione peroxidase activity and decrease xanthine oxidase level, thereby suggesting an antioxidant effect for the drug.

Chronic hypoperfusion decreases the contents of excitatory and inhibitory amino acids in rat brain and up-regulates the apoptosis-related protein (P53 and BAX). Moreover, piracetam inhibited the decrease amino acid content induced by chronic hypoperfusion and ameliorated the dysfunction of learning and memory in rats and improve the facilitating effects on the synaptic plasticity, and may be helpful in the treatment of vascular dementia.

Additionally, piracetam increase membrane fluidity, improved erythrocyte deformability, normalization of hyperactive platelet aggregation, mitochondrial membrane stabilization and protection has been optional to account for its effect on memory.

So from previous studies many neurotransmitters involved in the regulation of reaction time and all these neurotransmitters were improved by piracetam so most of mentioned studies support our results in that piracetam improve the simple reaction time.

Add to this, the piracetam improved the reaction time and cognitive by complex conduct need further researchers to identify the link between the central and peripheral stimulatory effects of piracetam.

**Conclusion(s)**

- Piracetam improve the cognitive function and reaction time.
- Piracetam significantly improve the processing time rather the nerve conduction time, reflecting the central effect of piracetam.

**Acknowledgement(s)**

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Illustrations

Illustration 1

Table (I): Characteristics of the study

<table>
<thead>
<tr>
<th>Number</th>
<th>30</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>20</td>
</tr>
<tr>
<td>Female</td>
<td>10</td>
</tr>
<tr>
<td>Age (year)</td>
<td></td>
</tr>
<tr>
<td>Lower – upper limit</td>
<td>20-22</td>
</tr>
<tr>
<td>Range</td>
<td>2</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>21.02±0.4</td>
</tr>
<tr>
<td>Domain hand</td>
<td></td>
</tr>
<tr>
<td>Right</td>
<td>25</td>
</tr>
<tr>
<td>Left</td>
<td>5</td>
</tr>
<tr>
<td>Brain hand distance(cm)</td>
<td>85-111</td>
</tr>
<tr>
<td>Range</td>
<td>26</td>
</tr>
</tbody>
</table>
Illustration 2

Table (II): Assessment of simple reaction time (baseline data)

<table>
<thead>
<tr>
<th>Ruler drop test</th>
<th>Male</th>
<th>Female</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n=20</td>
<td>n=10</td>
<td>n=30</td>
</tr>
<tr>
<td>Rt (msec)</td>
<td>281.31±29.71</td>
<td>275.61±41.9</td>
<td>292.25±31.2</td>
</tr>
<tr>
<td>Nt (msec)</td>
<td>3.41±0.16</td>
<td>4.04±0.22</td>
<td>4.30±0.21</td>
</tr>
<tr>
<td>pt (msec)</td>
<td>281.91±30.71</td>
<td>255.66±44.81</td>
<td>99.85±6.99</td>
</tr>
<tr>
<td>Hand–brain distance(cm)</td>
<td>102.69±5.49</td>
<td>91.71±6.92</td>
<td>98.85±7.94</td>
</tr>
</tbody>
</table>
Illustration 3

Table (III): Assessment of simple reaction time in respect to domain hand

<table>
<thead>
<tr>
<th>Ruler drop test</th>
<th>Right hand</th>
<th>Left hand</th>
</tr>
</thead>
<tbody>
<tr>
<td>rt(mess)</td>
<td>271.61±30.3</td>
<td>306.13±36.8</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>9</td>
</tr>
<tr>
<td>nt(mess)</td>
<td>4.222±0.301</td>
<td>3.31±0.11</td>
</tr>
<tr>
<td>pt(msec)</td>
<td>269.31±31.3</td>
<td>307.88±31.8</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>Hand –brain distance(cm)</td>
<td>98.33±9.02</td>
<td>100.4±3.20</td>
</tr>
</tbody>
</table>
Illustration 4

Table (IV): Effect of piracetam on simple reaction time regarding gender differences.

<table>
<thead>
<tr>
<th>Ruler drop test</th>
<th>Male n=20</th>
<th>Female n=10</th>
<th>Total n=30</th>
</tr>
</thead>
<tbody>
<tr>
<td>rt(msec)</td>
<td>250.21±21.6</td>
<td>231.51±40.8</td>
<td>190.21±12.14 *</td>
</tr>
<tr>
<td>nt(msec)</td>
<td>2.11±0.11</td>
<td>3.03±0.11</td>
<td>3.22±0.16</td>
</tr>
<tr>
<td>pt(msec)</td>
<td>251.81±30.6</td>
<td>211.12±33.1</td>
<td>22.71±3.31 **</td>
</tr>
</tbody>
</table>
Illustration 5

Table (V) Effect of piracetam simple reaction time regarding domain hand.

<table>
<thead>
<tr>
<th>Ruler drop test</th>
<th>Right hand</th>
<th>Left hand</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n=25</td>
<td>n=5</td>
</tr>
<tr>
<td>rt(msec)</td>
<td>261.62±30.21</td>
<td>299.14±29.79</td>
</tr>
<tr>
<td>nt(msec)</td>
<td>4.111±0.201</td>
<td>2.89±0.09</td>
</tr>
<tr>
<td>pt(msec)</td>
<td>259.30±30.34</td>
<td>299.89±30.79</td>
</tr>
</tbody>
</table>
Illustration 6

Figure (1): Effect of piracetam on simple reaction time.
Illustration 7

Figure 2: Effects of piracetam on processing time
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