

Pyridoxine hydrochloride attenuate and decrease the depressant effects of meclizine on human psychomotor performance: Randomized clinical trial, cross-over study.

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Abstract

The present study was conducted to assess and compare the cognitive and psychomotor effects of Pyridoxine HCl 50mg and meclizine 25mg or both in 30 healthy adult volunteers in a single blind, randomized cross over study. Following single dose of each drug, the volunteers were subjected to perform a series of tests of cognitive and psychomotor performance at 2 hours post dose. The Leeds Battery Psychomotor Instrument test consisted of both subjective and objective tests which were further grouped into Instrumental tests which included Simple reaction time (SRT), Choice Reaction Time Task (CRT) and Critical Flicker Fusion frequency threshold (CFFT). Meclizine at dose of 25mg was significantly different from placebo ($p < 0.05$) in most of the tests used except of insignificant effect on Critical Flicker Fusion frequency threshold (CFFT). However, as expected for a vernal result, all the measures were significantly disrupted by meclizine 25 mg up to 2 hours post dose. Pyridoxine at dose 50 mg has produced significant subjective improvement in all psychometrics measures ($p < 0.05$) except of critical fusion frequency were it produced insignificant effects ($p > 0.05$). The dual and combined effects of pyridoxine HCl 50mg plus meclizine 25mg attenuate and remove the depressant effects that mediated via meclizine. These results allow the conclusion that pyridoxine at its recommended therapeutic dose of 50mg is needed to be mixed with meclizine or others antihistamine to eliminate psychomotor and cognitive impairment as usual adverse effect of meclizine.

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Introduction

Vitamin B6, also notorious as pyridoxine, is the common name for three naturally occurring

compounds; pyridoxine, pyridoxal, and pyridoxamine, which are intimately related in form and function. Each of them can be metabolized and phosphorylated in the liver to attain the main biologically active form of the vitamin, pyridoxal 5'-phosphate, which has some roles as a coenzyme in many reactions, including decarboxylation and transamination of amino acids, deamination of hydroxyamino acids and cysteine, conversion of tryptophan to niacin, and metabolism of fatty acids⁽¹⁾. Pyridoxine is a water-soluble nutrient that cannot be stored in the body, but must be obtained daily from either dietary sources or supplements. It is excreted within eight hours after ingestion. Pyridoxine, is necessary for the proper function of more than 100 different enzymes that participate in amino acid, carbohydrate, and fat metabolism⁽²⁾. Moreover, pyridoxine is concerned in the synthesis of the neurotransmitters serotonin, dopamine, norepinephrine, and gamma-aminobutyric acid (GABA) in the brain and nerve cells, and may support mental function and nerve conduction⁽³⁾. It is well-known that deficiency of pyridoxine can instantaneously lead to insomnia and a profound malfunctioning of the central nervous system^(2,3). Meclizine is a H₁-receptor antagonist widely used in human and veterinary medicine to present symptomatic relief of allergic signs caused by histamine release, including pruritus and anaphylactic reactions. Meclizine is also frequently used as sedatives and antiemetic⁽⁴⁾. Antihistamines can be divided into first and second-generation antihistamines; first-generation antihistamines are small lipophilic molecules, so they may cause adverse effects because of their cholinergic activity and their capability to cross the blood-brain barrier while second-generation antihistamines are more lipophobic than first-generation antihistamines and are thought to lack central nervous system (CNS) and cholinergic effects when given at therapeutic doses^(3,4). Meclizine is a reversible, competitive

inhibitor of most of the pharmacologic actions of histamines; one exception is the stimulation of gastric acid secretion, which is mediated by H₂-receptors⁽⁵⁾. The majority of antihistamines do not chemically inactivate or physiologically antagonize histamine, nor do they prevent histamine release⁽⁶⁾. The exceptions are cetirizine hydrochloride and loratadine which reduce histamine release from basophil. Actions of histamine that inhibited by H₁-antagonists include constriction of respiratory smooth muscle, increased capillary permeability, edema and wheal formation⁽⁷⁾. The piperazines (cyclizine and meclizine) also have significant activity in preventing motion sickness and are less sedating than diphenhydramine in most patients.⁽⁸⁾ Meclizine has negligible anticholinergic properties that also causes less sedation⁽⁹⁾. It is used for the prevention of motion sickness and the treatment of vertigo due to labyrinth dysfunction⁽¹⁰⁾. They also have impact on various events of psychomotor performance such as hand-eye coordination or tracking tasks reaction time, spatial orientation, digit symbol substitution, and critical flicker fusion threshold⁽¹¹⁾, maximum impact on performance typically occurs two hours after ingestion and approaches normal performance 8-12 hours after ingestion⁽¹²⁾.

Psychomotor performance testing used to estimate the speed of cognitive processes. Therefore, many agents affecting the cognitive function can be assessed indirectly by psychomotor performance test⁽¹³⁾.

The aim of the present study was to assess the effect of meclizine and pyridoxine on psychomotor performance and to compare with combined effects of both agents.

Materials and Methods

This study was conducted in Department of Pharmacology, College of Medicine, Al-Mustansiriyah University, Baghdad, Iraq in 2010. Thirty healthy male

volunteers (medical students) aged between 20 and 24 years (mean age 22 years) were selected randomly from college by using randomized tables to contribute in a balanced one-period cross-over inquiry. All participants were in good health, without any significant clinical history of physical or mental illness and not taking any concomitant medication (including central stimulant or depressant drugs) that was likely to interfere with the study. Written informed consent was obtained from all participants. The study was approved by Local Scientific Committee of the institution.

This study was a randomized, single-blind, placebo-controlled one-way cross-over study where each subject acted as own control. The treatment sequence was balanced using Latin Square design. The drugs under investigation were pyridoxine HCl (50 mg tablet, Boehringer Ingelheim, Germany), meclizine (25 mg tablet, Pfizer, United States) and combined pyridoxine HCl 50mg+ meclizine 25mg (novidioxine ibn Al-Haytham Pharma-industries Co. Aleppo-syria) scored tablets and placebos. Each single drug dose tablet was taken 2 h before laboratory battery assessment at 9 a.m. All participants who entered the study were familiarized with the study procedures and trained on the Leeds Battery psychometric tests in order to preclude learning effects⁽¹⁴⁾.

The test began with pre-treatment baseline assessment on the test battery and then the treatment dose was administered. Performance, using Leeds Battery Psychomotor Instrument [choice reaction time (CRT) and critical flicker fusion (CFF)] was assessed 2 h after the administration of drug or placebo. Caffeine and other beverages were forbidden on study days.

The choice reaction time (CRT) task is used as an indicator of sensorimotor performance and in assessing the ability to attend and respond to a critical stimulus⁽¹⁵⁾. Participants are required to place the index finger of their preferred hand on a central starting button and are instructed to extinguish one of six equidistant red lights, illuminated at random, by pressing the response key in front of the light as quickly as possible. The mean of 5 consecutive presentations is recorded as

a response measure of three components of reaction time: recognition, motor and total reaction time. Recognition reaction time (RRT) is the time between stimulus (light) onset and the subject and lifting of the finger from the start button. Motor reaction time (MRT) indicates the movement component of this task and is the time between a participant lifting of his finger from the start button and touching the response button. Total reaction time (TRT) is the sum of RRT and MRT. The critical flicker fusion (CFF) task assessed the integrative capacity of the CNS and, more specifically, the ability to discriminate discrete task of sensory information⁽¹⁶⁾. In this, the participants are required to discriminate flicker from fusion and vice versa, in a set of four light-emitting diodes arranged in a 1-cm square. The diodes are held in foveal fixation at a distance of 1 m. Individual thresholds are determined by the psychophysical method of limits on five ascending (flicker to fusion) and five descending (fusion to flicker) scales. A decrease in the CFF threshold is indicative of a reduction in the overall integrative activity of the CNS.⁽¹⁷⁾

The results are expressed as mean \pm SD of the number of observations. The data were statistically analyzed by using paired t test, taking $P \leq 0.05$ as the lowest limit of significance.

Results

Pyridoxine HCl significantly improve all psychometric parameters ($p < 0.05$) except critical flickering (CFI) ($p > 0.05$) after single oral dose (table 1 and figure1)

Table (1): Effects of single oral dose of pyridoxine HCl (50mg) on psychomotor performances parameters.

Variable (msec)	before	after	p value
CRT	626.712 \pm 21.5	411.511 \pm 23.20	$P < 0.05$
RRT	341.71 \pm 21.31	219.119 \pm 11.51	$P < 0.05$
MRT	285.097 \pm 11.3	192.398 \pm 23.1	$P < 0.05$
CFI	25.82 \pm 2.1	21.22 \pm 1.8	$p > 0.05$
CFu	32.42 \pm 1.2	22.35 \pm 1.5	$p < 0.05$

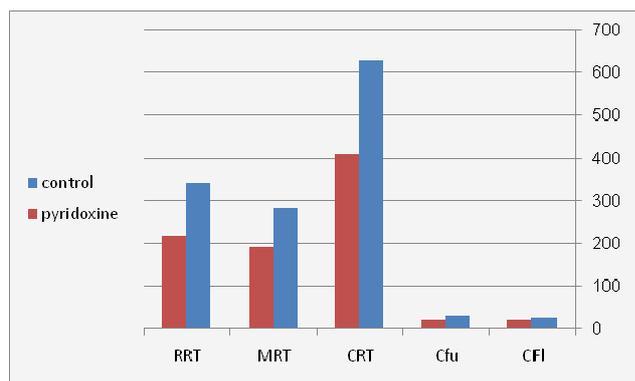


Figure (1): comparison between the effects of pyridoxine HCl on psychomotor performances measures.

Meclizine prolong and deteriorate all psychomotor performances parameters significantly ($p < 0.05$) except critical fusion (CFu) and critical flickering (CFI) threshold which is not affected by meclizine ($p > 0.05$) table 2 and figure 2.

Table (2): Effects of single oral dose of meclizine(25mg) on psychomotor performances parameters.

variables	before	after	P value
RRT	395.82±20.11	491.92±11.512	$P < 0.05$
MRT	315.31±1.22	401.81±2.32	$P < 0.05$
CRT	711.51±21.38	892.11±11.51	$P < 0.05$
Cfu	31.11±1.2	36.18±2.1	$P > 0.05$
CFL	26.31±1.4	25.41±2.15	$P > 0.05$

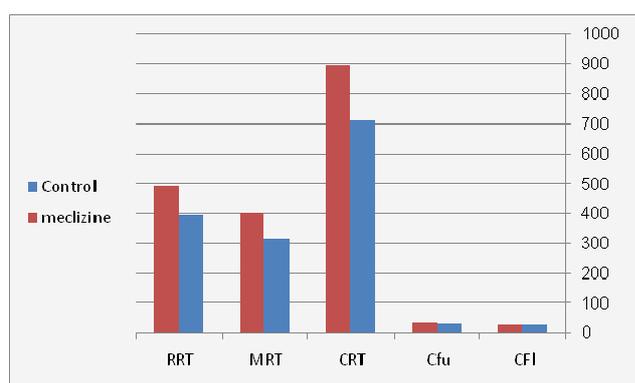


Figure (2): comparison between the effects of meclizine and control on psychomotor performances measures.

Dual and combined effects of pyridoxine and meclizine on psychomotor performances in present study produced improvement and significant effects

on all psychomotor performances data ($p < 0.05$) with exception of insignificant effects on critical flickering ($p > 0.05$) table 3 and figure 3.

Table (3): Effects of combined meclizine and pyridoxine HCl on psychomotor performances parameters.

Variable (msec)	before	after	P value
RRT	340.91±11.5	218.12±12.5	$P < 0.05$
MRT	260.30±11.4	92.30±1.1	$P < 0.05$
CRT	600.51±22.1	301.31±11.5	$P < 0.05$
Cfu	33.51±1.9	23.19±2.1	$P < 0.05$
CFL	26.81±11.5	21.72±1.8	$p > 0.05$

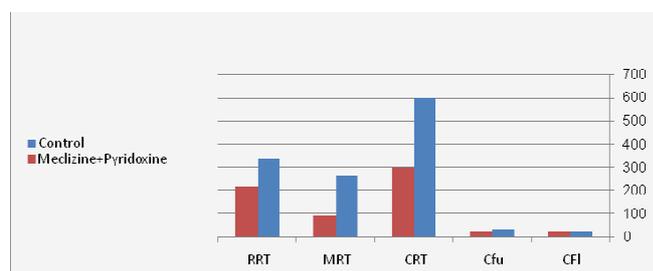


Figure (3): effects of combined pyridoxine HCl and meclizine on psychomotor performances measures.

Therefore; pyridoxine HCl showed in close proximity to similar effects to the combined effects on psychomotor performances measures; thus pyridoxine HCl eradicate the prolongation and depressant effects of meclizine on human psychomotor performances (figure 4).

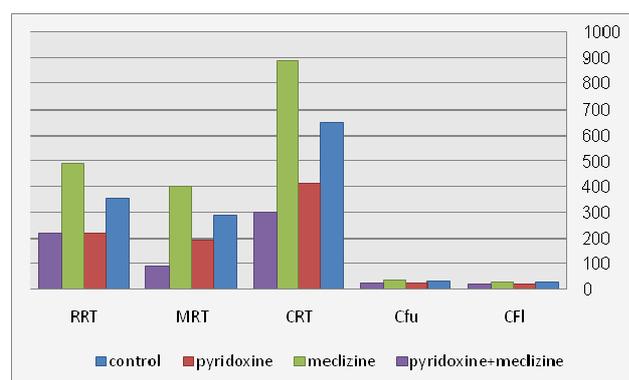


Figure (4): differential effects of pyridoxine HCl and meclizine or both.

Discussion

The present study showed that pyridoxine significantly advance human psychomotor performances but with petite effects on critical flickering frequency threshold which reflects central discrimination but improve critical fusion frequency threshold that reflect the central modulation of discrete task of sensory information ;those effect may be explained that Pyridoxine acts as a cofactor in enzymatic steps of tryptophan metabolism, in the synthesis of GABA and is an immediate precursor of dopamine and thus it increases the concentration of dopamine and serotonin⁽¹⁸⁾.

In one study, it was reported that the influx of calcium into artery segments was blocked by pyridoxal 5'-phosphate (biologically active form of pyridoxine),as well as by dihydropyridine-sensitive calcium channel blockers ⁽¹⁹⁾. In another study, it is suggested that pyridoxine decreases intracellular levels of glutamate by increasing glutamic acid decarboxylase activity and decrease of calcium influx through the actions on voltage gated L-type membranal calcium channels ; Pyridoxal phosphate inhibits calcium transport mechanisms and has a pivotal role in the neuroprotective actions of pyridoxine ⁽²⁰⁾.

On the other hand, administration of pyridoxine to convulsant-treated rats resulted in increased formation of GABA So, the GABAergic activity of pyridoxine may be responsible for the neuroprotective effect⁽²¹⁾.

Moreover; pyridoxine has a dual effect on neuronal cells, being neuroprotective at lower, but neurotoxic at higher, concentrations⁽²²⁾ but in this study lower dose used to avoid the neurotoxicity. Furthermore; enhancement of excitatory neurotransmitters by pyridoxine reflect the improvement in human psychomotor performances.

Meclizine is an antihistamines has been an effective anti-motion-sickness drug ; also antihistamine-H₁ receptor antagonists cause

sedation as the most common subjective side effect it also have impact on various measures of psychomotor performance such as hand-eye coordination or tracking tasks reaction time spatial orientation, digit symbol substitution and critical licker fusion threshold^(23,24,25,26,27). Maximum impact on performance typically occurs two hours after ingestion and approaches normal performance 8 to 12 h after ingestion⁽²⁸⁾.

On the other hand, promethazine and meclizine caused the largest increases in subjective impairment and sleepiness as well as the most profound and longest lasting impact on psychomotor performance also Meclizine caused a subjective performance impairment similar to promethazine but with slightly later onset. The impact of meclizine on objective measures of performance also began somewhat later than with promethazine, but overall the magnitude of objective performance decrement with meclizine was similar to that of promethazine⁽²⁹⁾.

The entire of these studies maintain the present study that showed meclizine was impaired the psychomotor performances but with minimal effects on critical flickering and fusion threshold may be explained by short experimental time(2h).

Pyridoxine HCl plus meclizine abolish the depressant effects of antihistamine that mediated all the way through meclizine ;the dual and combined effects of pyridoxine and meclizine produced significant effects on all psychomotor performances parameters with minimal and insignificant effects on the critical fusion frequency. Pyridoxine modulate synthesis of excitatory neurotransmitter that improve attention and eliminate the depressant effects at various brain levels⁽³⁰⁾.

Near the beginning, a versions of the activation hypothesis considered arousal to be mediated principally by the ascending reticular formation (ARAS), a network of neurons stretching from the diencephalon to the hindbrain⁽³¹⁾.

Next to, at least four main projection systems have been identified as playing functional roles in arousal and attention these include the cholinergic basal forebrain, the noradrenergic nucleus locus ceruleus (LC), the dopaminergic median forebrain bundle, and the serotonergic dorsal raphe nucleus^(32,33,34).

Numerous pharmacological studies conducted with animal and human observers have contributed to the view that the cholinergic system plays an important role in attention and arousal processes. Also activation of LC cells in awake monkeys and rats results in a widespread release of norepinephrine to cortical targets, Moreover LC cellular activity is also elevated during periods of behavioral alertness^(33,35,36). In a study designed to assess the role of noradrenaline in human sustained attention, Smith and Nutt reported that the drug clonidine, an alpha-2 adrenoreceptor agonist, which reduces the release of norepinephrine, increased the number of very long reaction times in a vigilance task and that this effect could be reversed by idazoxan, a drug that acts to increase levels of noradrenaline⁽³⁷⁾; conclusion such as these help support the role of noradrenaline in human sustained attention.

In addition to studies focusing upon specific neurotransmitters, the results of a wide range of investigations showing that stimulants such as amphetamine and caffeine improve vigilance performance, while depressants such as alcohol, chlorpromazine, hyoscine, and scopolamine impair performance, are consistent with the activation hypothesis⁽³⁵⁾.

From all these studies direct or indirect activation of excitatory neurotransmitter eliminate the central depressant effects of sedative antihistamine like

meclizine ,indirect through pyridoxine and direct through sympathomimetics agents^(36,38).

While ephedrine has been demonstrated to successfully improve the adverse effects of promethazine on performance⁽³⁷⁾, othe results indicated pseudoephedrine does not have the same protective effect but pseudoephedrine ameliorate the subjective adverse effects or the objective performance decrements caused by promethazine^(38,39,40).

However, the addition of d-amphetamine successfully mitigated both the adverse subjective and objective performance effects of promethazine^(39,41,42). A possible alternative for d-amphetamine as a counter measure to the adverse effects of promethazine is modafinil. The addition of pseudoephedrine to promethazine is less effective in reducing the negative effects of promethazine; however, the addition of d-mphetamine is remarkably effective in that role^(40,42,43).

The results of this study support the possibility for carefully supervised use of pyridoxine with meclizine to prevent antihistamine mediated central nervous system depression and impairments.

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