Levofloxacin Reverses Hydroxyzine Induced Psychomotor Performance Deterioration: A Randomized Crossover Study

Hayder M. Alkuraishy1* and Ali I. Al-Gareeb1

1Department of Pharmacology, Toxicology and Medicine, College of Medicine, Al-Mustansiriya University, Baghdad, Iraq.

Author’s contributions

This work was carried out in collaboration between both authors. Author HMA designed the study, wrote the protocol and wrote the first draft of the manuscript. Author AIAG managed the literature searches, analyses of the study performed the spectroscopy analysis. Both authors read and approved the final manuscript.

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ABSTRACT

Background: Levofloxacin is a third generation fluoroquinolone chemotherapeutic agent used in the treatment of severe and resistant bacterial infections; it exerts antibacterial effects in both blood and inflamed tissues. Levofloxacin leads to central nervous system stimulation via inhibition of GABA-A receptor complex like beta-lactam antibiotics. Hydroxyzines used for the treatment of insomnia, allergic reactions and for preoperative sedation because of blocking H-1 receptors and so blocking histaminergic signals.

Objectives: The aim of the present study is to elucidate the exciting effect of levofloxacin in hydroxyzine induced psychomotor performance deterioration in normal healthy volunteers.

*Corresponding author: Email: Hayderm36@yahoo.com, haydermu78@yahoo.com, dr.alialgareeb78@yahoo.com;
**Methods:** Thirty healthy medical student volunteers, aged between 22-25 years were allocating arbitrarily. All participants were habituated with the study measures and skilled on the Leeds psychomotor tester before and after levofloxacin (500 mg/day) alone or with hydroxyzine (10 mg/day).

**Results:** Hydroxyzine impaired psychomotor performance and cognitive function, it prolongs the total reaction time, movement reaction time, recognition reaction time and distort critical flicker and fusion frequency significantly p<0.05.

While levofloxacin activates psychomotor performance and cognitive function, it shortens the total reaction time, movement reaction time, recognition reaction time and regulate critical flicker and fusion frequency significantly p<0.05.

The combined effect of levofloxacin and hydroxyzine produced insignificant effects on psychomotor performance and cognitive function p>0.05.

**Conclusion:** Levofloxacin significantly improves psychomotor performance in normal, healthy volunteers and produced CNS stimulation that is able to reverse deteriorations in psychomotor performance and cognitive function induced by hydroxyzine.

**Keywords:** Levofloxacin; psychomotor performance; hydroxyzine.

### 1. INTRODUCTION

Levofloxacin is a third generation fluoroquinolone chemotherapeutic agent used in the treatment of severe and resistant bacterial infections. It exerts antibacterial effects in both blood and inflamed tissues. The most frequent side effects of levofloxacin are gastrointestinal upset (7%), cognitive disorders (5%), hematological disorders (5%), renal disturbances (4.5%) and dermatological disorders like photosensitivity and hypersensitivity (2%) [1].

Levofloxacin leads to central nervous system stimulation via inhibition of GABA-A receptor complex like beta-lactam antibiotics. Most of fluoroquinolone antibiotics have an epileptogenic potential through decrease seizure threshold except levofloxacin and moxifloxacin, which have chemical structures that not linked with toxicity or seizure induction when combined with theophylline [2,3].

Other receptors that are probably included in the CNS excitation of levofloxacin are NMDA (N-methyl-D-asparate), adenosine and amino acid receptors, also levofloxacin may modulate opioid and dopamine receptors through this activation [4-6].

Moreover, animal model study on third generation fluoroquinolones showed small considerable changes in locomotor activity [7].

Hydroxyzine blocks histamine receptor H-1 in CNS principally at frontal cortex, hippocampus and pains because of its low molecular weight and high lipophilicity. It is used for the treatment of insomnia, allergic reactions and for preoperative sedation because it blocks H-1 receptors and, so, blocking histaminergic signals.

The critical hazards/advantageous proportion linked with use of hydroxyzine to manage CNS and vestibular disorders are well known. These are sedation, psychomotor performance retardation and deterioration in the sensorimotor task reaction [8-10].

The amount of sedation produced by hydroxyzine at therapeutic dose affects psychomotor performance through histaminergic, and cholinergic blocking effects [11].

Moreover, there is a significant correlation between psychomotor deteriorating and antihistamine use, so, H-1 antagonist particularly hydroxyzine cause sedation and CNS deteriorations [12].

Therefore, the aim of the present study is to elucidate the attenuating effect of levofloxacin in hydroxyzine induced psychomotor performance deterioration in normal healthy volunteers.

### 2. SUBJECTS AND METHODS

This study is carried out in the Department of Clinical Pharmacology, College of Medicine, Almustansiriya University, Iraq-Baghdad in March and April 2014. Thirty healthy medical student volunteers, aged between 22-25 years, we're allocating arbitrarily from college classes via randomized tables to donate in an unbiased
single era crossover inquisition. Written knowledgeable approval was attained from all contributors. The drugs were levofloxacin (500mg) tablet (Ravivo, drogsan), hydroxyzine (10 mg tablet, Pfizer, United States), all drugs are purchased from private pharmacies.

All participants are males were dividing into three groups:

Group (A): takes hydroxyzine 10 mg, Group (B): take levofloxacin 500 mg and Group (C): take hydroxyzine and levofloxacin. All participants received the drugs at the same time for five days duration.

Each single drug dose tablet was taken before laboratory battery assessment at 9 a.m. and regarded as self-control, then after 4hours, the test started again and regarded the drug effect. All participants were habituated with study measures and skilled on the Leeds psychomotor tester [13]. The check commenced by way of baseline evaluation on the test battery and after that, the drug administered. Performance, via Leeds Battery Psychomotor Instrument [choice reaction time (CRT) and critical flicker fusion (CFF)] was assessed 4 h after the administration of the drug. Psychomotor performance parameters include:

- **Choice Reaction Time (CRT)** task is a marker of sensorimotor performance, assessing the capability to concentrate and react a stimulus [14]. Contributors are mandatory to situate the index finger of their favoured hand on a starting button and then teach to quench one of six equidistant red lights, illuminate at random, by urgent pressing the reaction key in front of the light as rapidly as achievable. Men of 4- 5 successive readings are traced as a reactive response of three components of reaction time: Recognition, motor and total reaction time.
- **Recognition Reaction Time (RRT):** Reflects the duration of time between stimulus (light) onset and the subject lifting of the finger from the start button (recognition reaction).
- **Motor Reaction Time (MRT):** Is the duration of time between contributors elating of his finger from the start button and moving the response button (motor reaction).
- **Total Reaction Time (TRT):** Is the computation of RRT + MRT.
- **Critical Flicker Fusion (CFF):** Evaluates the integrative aptitude of brain to distinguish a distinct task of sensory information and it measures central cognitive integrity [15].

The contributors were requested to distinguish flicker as of fusion and vice versa, in a set of four light-emitting red lights arranged in a 1-cm square [16].

Results are expressed as mean ± SD and is statistically analysed through using a paired T-test taking p value <0.05 as lowest of significant (SPSS version 22).

3. RESULTS

Hydroxyzine impairs psychomotor performance and cognitive function, it prolongs the total reaction time, movement reaction time, recognition reaction time and distorts critical flicker and fusion frequency significantly p<0.05 (Table 1).

While, levofloxacin activates psychomotor performance and cognitive function, it shortens the total reaction time, movement reaction time, recognition reaction time and regulates critical flicker and fusion frequency significantly p<0.05 (Table 2).

The combined effect of levofloxacin and hydroxyzine produced insignificant effects on psychomotor performance and cognitive function p>0.05 (Table 3).

| Variables              | Before (mean ± SD) | After (mean ± SD) | P value   |
|------------------------|--------------------|-------------------|-----------|
| TRT (ms)               | 534.23±43.65       | 745.33±32.45      | 0.000321  |
| MRT (ms)               | 168.51±21.2        | 286.1±10.04       | 0.0041    |
| RRT (ms)               | 345.72±22.45       | 487.23±22.41      | 0.0039    |
| Critical flicker (Hz)  | 40.23±0.55         | 37.35±0.45        | 0.0212    |
| Critical fusion (Hz)   | 31.87±0.43         | 33.67±1.08        | 0.0324    |

TRT (total reaction time), MRT (movement reaction time), RRT (recognition reaction time)
4. DISCUSSION

The present study showed that levofloxacin significantly improves the psychomotor performance in normal, healthy volunteers and produced CNS stimulation that able to reverse the psychomotor deterioration induced via hydroxyzine, which causes significant deteriorations in psychomotor performance and cognitive function. Levofloxacin alone produced significant central activation leading to improvements in cognitive function and psychomotor performance, this reflected via acceleration of total recognition and movement reaction time in the present study.

Fluoroquinolones generally produces cerebral activation, anxiogenic action, improves maze test and reverse phenobarbital cerebral depression, also, levofloxacin has an analgesic effect in the hot plate test in rodents [17].

The central activation effect of levofloxacin may link to the γ-aminobutyric acid (GABA) receptor antagonist or to the structure of GABA. Levofloxacin essentially act on GABA-A receptor subtype and hence; it acts on inhibitory neurotransmission for production of excitation effect and so; benzodiazepine agonists like diazepam attenuate the stimulatory effect of levofloxacin and decrease the epileptogenic effects of other fluoroquinolones [18,19].

Moreover, levofloxacin activates N-methyl-D-aspartate receptor (NMDA) which has an important stimulator action in the brain. This occurred because of the similarity of levofloxacin to the endogenous ligands that stimulates NMDA receptors like glutamate and kynurenic acid [20].

Nakamura et al. And Moorthy et al. [21,22] study showed MK-801 which is an NMDA antagonist attenuated and removed the potential neuroexcitatory effect of levofloxacin. This clarifies the activations role of NMDA receptor via levofloxacin, but levofloxacin and other fluoroquinolones did not bind to the glutamate binding site of NMDA, but; levofloxacin may reduce the blocking and antagonist effect of Mg$^{2+}$ ion on NMDA receptor resulting in prolongation of opening times of NMDA-ion channel, consequently, it augments Ca$^{2+}$ neuronal concentration leading to neuroexcitation and stimulation of psychomotor performance.

Additionally, there is a synergistic effect of nonsteroidal anti-inflammatory drugs (NSAID) with fluoroquinolones leading to the more cerebral activation and increase risk of convulsion this due to an additional blocking effect of NSAID on NMDA-ion channel. Therefore; NSAID should be used cautiously with fluoroquinolone with exception of levofloxacin because substitution of 7-pyrolidinyl levofloxacin structure made it less epileptogenic when combined with NSAID [23,24].

Dyskinesias and Tourette-like syndrome has been reported in fluoroquinolone therapy due to modulation of dopamine receptors [25].

Table 2. The effect of levofloxacin on psychomotor performance and cognitive function

| Variables                  | Before (mean ± SD) | After (mean ± SD) | P value |
|----------------------------|--------------------|-------------------|---------|
| TRT (ms)                   | 554.36±45.65       | 455.33±32.45      | 0.0023  |
| MRT (ms)                   | 119.14±19.2        | 68.1±10.10        | 0.0001  |
| RRT (ms)                   | 435.22±26.45       | 387.23±22.35      | 0.0026  |
| Critical flicker (Hz)      | 33.12±0.55         | 35.35±0.45        | 0.0247  |
| Critical fusion (Hz)       | 30.33±0.43         | 28.67±1.08        | 0.0356  |

TRT (total reaction time), MRT (movement reaction time), RRT (recognition reaction time)

Table 3. The combined effects of levofloxacin and hydroxyzine on psychomotor performance and cognitive function

| Variables                  | Before (mean ± SD) | After (mean ± SD) | P value |
|----------------------------|--------------------|-------------------|---------|
| TRT (ms)                   | 533.13±43.65       | 538.47±22.45      | 0.064   |
| MRT (ms)                   | 145.09±21.2        | 174.34±2.04       | 0.097   |
| RRT (ms)                   | 356.29±25.45       | 364.13±24.41      | 0.057   |
| Critical flicker (Hz)      | 40.23±0.55         | 40.25±0.45        | 0.127   |
| Critical fusion (Hz)       | 31.87±0.43         | 30.11±1.08        | 0.106   |

TRT (total reaction time), MRT (movement reaction time), RRT (recognition reaction time)
Therefore; levofloxacin may augment dopaminergic transmission at cerebral cortex and, consequently, improve reaction time and cognitive function, also; levofloxacin reduce the neuronal action potential threshold leading to more CNS stimulation. Moreover, electrophysiological studies showed that the excitatory potential of fluoroquinolones is linked to their structure, fluoroquinolones produced a dose dependent increase in the neuronal spike amplitude mainly at hippocampus, this is due to activation of NMDA receptor or blocking the GABA neurotransmission [26,27].

Furthermore, levofloxacin increase noradrenaline [28], asparagines [29] and inhibit acetylcholine-estrase enzyme (AChE) thus, it improves cholinergic transmission at frontal and hippocambal cortex [30].

Additionally; levofloxacin may improve and augment the cognitive function through activation and amelioration of CFF that reflect the cognitive integrity.

The flicker fusion is mainly a dependable method for measuring arousal functions and this can assess special effects of a variety of drugs on cognitive function and consequently the flicker fusion was observed as a guide of cortical stimulation thus; sedative drugs lessen CFFT pathway activation while stimulant agents augment it [31].

It has been designed that varieties between fusion and flicker threshold imitate a different pathway for cognitive function due to the attendance of varied pathways for fusion and flicker frequency and this may explain the effects of levofloxacin on flicker and the fusion frequency threshold [32,33].

Frequent studies show diversity in the CFFT between male and female subjects, but the data are extremely contradictory [34]. A number of studies enlightening higher CFFT values for men than for women, also; male subjects show a higher average CFFT than female subjects do and the sex difference is superior for the flicker than for the fusion [35]. Thus, in the present study a male young age was chosen to eliminate age and gender variations.

The CFFT is commonly used to determine the impact of drugs like analgesics, hypnotic and psychoactive drugs on the cognitive function so, antihistamines and anticonvulsants are apt to minimize the CFFT [36]. Although, the special effects of a definite drug on the CFFT were usually unachievable and because drugs affecting the CNS usually have an impact on a lot of CNS functions furthermore than the targeted one, thus, antidepressants lessen [37] or augment CFFT values [38], also, central stimulating agents, like nicotine and amphetamine, improves the CFFT. Nevertheless, there seems to be no simple relationship between the dose and the special effects on the CFFT [39,40].

Blandina et al. [41] study pointed that hydroxyzine deteriorates cognitive function and psychomotor performance via blocking excitatory histaminergic neurons.

Histamine act on specific CNS receptors (H1, H2, H3) and induce various effects like stimulation of attention, working memory excitation and appetite control [42]. Histaminergic neurons modulate other neurotransmitters and act through [43-45].

- Decreasing presynaptic acetylcholine secretion through activation of the presynaptic H3 receptor.
- Modulation of emotional memory acquisition.
- Increasing alertness and cognition.
- Activation of serotonergic neurons.
- Improving oxytocin secretion.

Stevenson et al. [46] study showed that energetic and psychomotor performance are decreased more via antihistamines, thus; hydroxyzine leads to clinical and subclinical cognitive impairment.

Therefore, hydroxyzine blocks the excitatory role of histamine leading to drowsiness, spatiotemporal disorientation and deregulation of psychomotor performance and because of receptor occupancy by hydroxyzine is irreversible so, alternative stimulatory pathway are required to eliminate this worsening, accordingly; activation of NMDA receptor and blocking GABA effects via levofloxacin be able to reverse CNS depression induced by hydroxyzine, this is of value because there is no significant pharmacokinetic interaction between hydroxyzine and levofloxacin [47].
5. CONCLUSION

Levofloxacin is significantly improved psychomotor performance in normal, healthy volunteers and produced CNS stimulation that is able to reverse deteriorations in psychomotor performance and cognitive function induced by hydroxyzine.

CONSENT

All authors declare that written informed consent was obtained from all the patients.

ETHICAL APPROVAL

All participants signed a deceleration manifesting their agreement to participate in all experiments.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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