Original Research Article

Effect of levofloxacin on psychomotor performance tests and blood sugar level in healthy human volunteers

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Abstract

Background: Levofloxacin, a third generation fluoroquinolone, is widely used antibiotic and considered to be safe and well-tolerated drugs. But Central nervous system disturbances and hypoglycemiaare known to be associated with levofloxacin use. Hence, this study was planned in healthy human volunteers to determine the effect of levofloxacin on psychomotor performance (using both subjective and objective tests) and simultaneously on blood sugar. **Material and Methods:** This prospective, randomized, double blind, placebo controlled single dose study was conducted over15 healthy volunteers between 20-40 years of age. Drug administered was levofloxacin 500 mg single dose and a placebo. The objective and subjective parameters were tested. Blood sugar level was measured at 2 hrs on each test day. **Results:** Levofloxacin did not show any effect on psychomotor performance tests. But anxiety was increased significantly at 2 hr and 4 hr and dullness at 4 hr. Only 6.26% subjects reported headache and dizziness. There was no any effect on blood sugar level. **Discussion:** A single dose of levofloxacin can cause significant anxiety and dullness on visual analogue scale but doesn't have effect on objective tests of psychomotor performance. Levofloxacin did not cause changes in the blood glucose concentration.

Key Words: Levofloxacin, psychomotor performance tests, blood sugar level, healthy volunteers.

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Email: gajananchavan2@gmail.com
Received Date: 12/04/2017 Revised Date: 19/06/2017 Accepted Date: 04/07/2017
DOI: https://doi.org/10.26611/1010311

Access this article online	
Quick Response Code:	Website: www.medpulse.in
	Accessed Date: 10 July 2017

INTRODUCTION

Fluoroquinolones (FQs) are widely used antibiotics and considered to be safe and well-tolerated drugs. Central nervous system (CNS) disturbances (5%) are the second most commonly reported adverse event after gastrointestinal disorders (7%), with an overall incidence of about 1–2%[1,2]. Symptoms like headache, dizziness, tremor, confusion, and drowsiness usually occur on the first day of therapy and resolve after discontinuation. They can also cause anxiety, impairment of concentration, abnormal vision. Levofloxacin has one of the most favorable adverse reaction profiles of all the FQs[3]. Levofloxacin is a third generation fluoroquinolone chemotherapeutic agent used in the treatment of severe and resistant bacterial infections. It leads to CNS stimulation via inhibition of GABA-A receptor complex like beta-lactam antibiotics. Other receptors that are probably included in the CNS excitation of levofloxacin are NMDA (N-methyl-D-asparate), adenosine and amino acid receptors. It may also modulate opioid and dopamine receptors through this activation[4]. Although hypoglycemia is known to be associated with levofloxacin, patients are continually being hospitalized because of this adverse events such asanxiety, dizziness, loss of concentration, confusion, drowsiness, blurred vision and tremors. Previous studies established the

How to cite this article: Amruta Dawari, Turankar A V, Bankar M A. Effect of levofloxacin on psychomotor performance tests and blood sugar level in healthy human volunteers. *MedPulse International Journal of Pharmacology.* July 2017; 3(1): 01-05. https://www.medpulse.in/Pharmacology/

causality relationship between the levofloxacin and the hypoglycemia using Naranjo's ADR probability scale and confirmed that serious hypoglycemia may develop due to the use of levofloxacin and appears to occur most frequently in elderly patients with Type 2 diabetes who are receiving oral hypoglycemic agents[5,6]. Hence, this study was planned in healthy human volunteers to determine the effect of levofloxacin on psychomotor performance (using both subjective and objective tests) and simultaneously on blood sugar.

MATERIAL AND METHODS

This prospective, randomized, double blind, placebo controlled single dose study was conducted over15 healthy volunteers between 20-40 years of age with minimum education up to senior secondary school. The study was approved by the Institutional Ethics Committee and written informed consent was obtained from each participant. Individuals with any addiction, history of any past or present illness, chronic drug consumption, allergy to fluoroquinolone antimicrobials and pregnant and lactating women were excluded from the study. Drug administered was levofloxacin 500 mg by Lupin Ltd.and a placebo. Formulations were packed in inert gelatin capsules of same color and dimensions and coded. The formulation was packed in inert gelatin capsule. Drugs administered orally in a single dose by Latin square technique. Before the study volunteers received training till a performance plateau was reached.

Tests for psychomotor functions:

A sensory component: *Six-digit cancellation test (6DCT)*[7]: Volunteers were required to cancel as many target digits as possible in a sheet consisting of 300 randomized digits in 2 min.

Test for recognition and recoding: *Digit symbol substitution test (DSST)*[7]: Volunteers were required to insert the corresponding symbol in the space below each digit in a sheet consisting of 200 randomized digits in 2 min.

Test for central integration: *Critical flicker fusion test (CFFT)*[8,9]: It is a reliable psychometric test as there is no learning curve effect. The Critical Fusion Frequency was determined by increasing the frequency from 5 Hz till a steady light source was seen and the Critical Flicker Frequency by decreasing frequency from 50 Hz till flickering was seen. Then mean of these two frequencies taken.

Test of processing: *Arithmetic ability test (AAT)*[7]: Subjects were asked to solve mathematical problems involving addition, subtraction, Multiplication and division (5 of each). All problems involved two digits. The time allotted for this test was 2 minutes. Two points were given for multiplication and division, while one point for subtraction and addition.

Test of Memory: *Digit span test (DST)*[7]: Subjects were asked to write down a 9 digit sequence after 10 seconds of hearing it. Five such different sequences were repeated and the score was given on number of correct number placements.

Motor component: *A test for steadiness: hand steadiness test (HST)*[7]: The hand steadiness was tested on the steadiness tester. The subject was asked to hold the stylus of instrument and insert it through serial holes in steady constant manner starting from the largest hole diameter and proceeding to smaller ones while avoiding contacts with boundaries of holes.

Subjective measures: *Visual analogue scales (VAS)*[10]: The volunteers were asked to indicate the state of their current feeling by marking on a 100 mm horizontal line. The parameters were headache, dizziness, restlessness, anxiety, loss of concentration, nausea, alert to dull, active to tired and any other symptoms. Blood sugar level was measured at 2 hrs on each test day. The volunteers were asked to note any side effects experienced by them during the course at any other symptom parameter in visual analogue scale section and also grade it.

RESULTS

In this prospective, randomized, double blind, placebo controlled study a total of 15 healthy volunteers were included. Out of these 15 volunteers, 8 were males and 7 were females. There was no change in scores of objective tests after single dose administration of levofloxacin. Significant increase in anxiety was observed compared with baseline and placebo and in levofloxacin groups at 2 hr ($P<0.05$) and it remained significantly increased at 4 hr. ($P<0.05$). No statistically significant difference was observed between VAS rating of anxiety in levofloxacin group. Dullness was significantly increased at 4 hrs in levofloxacin groups compared to placebo and baseline. (Table 1, 2). Levofloxacin group showed 6.26% incidence of headacheand dizziness. There was no significant change in blood sugar level in any group at 2 hr.

Table 1: Effects of Placebo and Levofloxacin at 0, 2 and 4 hr

Test	Drug	Mean ± SD			Mean difference	
		0 hr	2 hr	4 hr	2 hr	4 hr
DSST	Placebo	86.8 ±14.97	87.6 ±14.44	89.6 ±13.12	-0.8	-2.8
	Levofloxacin	89.33 ±13.52	91.27 ±13.77	92.67 ±17.35	-1.933	-3.333
6DCT	Placebo	53.47 ±7.09	51.67 ±4.186	53.4 ±3.996	1.8	0.0667
	Levofloxacin	53.47 ±4.389	51.27 ±5.725	54.33 ±3.374	2.2	-0.8667
CFFT	Placebo	39.03 ±1.685	38.73 ±1.86	38.5 ±1.89	0.3	0.5333
	Levofloxacin	39.5 ±1.5	40.53 ±3.843	39.5 ±1.476	-1.033	0
AAT	Placebo	16.4 ±3.776	18.07 ±4.008	17.73 ±4.008	-1.667	-1.333
	Levofloxacin	17.73 ±3.731	18.6 ±4.05	18.2 ±2.541	-0.866	-0.4667
DST	Placebo	35.47 ±6.198	37.07 ±5.8	36.4 ±7.119	-1.6	-0.933
	Levofloxacin	37.2 ±5.506	37.47 ±6.523	36.73 ±6.724	-0.266	0.4667
HST	Placebo	104.3±21.5	100.5 ±27.56	97.06±26.86	3.778	7.225
	Levofloxacin	100.4±26.59	96.98 ±28.84	95.35±26.23	3.458	5.088
VAS Anxiety	Placebo	5.867±2.295	7.267±1.534	7.200±1.320	-1.400	-1.333
	Levofloxacin	6.000±4.520	8.933±2.738	9.333±3.416	-2.933*	-3.333*
VAS Restlessness	Placebo	5.467±5.167	6.867±6.707	6.667±7.659	-1.400	-1.200
	Levofloxacin	5.733±3.674	6.533±5.514	8.467±5.370	-0.8000	-2.733
VAS Loss of concentration	Placebo	7.067±5.75	7.533±7.21	7.333±6.726	-0.467	-0.267
	Levofloxacin	7.733±3.990	8.067±5.021	9.667±4.746	-0.3333	-1.933
VAS Active-tired	Placebo	8.200±4.843	8.333±5.876	8.133±5.222	-0.1333	0.0667
	Levofloxacin	8.200±4.843	11.27±6.787	13.07±5.982	-3.067	-4.867
VAS Alert-dull	Placebo	8.733±5.444	9.067±7.186	8.533±4.719	-0.3333	0.2000
	Levofloxacin	9.667±3.155	11.93±6.053	13.8±3.448	-2.267	-4.133*

Test- repeated measures ANOVA, post hoc- Tuckey. (6DCT- 6 digit cancellation test, CFFT- critical flicker fusion test, AAT- arithmetic ability test, DST- digit span test, HST- hand steadiness test, VAS- visual analogue scale).

Table 2: Interdrug comparison of mean difference at 2 and 4 hr

Test	Drug	Mean difference	
		At 2 hr	At 4 hr
DSST	Placebo/Levofloxacin	-3.667	-3.067
6DCT	Placebo/Levofloxacin	0.4	-0.9333
CFFT	Placebo/Levofloxacin	-1.800	-1.1
AAT	Placebo/Levofloxacin	-0.5333	-0.4667
DST	Placebo/Levofloxacin	-0.4	-0.3333
HST	Placebo/Levofloxacin	3.519	1.702
VAS Anxiety	Placebo/Levofloxacin	-1.667*	-2.133*
VAS Restlessness	Placebo/Levofloxacin	0.3333	-1.800
VAS Loss of concentration	Placebo/Levofloxacin	-0.5333	-2.333
VAS Active-tired	Placebo/Levofloxacin	-2.933	-4.933
VAS Alert-dull	Placebo/Levofloxacin	-2.867	--5.267*

Test- repeated measures ANOVA, post hoc- Tuckey. (6DCT- 6 digit cancellation test, CFFT- critical flicker fusion test, AAT- arithmetic ability test, DST- digit span test, HST- hand steadiness test, VAS- visual analogue scale.)

DISCUSSION

Although the clinical utility of levofloxacin, a fluoroquinolone antibacterial agent is well known, it's increased use has revealed various adverse reactions that were not predicted by the nonclinical and clinical studies performed during drug development. The most problematic adverse reactions are those affecting the central nervous system. It has also been reported that some newer quinolones with strong activity against Gram-positive bacteria can cause adverse reactions such as hypoglycemia[11]. In present study, levofloxacin showed no significant changes in the scores of objective tests on single dose administration (Table 1, 2). Multiple dosing may have different effect on these parameters. Significant rise in anxiety in levofloxacin group when compared to baseline and placebo at 2 hr and 4 hr can be explained by work of some authors like, Kandasamy and Shrinath, who have reported acute induction of anxiety after single dose ingestion of levofloxacin in three patients between 30-32 years of age[12]. In present study VAS rating for dullness was increased at 2 hr in levofloxacin group compared to baseline and placebo, but the difference was significant at 4 hr. Mandell and Tillotson reviewed safety of fluoroquinolones and reported that fluoroquinolones can cause impaired thinking[13]. Incidence rate of headache in levofloxacin group was 6.6% in present study which was not statistically significant. According to Mandell and

Tillotson the incidence of levofloxacin related headache in patients is 6%[13], which is in accordance with our study. While Liu HH in his review article states that, at least 3% patients report headache due to levofloxacin[14]. Incidence of dizziness was 6.6% in levofloxacin group after 4 hr. According to review of Mandell and Tillotson, the incidence of levofloxacin related dizziness in patients is 3%[13]. Blood sugar level was within normal range after ingestion of drugs. It shows that whatever changes are observed in subjective parameters are not related to blood glucose level and they are pure CNS side effects. In present study, dysglycaemia was not reported in any volunteer. Levofloxacin did not cause changes in the blood glucose concentration or show direct toxicity for the pancreas in a studyby Yamaguchi H *et al*[3]. It is hypothesized that competitive antagonism of GABA (γ-aminobutyric acid) at its receptor by fluoroquinolones causes CNS stimulation or interaction with glutamate receptors results in CNS stimulation [15,16]. This mechanism can explain the CNS stimulatory symptom like anxiety. Some studies also suggest that CNS penetration by quinolones does not correlate with the reported incidence of CNS ADRs[17]. Mandell and Tillotson suggested that fluoroquinolone can also induce excitatory effect through activation of NMDA and adenosine receptors. Thus, they made an assumption that may be only under specific conditions of sufficient CNS penetration, coupled with threshold antagonism of GABA and stimulation of excitatory NMDA and adenosine receptor observable CNS symptoms may manifest[13]. The exact mechanism is yet to be established. Some studies have reported stimulatory effects of fluoroquinolones on CNS such as anxiety, insomnia, mania, hyperactive delirium, seizure[18], while other studies have reported contradictory effects of fluoroquinolones such as hypoactive delirium, somnolence[19]. The reason behind these contradictory and wide variety of findings is still not well understood. This contradiction is also observed in our study as subjective test of visual analogue scale is significant for anxiety (stimulatory effect) and dullness (inhibitory effect). The percentage of reporting of CNS side effects varies in various studies. According to Moorthy *et al*., CNS related side effects occur in 0.9-11% patients[18]. Francesco *et al*. have mentioned 6.5% incidence rate for levofloxacin related CNS ADRs[20]. The varying incidence of reporting of ADRs in clinical studies can be due to variation in the time of approval of a product, geographical variation, new knowledge of toxicity, media attention and improved diagnostic capabilities. This prospective, double blind, crossover, placebo controlled trial provides more insight information about effect of levofloxacin on psychomotor performance tests. It would have been more informative and useful to study effect of multiple doses of levofloxacin on healthy volunteers, than the single dose used in this study. A single dose of levofloxacin can cause significant anxiety and dullness on visual analogue scalebut doesn't have effect on objective tests of psychomotor performance. Levofloxacin did not cause changes in the blood glucose concentration.

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Source of Support: None Declared
Conflict of Interest: None Declared