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Original Article

A Correlational Research Study on Diurnal Chronopharmacovigilance Characterization of Levofloxacin, with Molecular Pharmacokinetics and Structural Variations, among Worldwide Respiratory Patients in Tertiary Healthcare Hospitals

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Abstract

Introduction: Levofloxacin, the S- or levorotatory isomer of racemic mixture of ofloxacin, has an inhibitory effect on DNA gyrase, DNA topoisomerase IV and interleukin (IL)-1α, IL-6, IL-8, Tumor necrosis factor-α (TNFα); and a super inducing effect on IL-2.

Objective: The objective of this study is a correlational research on diurnal chronopharmacovigilance characterization of levofloxacin, with molecular pharmacokinetics and structural variations, among worldwide respiratory patients in tertiary healthcare hospitals.

Methods: A worldwide, multi-center, prospective, open-labeled study was conducted, with 100 respiratory tertiary healthcare patients, who were prescribed oral levofloxacin 750 mg once daily for 5–7 days, depending on their disease severity and their suitable treatment regimen. The safety assessment of levofloxacin was done by adverse drug reactions (ADR) monitoring, of diarrhea, nausea, dizziness, arthralgia, headache, vomiting, rashes, hemoptysis, and chest pain, occurring due to levofloxacin therapy, with Adverse Event Case Report Forms. A chronopharmacotherapeutic pharmacovigilance analysis of the occurrence of the adverse effects, was also conducted, on diurnal basis, and subsequently correlated with molecular pharmacokinetics and structural variations. These research findings were thoroughly analyzed, along with statistical interpretations.

Results: The adverse effects were statistically non-significant, as there were no occurrence of any ADR. Levofloxacin was a safe respiratory tertiary healthcare drug, with sufficient tolerability found among the patients. This study delineated quite a predictable chronopharmacovigilance illustration, with clearly demarcated day-wise appearance of adverse reactions, if at all, any, without any variability in the pattern of any adverse reaction occurring; along with distinctly logical correlations with the molecular pharmacokinetics and structural variations of levofloxacin.

Conclusions: Levofloxacin demonstrated pharmacotherapeutic safety and tolerability among worldwide respiratory tertiary healthcare patients, with an anticipated chronopharmacovigilance presentation, correlated well with the molecular pharmacokinetics and structural variations.

Key words: Chronopharmacovigilance, Fluoroquinolones, Levofloxacin, Molecular pharmacokinetics, Respiratory tertiary healthcare, Structural variations

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INTRODUCTION

Levofloxacin, the S- or levorotatory isomer of racemic mixture of ofloxacin, has an inhibitory effect on DNA gyrase, DNA topoisomerase IV and interleukin (IL)-1α, IL-6, IL-8, Tumor necrosis factor-α (TNFα); and a super inducing effect on IL-2. Certain commonplace

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fluoroquinolones have profound bactericidal, antitubercular, antileprotic, antiviral including anticoronavirus, antifungal, antiprotozoal, comedolytic, anticomedogenic, anti-inflammatory, immunomodulatory, and antimalignant: pro-apoptotic and antiproliferative potential, including transforming growth factor beta 1 (TGFβ1) targeted G2 phase cell cycle arrest.[1-3]

According to the structure activity relationship studies of quinolones as antitubercular agents, the β-keto carboxylic acid moiety is required for hydrogen bonding interactions with DNA bases, and therefore, it is essential for their anti-tubercular activity. The substituent at N-1 and C-8 positions should be relatively small and lipophilic to enhance the activity. Fluorine at C-6 is the best substituent, and it improves cell penetration and gyrase affinity. Substituents at the C-7 position are very essential for the different physicochemical as well as pharmacological properties of levofloxacin.[4]

Objectives

The objective of this study was a correlational research on diurnal chronopharmacovigilance characterization of levofloxacin, with molecular pharmacokinetics and structural variations, among worldwide respiratory patients in tertiary healthcare hospitals.

METHODS

Ethical Approval

At first, the Institutional Ethics Committee clearance and approval was taken. The study was conducted in accordance with the ethical principles of Declaration of Helsinki and Good Clinical Practices contained within the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use, ICH-E6 and ICH-E17, and in compliance with the global regulatory requirements. The patients who were included in the study were assured confidentiality, and an informed consent was obtained from each patient.

Study Design

This study was a worldwide, multi-center, prospective, open-labeled, correlational study.

Place of Study

This research study and the compilation of study literature was conducted at the Departments of Pharmacology, Clinical Pharmacology, Molecular Pharmacology, Rational Pharmacotherapeutics, Pharmacovigilance, Clinical Pathology, Respiratory Medicine, Tuberculosis (TB) and Chest Diseases, in multi-center, tertiary care hospitals, medical colleges and laboratories: Dr. Moumita Hazra's Polyclinic And Diagnostic Centre, Hazra Nursing Home, Rama Medical College Hospital and Research Centre, Rama University, Mamata Medical College and Hospitals, J. J. M. Medical College and Hospitals, GIOSTAR Institute of Regenerative Medicine Institutes, Hospitals and Laboratories.

Study Period

The total study period for this research study and the compilation of the study literature was for 5 months, from January, 2015 to March, 2015; July, 2021; and November, 2021 to December, 2021.

Study Population

The study population consisted of a total of 100 patients, in respiratory tertiary healthcare.

Selection Criteria of the Study Population

Inclusion criteria

The inclusion criteria were as following: (i) patients of any gender, (ii) patients within 18 and 55 years, (iv) co-operative and conscious patients, (v) patients willing to undergo all pre- and post- treatment investigations and willing to complete entire course of treatment, (vi) patients who have given consent and are willing to go for a follow-up, (vii) patients not taking any concomitant medication.

Exclusion criteria

The exclusion criteria were as following: (i) uncooperative or unconscious patients, (ii) patients below 18 and above 55 years, (iii) patients with a history of hypersensitivity to any of the study drugs, (iv) patients with high risk diseases or co-morbidities, (v) cardiac, renal or any other associated complications or co-morbidities, (vi) any chronic disease intervening with the study data, (xi) children or very old patients, (xii) other associated medical illness or disorders having impact on study results.

Study Procedure

About 100 respiratory tertiary healthcare patients were prescribed oral levofloxacin 750 mg once daily for 5–7 days, depending on their disease severity and their suitable treatment regimen. The following data of the patients' thorough history with complete examination details were obtained: The patients' participation assessment and adherence to treatment, including patients who completed the study thoroughly, number of drop-out patients to adverse effects, patients who were lost to follow-up and patients who withdrew voluntarily; the demographic characteristics, including age, gender, race, body mass index (BMI), duration of symptoms of the respiratory diseases; severity of disease symptoms, present controller medications, the patients' present and past history, gastrointestinal history, respiratory history including

respiratory immunological history and history of allergy, chronic obstructive pulmonary disease and asthma, history of multidrug-resistant TB (MDR-TB) contacts, past TB treatment history, and drug susceptibility testing results, cardiac history, history of co-morbidities, family history, personal history, socioeconomic history, metabolic history, history of any chronic disease, reproductive history, concomitant medication history, and surgical history, and the findings were recorded.

The details of complete general physical examination, and systemic examination, including oto-rhino-laryngo-tracheal, respiratory including obstructive pulmonary and tubercular, and cardio-pulmonary examinations, were recorded. Blood pressure, pulse rate, oxygen saturation of arterial hemoglobin (SpO2) measurements, and respiratory rate were recorded. Antibiotic culture and sensitivity were done for each patient.

The safety assessment of levofloxacin was done by monitoring any adverse drug reactions (ADRs), such as, diarrhea, nausea, dizziness, arthralgia, headache, vomiting, rashes, hemoptysis, and chest pain, that had occurred due to the drug therapy, witnessed by the patient or the doctor, during the treatment period or during the follow-up, with Adverse Event (AE) Case Report Forms, on days 0, 3, 5, 7, 10, 15, 21, 30 and on further follow-ups. A chronopharmacotherapeutic pharmacovigilance analysis was also done by the day-wise appearance of various potential adverse effects, that is, any occurrence of diarrhea on day 2, nausea on day 3, dizziness on day 4, arthralgia on day 4, headache on day 5, vomiting on day 5, rashes on day 6, hemoptysis on day 7, and chest pain on day 7. The analytical findings were correlated with the molecular pharmacokinetics and structural variations of levofloxacin.

Complete blood examination, complete respiratory diseases examinations including Mantoux test, chest X-ray, sputum examination, coronavirus reverse transcription polymerase chain reaction examination, respiratory spirometry variables, lesion biopsies, routine metabolic examinations, and imaging examinations were performed, for (i) the baseline assessment values on day 0, (ii) the values after the completion of the required prescribed regimens administration, (iii) the values after the complete recovery, and (iv) the values on each follow-up visit.

Statistical Analysis

The research findings were thoroughly analyzed, along with statistical interpretations, and subsequent tabular illustrations, along with the test of significance, being denoted by the *P*-value.

RESULTS

All 100 patients had participated and adhered to levofloxacin treatment and had subsequently completed the study thoroughly. There were no drop-out patients due to any ADRs, no patients who were lost to follow-up and no patients who withdrew voluntarily. The demographic characteristics of the patients were comparable.

There was no occurrence of any ADR among the patients, with oral levofloxacin treatment. Therefore, the occurrence of adverse effects was statistically non-significant. Levofloxacin was a safe respiratory tertiary healthcare drug, with sufficient tolerability found among the patients. This study delineated quite a predictable chronopharmacovigilance illustration, as depicted in Table 1, with clearly demarcated day-wise appearance of adverse reactions, if at all, any, without any variability in the pattern of any ADR occurring; along with distinctly logical molecular pharmacokinetic correlations and structural variations of levofloxacin.

DISCUSSION

With the advent of quinolones, and later the fluorinated 4-quinolones, the fluoroquinolones, the medical world has certainly taken long strides in treating enormous number of maladies.[1]

Fluoroquinolones, like levofloxacin, are chemical derivatives of quinoline, the prodrome of chloroquine. Fluoroquinolones, a family of 6-fluoro-7-piperazinyl-4-quinolones, are broad spectrum synthetic antimicrobial agents derived from quinolones with the addition of a fluorine atom attached to the central ring.[2,5]

Substitution at C-7 or its N-4-piperazinyl moiety was found to affect physicochemical properties, potency, bioavailability, lipophilicity, and safety of fluoroquinolones, like levofloxacin. The presence of DNA topoisomerases in both eukaryotic and prokaryotic cells makes them excellent targets for chemotherapeutic intervention in antibacterial therapies.[4]

Fluoroquinolones, like levofloxacin, are quite significantly efficacious for their bactericidal inhibitory effect on:

1. DNA gyrase, caused by the binding of fluoroquinolones to the A subunits (gyr A), thus inhibiting the replication and transcription of bacterial DNA, responsible for the proper functioning of the cell, and the subsequent change of conformity of DNA gyrase molecule caused by the binding of fluoroquinolones to the DNA binding groove between A (gyr A) and B (gyr B) subunits

Table 1: The chronopharmacological representation of the occurrence of adverse drug reactions with oral levofloxacin administration, among the patients

Adverse drug reactions due to levofloxacin therapy	Average day of occurrence from initiation of levofloxacin therapy	Number of patients having adverse reactions	*Z*-value	*P*-value
Diarrhea	Day 2	0	–	Non-significant
Nausea	Day 3	0	–	Non-significant
Dizziness	Day 4	0	–	Non-significant
Arthralgia	Day 4	0	–	Non-significant
Headache	Day 5	0	–	Non-significant
Vomiting	Day 5	0	–	Non-significant
Rashes	Day 6	0	–	Non-significant
Hemoptysis	Day 7	0	–	Non-significant
Chest Pain	Day 7	0	–	Non-significant

2. Par C subunits (par C) and Par E subunits (par E) of DNA topoisomerase IV, thus inhibiting decatenation and relaxation of DNA and segregation of replicating chromosomes or plasmids in bacteria
3. Pro-inflammatory cytokines, like ILs: IL-1α, IL-6, IL-8, and tumor necrosis factor α, leading to attenuation of inflammatory response and exhibiting multiple immunomodulatory actions.[1-3]

Fluoroquinolones also have super inducing effect on IL-2.[1] Third-generation quinolones, for example, levofloxacin, have expanded activity against gram-positive bacteria and atypical pathogens.[1]

In this study, there was no occurrence of any ADR among the patients, with oral levofloxacin treatment. Therefore, the occurrence of adverse effects was statistically non-significant. Levofloxacin was a safe respiratory tertiary care drug, with sufficient tolerability found among the patients. This study delineated quite a predictable chronopharmacovigilance illustration, with clearly demarcated day-wise appearance of adverse reactions, if at all, any, without any variability in the pattern of any adverse reaction occurring; along with distinctly logical molecular pharmacokinetic correlations and structural variations of levofloxacin.

Figure 1 depicts the pharmacokinetics of quinolones as improved by the modifications of different substituents in different positions. The development of quinolones, like levofloxacin, in terms of pharmacokinetics and pharmacodynamics, relates to improvements in metabolism, elimination, and transportation, leading to improved antibiotic dosing strategies to enhance the efficacy and prevention of resistant mutations. Use of the very first quinolone agent, nalidixic acid, was limited because it had low serum levels; therefore, it was used as a urinary agent only. The modifications in the structure of later generations of quinolones led to improved oral absorption as well as larger area under the curve (AUC) and/or maximum serum concentrations (Cmax) compared to nalidixic acid. Those modifications also produced longer elimination half-lives, which permitted once-daily dosing for some agents of the second generation and all agents of later generations. Since most of the earlier quinolones had low serum levels and moderate potency, they required frequent doses, with the once-daily dosing of latter agents resulting not only from better exposure but also from their significantly enhanced potency. They also had better tissue penetration. There is no trend in the extent of protein binding related to the structural modifications. This parameter varies between agents, with some <30% (norfloxacin, lomefloxacin, and gatifloxacin) and others >80% (nalidixic acid, trovafloxacin, and garenoxacin).

Gradually, changes in the metabolism of quinolones were observed; although earlier quinolones were primarily eliminated by metabolism and renal clearance, later quinolones were modified to become non-renal clearance agents (sparfloxacin, moxifloxacin, gemifloxacin, trovafloxacin, and garenoxacin). The quinolones show concentration-dependent killing with persistent post-antibiotic effect, and the therapeutic outcomes of this group are based on either the AUC/minimum inhibitory concentration (MIC) ratio or the Cmax/MIC ratio. Thus, a high AUC or Cmax value combined with low MIC is ideal for increasing the ratio and thereby improving the efficacy. The increase in resistance to ciprofloxacin when treating infections with common low-dose regimens, ultimately led to innumerous clinical studies to define the pharmacodynamic parameters for predicting efficacy, and this finally concluded the prolonged deliberations regarding the quantitative indicators, like ratio, of microbiological, as well as, clinical outcomes of quinolones. According to several studies, the second-generation quinolones did not obtain a high Cmax/MIC ratio, with the AUC/MIC ratio more accurately reflecting their efficacy. It was shown that an AUC/MIC ratio of >125 indicated the best therapeutic outcomes, and any agent with a Cmax/MIC ratio lower than four indicated

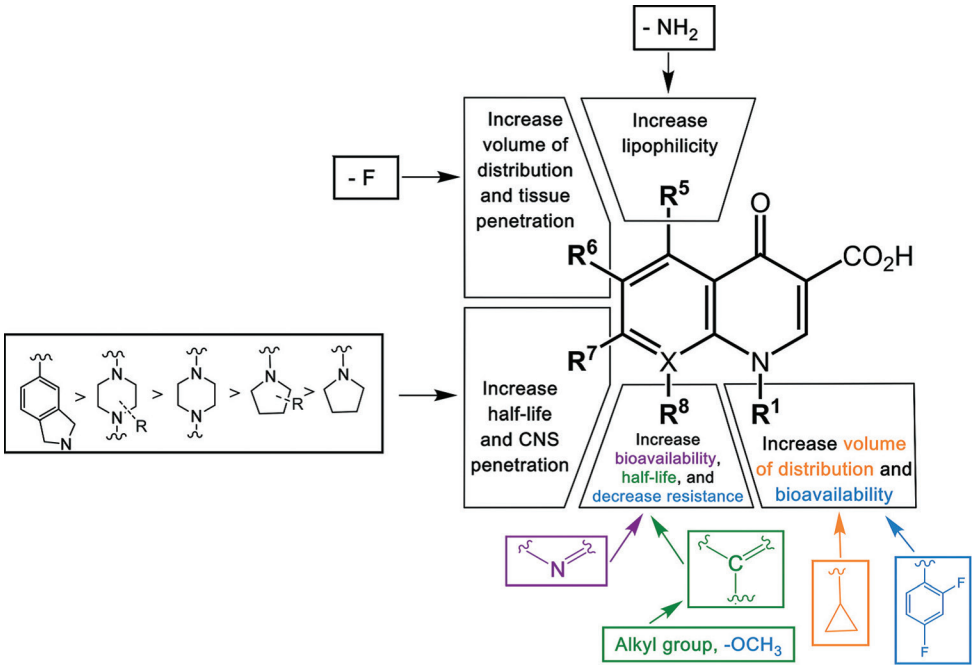

Figure 1: The structure–pharmacokinetic relationship of quinolones[6]

suboptimal outcomes. However, the minimum acceptable AUC/MIC ratio is still uncertain. Some researchers have proposed that an AUC/MIC ratio of 25 is appropriate for use in mild infections and immunocompetent patients, while a value of ≥100 is needed for serious infections and immunocompromised patients. While the AUC/MIC ratio is used to determine the microbiological outcome of quinolone treatment, the Cmax/MIC ratio has been determined to be a factor for preventing the emergence of resistance to quinolones. A higher Cmax is preferable for lower resistance occurrence. Many *in vitro* studies showed that a low AUC/MIC ratio will increase the selection of resistant mutants, even if this ratio is clinically effective for the infections. Combined with the Cmax/MIC ratio, a "mutant prevention concentration" (MPC) was developed for prevention of resistance. It is the concentration necessary to prevent the growth of the least susceptible, single step mutants, with 1010 bacteria incubated in the presence of different increasing concentrations of the antibiotics. The MPC is the concentration in which there is no observation of growth of those bacteria. This MPC is used to prevent resistance during therapy, suggesting a minimum serum concentration to be achieved. This target was used during the development of the third generation of quinolones (gatifloxacin, gemifloxacin, moxifloxacin); they exert lower MPC values than the earlier quinolones when used against *Streptococcus pneumoniae*. Accordingly, the MPC of ciprofloxacin for *Pseudomonas aeruginosa* is lower than that of levofloxacin. Key structural modifications for improving the pharmacokinetics of quinolones are presented at the R5, R6, R7, and R8 positions, which result in longer elimination half-life, better tissue penetration, increased volume distribution, and better bioavailability. The addition of an amino group at R5 increased the quinolones' lipophilicity, which can be seen from the structure of sparfloxacin. The fluorine substituent at position R6 proved to facilitate penetration into the bacterial cell and also improve the volume of distribution of the drug. This improvement was observed during the development of the second-generation of quinolones and was retained until the latest agent of the fourth generation, garenoxacin. The addition of substituents at the R7 position mediated the improvement of the half-life and bacterial tissue penetration. The azabicyclic group and piperazine group at R7 extended the agents' half-life to >10 h by increasing the lipophilicity. Another substituent at this position is the pyrrolidine rings; while this modification is critical for enhancing the potency of quinolones; it was associated with unfavorable water solubility and oral bioavailability. To overcome these physical properties, subsequent generations of quinolones introduced a methyl group into the rings, which can be seen from the examples of gemifloxacin and trovafloxacin. Furthermore, the alkylation of the rings at the R7 position increased the elimination half-life and bioavailability of the agents. The addition of a methyl group to the piperazine rings significantly increased the elimination half-life of ofloxacin, lomefloxacin, sparfloxacin, grepafloxacin, and gatifloxacin compared to enofloxacin, norfloxacin, and ciprofloxacin, which have only the piperazine group in the structure. Alkylation at the R8 position increased the elimination half-life. The latest key modification is

a methoxy group at this position, which lowered the development of resistance to quinolones.

The most common adverse effects of the quinolones are gastrointestinal effects and, less commonly, arthralgia (or joint pain), which are associated with the structural feature of the quinolone pharmacophore. Due to these primary adverse effects, this class is limited for pediatric prescriptions. On account of these class-related ADRs, quinolones are usually clinically prescribed less commonly. These disadvantages were reported to be dependent on the substituents in different positions on the pharmacophore and specific to particular agents. Very rarely, QTc prolongation and cardiac arrhythmia might occur in patients using sparfloxacin and grepafloxacin. Infrequently, phototoxicity was observed when using clinafloxacin and sparfloxacin. There were very rare, transient occurrences of tendon rupture, nerve damage, and fluoroquinolone-associated disability syndrome, only with prolonged use of fluoroquinolones. Other rare adverse effects included hematological toxicity with temafloxacin, hepatitis with trovafloxacin, and hypoglycemia effects with clinafloxacin and gatifloxacin. Immunological side effects, central nervous system (CNS) effects and genotoxicity, were also rarely observed. The genotoxicity of quinolones is only seen in some fluoroquinolones when exposed to ultraviolet light, such as lomefloxacin, ciprofloxacin, and moxifloxacin. Numerous and varied types of recent structural modifications of quinolones, have caused an adequate reduction in these ADRs, and some recent quinolones, like garenoxacin and others, have proved to cause negligible adverse effects. The safety profile of quinolones is being updated constantly. The substituent at the R1 position was shown to be related to the inhibition of cytochrome P450, with cyclopropyl and the alkyl groups at this position affected more than when substituted with a 2,4-difluorophenyl group. Other modifications leading to cytochrome P450 interactions were the replacement of the carbon atom with nitrogen at the X position, and the addition of a bulky side chain into the X8 of quinolones. Genotoxicity, which does not occur in usual clinical treatment, was shown to occur rarely, if at all, in agents with –NH2 and –CH3 substituents at the R5 position, fluorine (F) at the R6 and R8 positions, and chlorine (Cl) at the R8 position. Another specific structural change associated with the genotoxicity was modifications of the group at position 7, with a decrease in severe effects by pyrrolidinyl, piperazine, and alkyl groups, respectively. Phototoxicity is also a rare adverse effect caused by the accumulation of susceptible drugs in the skin where they can be activated by exposure to sunlight, causing damage to the skin. This was observed in agents with an –NH2 group at the R5 position and fluorine (F) or chlorine (Cl) at the R8 position. Quinolones possessing this adverse effect include lomefloxacin, sparfloxacin, and clinafloxacin. CNS reactions including dizziness, insomnia, and headache have been induced by some quinolones, although very infrequently. This adverse effect has been shown to be associated with the inhibition of GABA receptors, a major inhibitory neurotransmitter, and was observed in agents with additional groups at position R7.[6]

Yet, as applicable to any clinical pharmacotherapeutic characterization of drug efficacy and safety, the extensive and infinite spectrum of the clinical pharmacotherapeutic uses of quinolones, for example, levofloxacin, included extremely complicated, recurrent, relapsing and refractory diseases and disorders, complemented with highly efficacious clinical pharmacotherapeutic outcomes, from time immemorial; and quinolones have always very efficiently overwhelmed the minimal ADRs observed, with these extensive range of pharmacotherapeutic applications, thus retaining the unyielding efficacy of this clinical pharmacotherapeutically successful drug category, to remain a novel pharmacotherapeutic, as always. Moreover, throughout the continuing clinical trials, conducted on quinolones, from time even more than the decades, the occurrence of ADRs were almost always statistically non-significant, along with statistically highly significant efficacy levels, thus concluding the immense significance of the quinolones, as a multi-dimensional pharmacotherapeutic agent.

As an anti-microbial agent, fluoroquinolones are active against *Haemophilus influenzae*, *Moraxella catarrhalis*, *Mycoplasma* species, *Chlamydia* species, *Chlamydophila* species, *Legionella* species, *Enterobacteriaceae*, *P. aeruginosa* (particularly ciprofloxacin), *Mycobacterium* TB, some atypical mycobacteria, some methicillin-sensitive Staphylococci, *Campylobacter* species, Salmonellae, *Shigella*, Vibrios, *Yersinia enterocolitica*, *Chlamydia trachomatis*, *Legionella*, and are also indicated in anthrax prophylaxis and meningococcal prophylaxis. The dual inhibitory activity of fluoroquinolones against the bacterial replication enzymes, DNA gyrase and topoisomerase IV, protects them from the development of resistance. For *Mycobacterium* TB, the MPC90 (MPC for 90% of strains) for fluoroquinolones have been found to be ciprofloxacin >levofloxacin >gatifloxacin >moxifloxacin respectively. Hence, gatifloxacin and moxifloxacin are less likely to provoke the development of resistance. Several studies have recommended that levofloxacin is the first-choice fluoroquinolone for MDR-TB. Ofloxacin is also effective for MDR-TB, being the racemic mixture of the S- or levorotatory isomer of ofloxacin: levofloxacin.[7]

Fluoroquinolones, like of loxacin, levofloxacin, ciprofloxacin and moxifloxacin, are relatively new potent oral bactericidal drugs for TB, that have gained prominence

as well tolerated alternatives to first line anti-tubercular drugs. They are active against *Mycobacterium avium* complex, *Mycobacterium fortuitum* and some other atypical mycobacteria as well. Moxifloxacin is the most active fluoroquinolone against *Mycobacterium* TB, while levofloxacin is more active than ofloxacin and ciprofloxacin. Fluoroquinolones are a key component of all regimens for MDR-TB, except when the bacilli are found to be resistant to them. The Revised National TB Control Program of India has included ofloxacin or levofloxacin in the standardized regimen for MDR-TB. If used alone, mycobacterial resistance to ofloxacin, levofloxacin and ciprofloxacin develops rapidly by the mutation of DNA gyrase gene. Experimental data indicates that the resistance against moxifloxacin is slow to develop.[8]

Fluoroquinolones have early bactericidal activity, which is the decline in colony-forming units in sputum over the first 2 days of treatment, reflecting rapid killing of metabolically active organisms, an important factor in interrupting transmission, over days 2–7.

Experimental studies have demonstrated that levofloxacin exerts antioxidative and nitric oxide (NO) regulatory effects in an animal model of H1N1 influenza virus induced lung injury, and significantly improves survival. In particular, levofloxacin exhibited scavenging actions against neutrophil-derived hydroxyl radicals and suppressed NO production, leading to decreased markers of oxidative stress and NO metabolites in the lungs of H1N1 influenza virus infected animals. A recent *in silico* study demonstrated that the fluoroquinolones, ciprofloxacin and moxifloxacin, exert strong capacity for binding to SARS-CoV-2 main protease (Mpro), indicating that fluoroquinolones may inhibit SARS-CoV-2 replication.[5]

Ofloxacin has more potent gram-positive activity; separation of the more active S- or levo rotatory isomer yields levofloxacin, which has even better anti-microbial activity. Bioavailability of both of these drugs is excellent, such that intravenous (IV) and oral doses are the same; levofloxacin is dosed once daily as opposed to twice daily dosing for ofloxacin.[9]

Fluoroquinolones are active against Gram-negative and Gram-positive bacteria, anaerobes, mycobacteria and atypical pathogens. Respiratory fluoroquinolones, levofloxacin and moxifloxacin, constitute fist line therapeutic agents for the management of severe community-acquired pneumonia, according to the treatment guidelines.[1,2]

In yet another study, the add-on dry powder inhaler of combined anti-TB therapy (each capsule contained isoniazid 5 mg, rifampicin 2 mg, pyrazinamide 16 mg, and levofloxacin 2 mg) was administered throughout the course of the standard oral anti-TB treatment. The percentage of patients achieving primary outcome of *Mycobacterium* TB sputum culture conversion measured after receiving treatment for 8 weeks, were similar in both study and control groups; and the study group patients seemed to achieve the primary outcome earlier, along with lessened cough, than the control group; at the end of week 4 of treatment; and reduced hemoptysis in the study group at week 2 of treatment. Secondary outcomes were clinical signs and symptoms of pulmonary TB and ADRs related to anti-TB agents. Regarding safety outcomes, no dyspnea or severe ADRs were reported. AEs related to oral anti-TB agents, (e.g. liver function tests) were in normal ranges in most patients in both groups during the treatment. The incidences of common AEs reported (e.g., anorexia, dizziness, numbness, arthralgia, rash, and itching) were similar between the two groups, while the incidences of nausea and vomiting were significantly lower in the study group than the control group.[10]

In a study, the efficacy of inhaled levofloxacin solution in 86 patients with cystic fibrosis (CF) in terms of the following outcome parameters: changes in %-predicted forced expiratory volume in 1 s (FEV1), BMI, and exacerbation rate, was evaluated, and an intraindividual analysis of patients who received levofloxacin inhalation solution twice daily 240 mg for at least 4 weeks, was done. Change in FEV1% predicted for the treatment period was +2.27% after 4 weeks; there was no change in BMI for overall group, but exacerbation rate compared to 1 year before initiation of inhaled levofloxacin decreased significantly after 1 year of treatment. In patients with CF, inhaled levofloxacin solution has the potential to improve FEV1 and to reduce the number of bronchopulmonary exacerbations.[11]

Levofloxacin inhaled solution (LIS) joins the limited number of antimicrobials with evidence to support their use in CF. Among oral and IV use, the European Medical Association has confirmed that there is a positive benefit–risk ratio for the use of inhaled levofloxacin in adult patients with CF with chronic *P. aeruginosa* lung infections. LIS provides antimicrobial therapy at high concentrations topically, reducing systemic exposure compared with oral or IV levofloxacin administration. The overall efficacy and safety data suggest that LIS is a viable therapy for patients with CF and is a valuable addition to the toolbox clinicians possess to manage chronic *P. aeruginosa* infection in adults with CF, particularly with the potential to penetrate the biofilm and the positive effect on exacerbations; the broad spectrum of action that it offers in comparison to existing inhaled antimicrobials might be of additional interest considering the growing appreciation of the prevalence and complex nature of coinfections such as *Staphylococcus aureus*.[12]

This research study on molecular pharmacokinetics, correlated with the diurnal chronopharmacovigilance of levofloxacin, would remain a milestone in the development of yet more efficacious and safe pharmacotherapeutic agents for respiratory diseases, while improvising the respiratory health, for every generation.

CONCLUSIONS

Levofloxacin demonstrated pharmacotherapeutic safety and tolerability among worldwide respiratory tertiary healthcare patients, with an anticipated chronopharmacovigilance presentation, correlated well with molecular pharmacokinetics and structural variations.

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REFERENCES

1. Hazra M. A multivariate comparative clinical pharmacotherapeutic efficacy and chronopharmacovigilance assessment study of ofloxacin, one of the commonplace TGFβ1 inducing and telomerase impairing fluoroquinolones, in treating acute gastroenteritis, chronic obstructive pulmonary disease, new drug-sensitive tuberculosis, recurrent mixed cutaneous infections, and post-surgical refractory wound infections, among the global patients, with heterogenous pharmacogeographic and pharmacogenomic constitution. Int J Basic Clin Pharmacol 2021;10:270-80.
2. Petri WA Jr. Sulfonamides, trimethoprim-sulphamethoxazole, quinolones, and agents for urinary tract infections. In: Laurence LB, Bruce AC, Bjorn CK, editor. Goodman and Gilman's The Pharmacological Basis of Therapeutics 12th ed. United States: McGraw Hill; 2011. p. 1463-76.
3. Brar RK, Jyoti U, Patil RK, Patil HC. Fluoroquinolone antibiotics: An overview. Adesh Univ J Med Sci Res 2020;2:26-30.
4. Mohammed HH, Abuo-Rahma GE, Abbas SH, Abdelhafez EM. Current trends and future directions of fluoroquinolones. Curr Med Chem 2019;26:3132-49.
5. Karampela I, Dalamaga M. Could respiratory fluoroquinolones, levofloxacin and moxifloxacin, prove to be beneficial as an adjunct treatment in COVID-19? Arch Med Res 2020;51:741-2.
6. Pham TD, Ziora ZM, Blaskovich MA. Quinolone antibiotics. Med Chem Commun 2019;10:1719-39.
7. World Health Organization. Differences among Fluoroquinolones in the Treatment of MDR-TB. Geneva, Switzerland: World Health Organization Archives; 2020. Available from: https://www.archives.who.int [Last accessed on 2021 Sep 21].
8. Tripathi KD. Antitubercular drugs. In: Tripathi M, editor. Essentials of Medical Pharmacology. 7th ed. New Delhi, London: Jaypee Brothers Medical Publishers Ltd.; 2013. p. 765-79.
9. Gumbo T. Chemotherapy of tuberculosis, Mycobacterium avium complex disease, and leprosy. In: Brunton LB, Hilal-Dandan R, Knollmann BC, editors. Goodman and Gilman's the Pharmacological Basis of Therapeutics. 13th ed. New York, Chicago: McGraw-Hill; 2018. p. 1067-86.
10. Laohapojanart N, Ratanajamit C, Kawkitinarong K, Srichana T. Efficacy and safety of combined isoniazid-rifampicin-pyrazinamide-levofloxacin dry powder inhaler in treatment of pulmonary tuberculosis: A randomized controlled trial. Pulm Pharmacol Ther 2021;70:102056.
11. Schwarz C, Grehn C, Temming S, Holz F, Eschenhagen PN. Clinical impact of levofloxacin inhalation solution in cystic fibrosis patients in a real-world setting. J Cyst Fibros 2021;20:1035-9.
12. Elborn JS, Flume PA, Van Devanter DR, Procaccianti C. Management of chronic *Pseudomonas aeruginosa* infection with inhaled levofloxacin in people with cystic fibrosis. Future Microbiol 2021;16:1087-104.

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