Original Research Article

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

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ABSTRACT

Background: Ofloxacin has an inhibitory effect on DNA gyrase, DNA topoisomerase IV and IL-1α, IL-6, IL-8, TNFα; and a superinducing effect on IL-2. Ofloxacin has profound bactericidal, anti-tubercular, anti-leprotic, anti-viral including anti-coronavirus, anti-fungal, anti-protozoal, comedolytic, anti-comedogenic, anti-inflammatory, immunomodulatory, and anti-malignant: pro-apoptotic and anti-proliferative potential, including TGFβ1 targeted G2 phase cell cycle arrest and telomerase activity impairment. Objectives of the study were a comparative clinical pharmacotherapeutic efficacy and chronopharmacovigilance assessment study, of ofloxacin, one of the commonplace TGFβ1 inducing and telomerase impairing fluoroquinolones, in treating heterogenous global patients, suffering from different diseases.
Methods: A prospective, multivariate study of 100 patients, allotted into group A (acute gastroenteritis) =20, group B (chronic obstructive pulmonary disease) =20, group C (new drug-sensitive tuberculosis) =20, group D (recurrent mixed cutaneous infections) =20, and group E (post-surgical refractory wound infections) =20, was prescribed ofloxacin 200-400 mg twice daily, according to required prescribed regimens. A comparative pharmacotherapeutic efficacy assessment was made from the complete recovery time-periods, including the residual recovery time-periods. The chronopharmacovigilance assessment was made by adverse effects occurrence monitoring during treatment period or follow-up, with an Adverse Event Case Report Form.
Results: The residual recovery time-periods, in group A=0 days, group B=2 days, group E=3 days, group D=3 days, and group C=7 days. Adverse effects were not statistically significant, with a predictable chronopharmacovigilance illustration.
Conclusions: The pharmacotherapeutic efficacy of ofloxacin was more for treating group A, followed by group B, followed by group E and group D, and finally followed by group C. Ofloxacin was safe, without any pharmacogenomic or pharmacogeographic heterogeneity related fluctuation.

Keywords: Ofloxacin, TGFβ1, Telomerase, Pharmacotherapeutic efficacy, Chronopharmacovigilance, Indication spectrum

INTRODUCTION

Quinolones, the curiously novel pharmacotherapeutics, and ofloxacin, one of the commonplace quinolones, would always remain wonderful, due to the infinite metamorphosis of their extensive spectrum of therapeutic indications. With the advent of quinolones, and later the fluorinated 4-quinolones, the fluoroquinolones, the medical world has certainly taken long strides in treating in numerous maladies.[1-3]

Fluoroquinolones, like ofloxacin, are synthetic fluorinated analogues of nalidixic acid, a monocarboxylic acid comprising 1,8-naphthyridin-4-one substituted by carboxylic acid, ethyl and methyl groups at positions 3, 1, and 7, respectively, possessing a 4-quinolone nucleus. The quinolone structure consists of a bicyclic system with a substituent at position N-1, a carboxyl group at position 3, a keto group at position 4, a fluorine atom at position 6, and a substituent (often nitrogen heterocycle moiety) at the C-7.[4]

Ofloxacin is quite significantly efficacious for its (a) bactericidal inhibitory effect on: (i) 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; (ii) 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; (iii) Pro-inflammatory cytokines, like interleukins: IL-1α, IL-6, IL-8, and tumour necrosis factor α, and, (b) a superinducing effect on IL-2, causing an indirect immunomodulation, tending to increase both the growth and activity of T and B lymphocytes; and also affecting the development of immune responses by influencing of the expression of other cytokines and mediators.[1-5]

The dual inhibitory activity of fluoroquinolones against the bacterial replication enzymes, DNA gyrase and topoisomerase IV, protects them from the development of resistance.[1-7]

Quinolones, like ofloxacin, possess an ever-expanding spectrum of clinical indications like : (i) multiple, multi-resistant, concurrent and recurrent infections, including drug-resistant tuberculosis, drug-resistant leprosy and coronaviridae-19; (ii) refractory inflammations; (iii) diabetes mellitus; (iv) obesity; (v) anti-cancer radiotherapy; (vi) immune disorders; (vii) malignancies; and (vii) complicated and refractory diseases and disorders; due to their profound a. bactericidal, b. anti-viral, c. anti-fungal, d. anti-protozoal, e. comedolytic, f. anti-comedogenic, g. anti-inflammatory, h. anti-diabesity, i. radioprotective, j. immunomodulatory (transcription factors - like NF-kB/NFAT/AP1 - mediated, and on regulation of cyclic AMP or phosphodiesterase), k. anti-neoplastic, pro-apoptotic, p53 mediated S phase arrest/TGFβ1 targeted G2 phase cell cycle arrest, anti-proliferative (by suppression of OncomiR expression, impairment of telomerase activity, DNA synthesis inhibition, inhibition of cell colony formation, mitochondrial membrane potential disruption), anti-metastatic (migration, invasion and metastasis-MET inhibitor), and cancer stemness regulator potential.[1-12]

As an anti-cancer drug, ofloxacin, when administered, has the following actions: (i) in a dose >200 μg/ml for >48 hours, in transitional cell carcinoma, ofloxacin inhibits proliferation by impairment of telomerase activity in MBT-2 and T24 type of tumour cells; (ii) at a dose of 0-800 μg/ml for 24-120 hours, in transitional cell carcinoma, ofloxacin inhibits proliferation and DNA synthesis in TCCSUP, T24 and J82 type of tumour cells; (iii) 1000 μg/ml ofloxacin, administered for 24-96 hours, in bladder cancer, would inhibit proliferation in the T24, HTB9 and TccSup type tumour cells; (iv) at a dosage of 100 μg/ml for 24 hours, under the exposure of 3.5 W/cm^2 UVA for 30 mins, ofloxacin causes apoptosis and S/G2 - phase arrest in the HeLa and A431 tumour cell lines, in epidermoid carcinoma, by DNA plasmid photocleavage via carbocation; (v) with 0-100 μg/ml, administered for 0-5 days, ofloxacin inhibits proliferation by suppressing OncomiR expression, in the A375, Mel-Ho, and Mel-Juso type melanoma tumour cells, MCF7 type breast tumour cells, A2780 type ovarian tumour cells and H1299 type lung tumour cells, by suppressing OncomiRs targeting splicing machinery, and activating the wild type p53, with the downregulation of MdmX.[1,2,8-10]

Therefore, this study was performed for a comparative assessment of the clinical pharmacotherapeutic efficacy and a comparative chronopharmacovigilance assessment of ofloxacin, which is 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 multi-centre, rural and urban patients, with heterogenous pharmacogeographic and pharmacogenomic constitution; and also to enlighten about the wide-ranging pharmacological benefits and extensive clinical pharmacotherapeutic indications spectrum of ofloxacin, one of the commonplace TGFβ1 inducing and telomerase impairing fluoroquinolones.

Objectives

The objective was to perform a multivariate, comparative clinical pharmacotherapeutic efficacy assessment study, along with the comparative chronopharmacovigilance assessment, of ofloxacin, which is 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 global multi-centre, rural and urban patients, with heterogenous pharmacogeographic and pharmacogenomic constitution.

METHODS

Ethical approval

In the beginning, before conducting this research project, 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 in compliance with the regulatory requirements. The study involved almost negligible risk, of any type, to the patients. The design provided an equal opportunity to all the eligible patients to be included in the study. The patients who were included in the study were assured confidentiality, and a written informed consent was obtained from each patient.

Study design

This study was a global, multi-centre, prospective, multivariate, open-labelled, comparative 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, Pathology, Internal Medicine, Gastroenterology, Respiratory Medicine, Tuberculosis and Chest Diseases, Dermatology, General Surgery, Ophthalmology, Obstetrics and Gynaecology, Medical Oncology, and Molecular Medicine, in the global, multi-centre, tertiary care hospitals, medical colleges and laboratories: Dr. Moumita Hazra's Polyclinic And Diagnostic Centre, Hazra Nursing Home, J. J. M. Medical College, Bapuji Hospital, Chigateri General Hospital, Dr. B. R. Ambedkar Medical College and Hospital, K. C. General Hospital, Rama Medical College Hospital and Research Centre, Rama University, K.D. Medical College Hospital and Research Center, Gouri Devi Institute of Medical Sciences and Hospital, Shri Ramkrishna Institute of Medical Sciences and Sanaka Hospitals, Hi-Tech Medical College and Hospital, Fortis Hospitals, GIOSTAR Institute of Regenerative Medicine Institutes, Hospitals and Laboratories, Presidency College, Presidency University.

Study period

The total study period for this research study and the compilation of the study literature was for a period of 5 years 9 months, from June, 2015 to February, 2021. The study period included (a) the time-period for the completion of the required prescribed regimen; and (b) further 1 month: this study period includes (i) the complete recovery time-period, including the residual recovery time-period (which is calculated from the last day of the required prescribed drug regimen administration till the day of the recovery confirmation, indicated by the performed investigations, appropriate for each group) and, (ii) the time-period for post-recovery follow-up (the study period completed in February, 2021).

Study population

A total of 100 global patients, with heterogenous pharmacogeographic and pharmacogenomic constitution, suffering from acute gastroenteritis, chronic obstructive pulmonary disease, new drug-sensitive tuberculosis, recurrent mixed cutaneous infections, and post-surgical refractory wound infections.

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

In this study, 100 patients were allotted into group A=20, group B=20, group C=20, group D=20, and group E=20, suffering from acute gastroenteritis, chronic obstructive pulmonary disease, new drug-sensitive tuberculosis, recurrent mixed cutaneous infections, and post-surgical refractory wound infections, respectively.

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, duration of symptoms of acute gastroenteritis, chronic obstructive pulmonary disease, new drug-sensitive tuberculosis, recurrent mixed cutaneous infections, and post-surgical refractory wound infections; 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 MDR-TB contacts, past TB treatment history, defined as new cases (≤1 month of antituberculosis treatment), previously treated cases (first and second line anti-tuberculosis drugs), presence of cavities on chest radiograph, sputum smear microscopy results (negative, low [scanty or 1+] and high bacillary load [2+ or 3+]), and drug susceptibility testing results, cardiac history, history of cutaneous infections, history of any recurrent cutaneous inflammations, history of any prolonged non-healing or recurring cutaneous lesions, history of post-surgical refractory wound infections, history of co-morbidities, family history, personal history, socio-economic history, metabolic history, history of any chronic disease, reproductive history, concomitant medication history, and surgical history were recorded.

The details of complete general physical examination, and systemic examination, including gastrointestinal, oto-rhino-laryngo-tracheal, respiratory including obstructive pulmonary and tubercular, cardio-pulmonary, cutaneous, and surgical wound examinations, were recorded. Blood pressure, pulse rate, oxygen saturation of arterial haemoglobin (SpO_2) measurements, and respiratory rate were recorded. Antibiotic culture and sensitivity were done for each patient.

Each group was prescribed oral ofloxacin 200-400 mg twice daily, according to the required prescribed regimens, with group A, group B, group D, and group E, being prescribed the shortest duration regimens of 5-7 days with the least dosage of 200 mg ofloxacin twice daily, according to the severity of the disease, and group C being prescribed the medium duration regimen of 24-48 weeks with the dosage of 400 mg ofloxacin twice daily.

The total recovery time-period had included the total duration of the treatment regimens, as well as the duration till the complete recovery of the patient, the latter being calculated till the day of the recovery confirmation, indicated by the performed investigations, appropriate for each group. The total study period is (a) the time-period for the completion of the required prescribed regimen; and (b) further 1 month : this study period includes (i) the complete recovery time-period, including the residual recovery time-period (which is calculated from the last day of the required prescribed drug regimen administration till the day of the recovery confirmation, indicated by the performed investigations, appropriate for each group) and,

(ii) the time-period for post-recovery follow-up (the study period completed in February, 2021).

The efficacy assessment was made by a comparative assessment of the complete recovery time-period, including the residual recovery time-period (which is calculated from the last day of the required prescribed drug regimen administration till the day of the recovery confirmation, indicated by the performed investigations, appropriate for each group).

The safety assessment was made by monitoring any adverse effect 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 an Adverse Event Case Report Form, and a chronopharmacological pharmacovigilance analysis of the occurrence of the adverse effects, was done.

Complete blood examination, routine stool examination including occult test, complete gastrointestinal, respiratory, tubercular, cutaneous infectious diseases, post-surgical wound, inflammatory diseases and neoplastic diseases examinations including Widal test, Mantoux test, chest X-ray, sputum examination, coronavirus RT-PCR examination, stool culture, respiratory spirometry variables, pus culture, 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 the day after the last day of the completion of the study period in February, 2021.

A thorough consideration was given to detect any pharmacogenomic or pharmacogeographic fluctuation among the study observations.

Statistical analysis

At the study completion point, the observations recorded in this study, were statistically analysed by Z Test, and Test of significance with p values. Subsequently, a graphical analysis was also done, through various types of diagrammatic illustrations.

RESULTS

In this study, 100 patients had participated. All the patients completed the study thoroughly. There were no drop-out patients due to adverse effects, none was lost to follow-up and none withdrew voluntarily. The patients' adherence to the treatment was very high.

Figure 1 depicts the adherence of the patients, under study, to the treatment regimens.
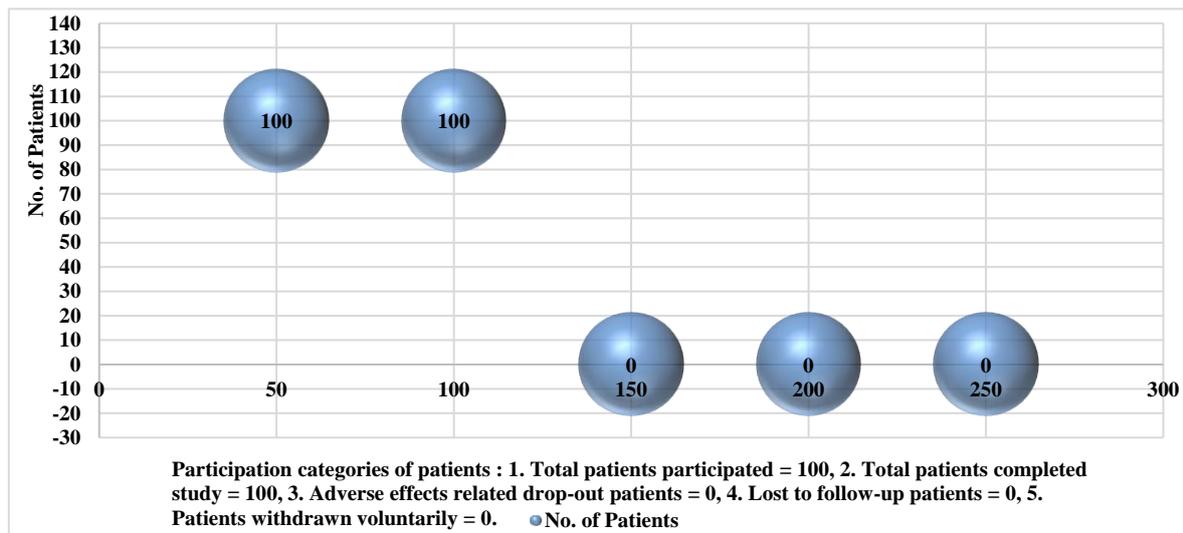
Figure 1: Adherence of total patients to the treatment regimens.

The demographic characteristics of 5 groups had shown respective variations, without affecting the study results.

The residual recovery time-periods (which is calculated from the last day of the required prescribed drug regimen administration till the day of the recovery confirmation, indicated by the performed investigations, appropriate for each group) in group A=0 days, group B=2 days, group E=3 days, group D=3 days, and group C=7 days.

Thus, the complete recovery time-period, including the residual recovery time-periods in group A=5-7 days (time-period for required prescribed drug regimen administration, depending on the severity of the disease) and 0 days (residual recovery time-period), group B=5-7 days and 2 days, group E=5-7 days and 3 days, group D=5-7 days and 3 days, and group C=24-48 weeks and 7 days.

Hence, ofloxacin was found to be highly efficacious, and the therapeutic efficacy of ofloxacin was more for treating acute gastroenteritis, followed by chronic obstructive pulmonary disease, followed by post-surgical refractory wound infections and recurrent mixed cutaneous infections, and finally followed by new drug-sensitive TB.

The therapeutic efficacy of ofloxacin for: acute gastroenteritis >chronic obstructive pulmonary disease >post-surgical refractory wound infections=recurrent mixed cutaneous infections >new drug-sensitive TB.

Figure 2 depicts the residual recovery time-periods (which is calculated from the last day of the required prescribed drug regimen administration till the day of the recovery confirmation, indicated by the performed investigations, appropriate for each group) in no. of days for patients in: group A with acute gastroenteritis, group B with chronic obstructive pulmonary disease, group C with new drug-sensitive tuberculosis, group D with recurrent mixed

cutaneous infections, and group E with post-surgical refractory wound infections, which is, group A=0 days, group B=2 days, group E=3 days, group D=3 days, and group C=7 days.
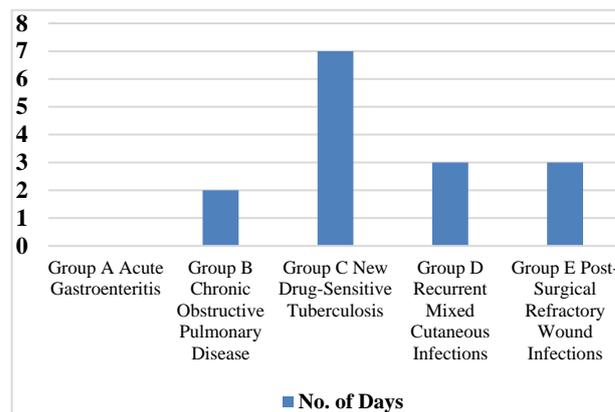

Figure 2: The residual recovery time-periods (which is calculated from the last day of required prescribed drug regimen administration till the day of recovery confirmation, indicated by performed investigations, appropriate for each group) in no. of days for patients in : group A with acute gastroenteritis, group B with chronic obstructive pulmonary disease, group C with new drug-sensitive tuberculosis, group D with recurrent mixed cutaneous infections, and group E with post-surgical refractory wound infections.

Adverse effects were negligible and were not statistically significant. Tolerability was good among all the 5 groups of patients. This delineated quite a predictable chronopharmacovigilance illustration.

These observed results were without any pharmacogenomic or pharmacogeographic fluctuation.

Table 1: The chronopharmacological representation of the occurrence of adverse effects with oral ofloxacin administration, among the patient groups.

Adverse effects	Average day of occurrence from initiation of ofloxacin therapy	Group A: acute gastroenteritis (no. of patients)	Group B: chronic obstructive pulmonary disease (no. of patients)	Group C: New drug-sensitive tuberculosis (no. of patients)	Group D: Recurrent mixed cutaneous infections (no. of patients)	Group E: Post-surgical refractory wound infections (no. of patients)	Z value	P value
Nausea	Day 3	1	0	0	0	0	0	0, ns
Dizziness	Day 4	0	0	1	0	0	0	0, ns
Bland Taste	Day 3	0	0	0	0	0	0	0, ns
Headache	Day 5	0	0	0	0	0	0	0, ns
Insomnia	Day 5	0	0	0	0	0	0	0, ns
Rashes	Day 6	0	0	0	0	0	0	0, ns

ns= non-significant

Table 1 depicts the chronopharmacological representation of the occurrence of adverse effects with oral ofloxacin administration, among the patient groups.

DISCUSSION

This prospective, multivariate, open-labelled, clinical pharmacotherapeutic study was performed to make a comparative therapeutic efficacy assessment of the very common fluoroquinolone, ofloxacin, which is one of the TGFβ1 inducing and telomerase impairing fluoroquinolones, among 100 global multi-centre patients, with heterogenous pharmacogeographic and pharmacogenomic constitution, allotted into group A=20, group B=20, group C=20, group D=20, and group E=20, suffering from different diseased conditions, like acute gastroenteritis, chronic obstructive pulmonary disease, new drug-sensitive tuberculosis, recurrent mixed cutaneous infections, and post-surgical refractory wound infections, respectively. The pharmacovigilance considerations were also assessed with a significant emphasis on its chronopharmacological presentation among the patients, in the study. The 100 participant patients had completed the study thoroughly, with no adverse effects related drop-out patients, lost to follow-up patients or voluntarily withdrawn patients, proving a very high adherence of the patients to the treatment; which is another finding attributing to the quite high therapeutic efficacy of ofloxacin.

The demographic characteristics of all the 5 above-mentioned groups had shown respective variations, without affecting the study results. These variations, as well as the vast pharmacogenomic and pharmacogeographic heterogeneity of the patients, did not cause any fluctuation in the study results.

Although each group was prescribed oral ofloxacin 200-400 mg twice daily, according to the required prescribed regimens, with group A, group B, group D and group E being prescribed the shortest duration regimens of 5-7 days

with the least dosage of 200 mg twice daily, and group C being prescribed the medium duration regimen of 24-48 weeks with the dosage of 400 mg twice daily, the patients recovered rapidly; the complete recovery time-periods being (a) the duration of the administered treatment regimens, as well as (b) the residual recovery time-period of 0 days in group A, 2 days in group B, 3 days in group E, 3 days in group D, and 7 days in group C. Thus, the complete recovery time-period, including the residual time-periods in group A=5-7 days (the time-period for required prescribed drug regimen administration, depending on the severity of the disease) and 0 days, group B=5-7 days and 2 days, group E=5-7 days and 3 days, group D=5-7 days and 3 days, and group C=24-48 weeks and 7 days. Hence, ofloxacin was found to be highly efficacious, in the treatment of these diseased conditions.

The therapeutic efficacy of ofloxacin was more for treating acute gastroenteritis, followed by chronic obstructive pulmonary disease, followed by post-surgical refractory wound infections and recurrent mixed cutaneous infections, and finally followed by new drug-sensitive tuberculosis. This hugely illuminates on the respective sensitivity of the disease treatments to ofloxacin. This study represents the investigated bactericidal, anti-tubercular, anti-viral, anti-fungal, anti-protozoal, as well as anti-inflammatory, immunomodulatory and probable anti-neoplastic or anti-malignant therapeutic uses of ofloxacin, in these multiple, multi-resistant, recurrent, concurrent and refractory disease conditions.

The chronopharmacovigilance monitoring delineated a predictable illustration, showing that the adverse effects were negligible and were not statistically significant. Tolerability was good among all the 5 groups of patients.

This study re-emphasised, with all its investigative aspects, that ofloxacin was, is, and would always remain an extremely necessary 'essential drug', as it has numerous therapeutic uses, high efficacy, confirmed safety, easy availability and accessibility, and suitability in both acute

and chronic complicated disease conditions; shown also in several studies, performed throughout the world.[1-15]

The initial quinolone compounds had a limited spectrum of activity against gram negative organisms thus, restricting their clinical use. To the core quinolone ring structure, addition of moieties like fluorine at C6 and piperazinyl at C7, increased the gram-negative coverage and improved the systemic retention of the drugs. This new class of compounds is termed as fluoroquinolones. By addition of different substitutes at different sites like N1, C6, C7 and C8 of the quinolone nucleus, newer compounds with better antimicrobial activity, pharmacokinetics and metabolic properties were synthesised. In ciprofloxacin the addition of cyclopropyl group at position 3 increased the potency of this compound against gram positive and negative organisms. Antibacterial activity against aerobic gram-negative organisms, *Pseudomonas* and Staphylococci was enhanced by addition of piperazine group at C7. The augmentation of the antibacterial activity against gram positive organisms was achieved by alkylation of the piperazinyl group at C7, amino or methyl substitutes at position 5 and pyrrolidinyl derivative at position C7. Addition of halides (chlorine or fluorine) at C8 to quinolone compounds having a cyclopropyl group at N1 lead to activity against anaerobes, *Mycoplasma* and *Chlamydia*. Increase in the elimination half-life can be achieved by addition of a second fluorine group at C8, alkylation of C7 and methylation of distal nitrogen of the C7 of piperazine ring. The newest modification of adding a methoxy group at position C8 decreases the possibility of resistance. This group is also known as the newer fluoroquinolones.

These stepwise modifications are useful to: (i) Expand the fluoroquinolone spectrum of activity, (ii) Increase tissue levels after topical instillation, (iii) Reduce the development of resistance.[13]

During DNA replication and transcription, double-stranded DNA goes to uncoil into a single-stranded structure by enzymes called DNA gyrase or DNA topoisomerase. DNA gyrase is an essential adenosine triphosphate-hydrolysing topoisomerase II enzyme that prevents the detachment of gyrase from DNA. It consists of two A subunits (gyrA) and two B subunits (gyrB). DNA gyrase establishes negative super-helical twists in the bacterial DNA.[4]

Ofloxacin has an inhibitory effect on DNA gyrase, DNA topoisomerase IV and IL-1α, IL-6, IL-8, TNFα; and a superinducing effect on IL-2.

Newer generation fluoroquinolones, like ofloxacin, inhibits cytokine synthesis even at lower concentrations.[1-5]

In gram-negative bacteria, the interplay between membrane permeability and drug efflux pumps is a significant correlation. In a study, the intracellular accumulation of a series of fluoroquinolones in population and in individual cells of *Escherichia coli* according to the expression of the AcrB efflux transporter has been investigated. Computational results have supported the accumulation levels measured experimentally and have highlighted how fluoroquinolones side chains interact with specific residues of the distal pocket of the AcrB tight monomer during recognition and binding steps. The study aims at getting insights into the molecular bases of drug translocation by comparing a large set of fluoroquinolones in *E. coli* as a model of gram-negative bacteria, as well as their sensitivity to AcrB mediated transport. Drug susceptibility assays, spectro- and microfluorimetry, molecular docking, molecular dynamics simulations, and binding free-energy calculations were combined to investigate antibacterial drug activity, accumulation, and extrusion, respectively, in isogenic strains expressing different levels of AcrAB. The findings provide a robust correlation between internal drug concentration and efflux activity, which paves the way for the design of predictive fluoroquinolone accumulation rules in gram-negative bacteria.[14]

In another study, the aim of the research was to synthesize novel fluoroquinolones and evaluate their *in vitro* antilipolytic and antiproliferative properties. Characterization of the synthesized fluoroquinolones was carried out with NMR, MS, IR, and EA. Like orlistat, potential fluoroquinolones' modulation of pancreatic triacylglycerol lipase (PL) was quantified colorimetrically and was further supported by docking studies. Compared with cisplatin, fluoroquinolones' antiproliferative propensities against a panel of obesity related colorectal cancer cell lines were investigated with sulforhodamine B assay. Twelve novel fluoroquinolones (2A-5A, 2B-5B, and 2C-5C) were synthesized and characterized. The PL-IC values of tested fluoroquinolones were in the range of 6.8-165.7 μmol/L. Fluoroquinolone 4A was the most active antiproliferative compound against HCT116 with an IC value of 3.5 μmol/L. Their selectivity of growth inhibition for safety examination using normal periodontal ligament fibroblasts (PDL) in comparison with cisplatin's lack of differential cytotoxicity was reported. Lipophilicity and hydrogen bonding were found essential for both activities. Conclusively, fluoroquinolones are robustly proven for their emerging *in vitro* anti-obesity and antiproliferative activities.[15]

Ofloxacin, one of the antibiotic fluoroquinolones, is an ideal anticancer drug repositioning candidate. Fluoroquinolones induce cell cycle arrest, apoptosis, modulate epithelial-mesenchymal-transition and cancer stemness. Fluoroquinolones stimulate cancer specific microRNA biogenesis. Metal ion complexes of fluoroquinolones possess enhanced anticancer activity. Derivatives and salt complexes of fluoroquinolones are highly effective anticancer molecules than parent molecule. With the spreading of antibiotic resistance, the translocation of antibiotics through bacterial envelopes is crucial for their antibacterial activity.[8]

Table 2a: Anti-cancer activity of fluoroquinolones with their mechanism of action.[8]

Fluoroquinolone	Dose and time	Type of tumor cells	Mode of anticancer activity	Mechanism of action
Ciprofloxacin Moxifloxacin	0-1.0 μmol/ml (0-72 h)	U87MG (Glioblastoma)	Apoptosis, S-phase arrest	Glutathione levels ($\downarrow$), mitochondrial dysfunction, Caspase-3/7 ($\uparrow$),
Ciprofloxacin	0-1.0 μmol/ml (0-72 h)	MDA MB-231 (Breast)	Apoptosis, S-phase arrest	Oxidative stress, p53($\uparrow$), Bax:Bcl2($\downarrow$)
Ciprofloxacin	0.1-1.0 m mol/l (0-72 h)	Colo 829 (Melanoma)	Apoptosis, S-phase arrest	DNA fragmentation, mitochondrial dysfunction
Enoxacin	UVA (20 min) and 100 μg/ml (4 h)	AsPC-1 (Pancreatic cancer)	Apoptosis	Oxidative stress, ROS production
Lomefloxacin	0.1-1.0 m mol/l (0-72 h)	Colo 829 (Melanoma)	Apoptosis, S/G_2 - phase arrest	Oxidative stress, glutathione levels ($\downarrow$), mitochondrial dysfunction
Lomefloxacin	1.1 mW/cm^2 UVA (20 min) and 100 μg/ml	HL-60 (Leukemia)	Apoptosis	Caspase-3($\uparrow$),
Enoxacin, Ciprofloxacin, Ofloxacin	0-100 μg/ml (0-5 days)	A375, Mel-Ho, Mel-Juso (Melanoma), MCF7 (Breast), A2780 (Ovarian) H1299 (Lung)	Inhibits proliferation by suppressing OncomiR expression	Suppresses OncomiRs targeting splicing machinery, activates wild type p53, MdmX ($\downarrow$)
Levofloxacin (¥)	0.1-1.0 m mol/l (0-72 h)	MCF7, MDA MB-231, MDA MB-468, SkBr3 (Breast cancer)	Apoptosis, S / G_2 - phase arrest	Inhibition of mitochondrial biogenesis and respiration, pPI3K($\downarrow$), pAKT ($\downarrow$), mTOR($\downarrow$), pc-Raf($\downarrow$), pERK($\downarrow$)
Levofloxacin (¥)	200 μg/ml (0-72 h)	H460, H3255, A549 (Lung cancer)	Apoptosis	Oxidative stress, mitochondrial dysfunction
Ciprofloxacin	10 μg/ml (0-7 days)	H460 (Lung cancer)	Cancer stem cells	CD133($\uparrow$), CD44($\uparrow$), ABCG2($\uparrow$), Oct4($\uparrow$), Sox2($\downarrow$), AKT($\uparrow$), ALH1A1($\uparrow$), Slug($\downarrow$), Nanog($\uparrow$), Snail($\downarrow$), Cav-1($\uparrow$), ERK($\uparrow$)
Moxifloxacin, Ciprofloxacin	400 μg/ml (0-48 h)	MIA PaCa-2, Panc-1 (Pancreatic cancer)	Apoptosis, S-phase arrest	ERK 1/2 ($\uparrow$), Bak($\uparrow$), Bid($\uparrow$), Bax ($\downarrow$), BcLxL($\downarrow$), Csp-8/9/3($\uparrow$), p21($\downarrow$), p27($\downarrow$), p53($\downarrow$), CDK2($\downarrow$), Cyclin A/E ($\downarrow$)
Ciprofloxacin Lomefloxacin Ofloxacin	3.5 W/cm^2 UVA (30 min) and 100 μg/ml (24 h)	HeLa, A431 (Epidermoid carcinoma)	Apoptosis, S/G_2-phase arrest	DNA plasmid photocleavage via carbocation
Ciprofloxacin	330 μg/ml (5 days)	LOVO (Colon cancer)	Apoptosis	ERK1/2($\uparrow$)
Gemifloxacin (¥)	20 μg/ml (24-48 h)	MDA MB-231, MDA MB-453 (Breast Cancer)	Inhibits migration, invasion and metastasis (MET)	NFκB($\downarrow$), Snail($\downarrow$), pIƙB($\downarrow$), IƙB($\uparrow$), RKIP($\uparrow$), N-Cad($\downarrow$), Vimentin($\downarrow$), E-Cad($\uparrow$), SM-actin($\downarrow$),
Gemifloxacin	20 μg/ml (24-48 h)	SW620, LoVo (Colon cancer)	Inhibits migration, invasion and metastasis (MET)	NFκB($\downarrow$), Snail($\downarrow$), E-Cad($\uparrow$), N-Cad($\downarrow$), Claudin3 ($\uparrow$), Vimentin($\downarrow$), pIƙB($\downarrow$), IƙB($\uparrow$), TAK1($\downarrow$)

Continued.

Fluoroquinolone	Dose and time	Type of tumor cells	Mode of anticancer activity	Mechanism of action
Enoxacin	40 μg/ml (5 days)	LNCaP, VCaP, PC-3, DU145, 22Rv1 (Prostate cancer)	Apoptosis, S/G$_2$-phase arrest, Inhibits migration and invasion	Restoration of microRNA biogenesis, HDAC1($\downarrow$), Sirt1($\downarrow$)
Gatifloxacin	400 μg/ml (24-48 h)	MIA PaCa-2, Panc-1 (Pancreatic cancer)	S / G$_2$ - phase arrest	TGFβ1($\uparrow$), p21($\uparrow$), p27($\uparrow$), p53($\uparrow$), cyclin A/B1($\downarrow$), CDK2($\downarrow$), pCDC2($\uparrow$)
Ciprofloxacin	1000 μg/ml (48-96 h)	A549, A375.S2, B16, C6, HepG2	Inhibits proliferation	-
Sparfloxacin	500 μmol/l (24-48 h)	C26, HCT116, HT29 (Colon cancer)	Apoptosis, Inhibits migration and invasion	HERG K$^+$ channel, Bcl2($\downarrow$), Csp-3($\uparrow$), MMP-2**($\downarrow$)**, MMP-9($\downarrow$)
Ciprofloxacin	100 μg/ml (6 days)	HT29, Caco-2 (Colon cancer)	S-phase arrest	TGFβ1($\uparrow$)
Ciprofloxacin	100 μg/ml (24-48 h)	TK6, WTK1, NH32 (Lymphoblastoid cells)	G$_2$ - phase arrest and apoptosis	γH2AX ($\uparrow$), Csp3 ($\uparrow$), Stabilized TopoIIα ($\uparrow$)
Enoxacin	40 μg/ml (5 days)	MCF-7 (Breast cancer)	G$_2$/M- phase arrest	-
Ciprofloxacin	100 μg/ml (48-72 h)	HeLa	Apoptosis, Inhibits proliferation	-
Enoxacin, Norfloxacin, Ciprofloxacin, Levofloxacin	20-100 μg/ml (3 days)	H-460 (Lung cancer)	Apoptosis, Inhibits proliferation	-
Ciprofloxacin	0-2000 μg/ml (24- 96 h)	HTB9, T24, TccSup (Bladder cancer)	Inhibits proliferation	-
Ciprofloxacin	50-400 μg/ml (3 days)	PC3, MLC9981 (Prostate cancer)	S and G2-phase arrest, Apoptosis	Bax:Bcl2($\uparrow$), Caspase3($\uparrow$), p21($\downarrow$)
Ciprofloxacin	200-500 μg/ml (24 h)	CC-531, SW-403, HT-29 (Colorectal carcinoma)	Apoptosis	Bax:Bcl2($\uparrow$), Caspase-3, -8, -9 ($\uparrow$)
Ciprofloxacin	50-400 μg/ml	HTB9 (Bladder cancer)	Apoptosis, S/G2-phase arrest	Cytochrome c release ($\uparrow$), Bax:Bcl 2($\uparrow$), p21($\downarrow$), Caspase3($\uparrow$), pCDK2($\downarrow$), Cyclin B/E ($\downarrow$), CDK2($\uparrow$)
Ciprofloxacin, Ofloxacin	1000 μg/ml (24-96 h)	T24, HTB9, TccSup (Bladder cancer)	Inhibits proliferation	-
Ciprofloxacin, Fleroxacin	50-800 μg/ml (24 h)	MBT-2, T24 (Transitional cell carcinoma)	Inhibits proliferation	-
Ofloxacin, Levofloxacin	>200 μg/ml (>48 h)	MBT-2, T24 (Transitional cell carcinoma)	Inhibits proliferation by impairment of telomerase activity	-
Ciprofloxacin Ofloxacin	0 – 800 μg/ml (24-120 h)	TCCSUP, T24, J82 (Transitional cell carcinoma)	Inhibits proliferation and DNA synthesis	-
Ciprofloxacin Pefloxacin	>50 μg/ml	K562 (Leukaemia cells)	Inhibits proliferation and colony formation	-

($\uparrow$) Up-regulated, Down-regulated ($\downarrow$), (¥) *in vivo* validation.

Table 2b: Anti-cancer activity of fluoroquinolones.[10]

Fluoroquinolone	Type of cancer cell	Mode of anti-cancer activity	Mechanism of action
Ciprofloxacin	Melanoma cells	S-phase arrest	Topoisomerase II inhibition
	Human non-small cell lung cancer	G2/M checkpoint arrest	The expression of p53 (↑), p21 (↑), cyclin B1 (↓), Cdc2 (↓)
	-	Disruption of mitochondrial membrane potential	Oligonucleosomal DNA fragmentation, p53 (↑)
	Human triple-negative breast cancer MDA-MB-231 cells	Disruption of mitochondrial membrane potential	Bax/Bcl-2-dependent pathway (↑)

As anti- breast cancer agents, quinolones significantly inhibit snail expression, which blocks highly metastatic NF-κB, TNF-α induced cell migration and invasion, and restores E-cadherin.[10]

This study was performed to develop newer anti-microbial, anti-inflammatory and anti-neoplastic or anti-malignant diagnostics and therapeutics; to develop faster, better, safer, and more precise therapeutics and cure in patients suffering from an extensive spectrum of indications; to enhance comprehensive health and cure from varied types of infectious and neoplastic or malignant diseases; and finally, to enhance healthy life and life span among each individual.

CONCLUSION

Ofloxacin was more efficacious for treating acute gastroenteritis, than chronic obstructive pulmonary disease, followed by post-surgical refractory wound infections and recurrent mixed cutaneous infections, and finally by new drug-sensitive tuberculosis. Ofloxacin was safe and tolerable, among all the five above-mentioned groups of patients, with a predictable chrono pharmacovigilance illustration, and without producing any pharmacogenomic or pharmacogeographic heterogeneity related fluctuation, in this study.

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