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Original Research Article

A clinical pharmacological experimental research analysis of the evidence-based rational pharmacotherapeutics of pefloxacin and newer quinolones

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ABSTRACT

Background: Pefloxacin is a newer broad-spectrum bactericidal fluoroquinolone antibiotic, with superior antibacterial activity *in vivo* against pathogenic ocular gram-negative and anaerobic microorganisms and better pharmacokinetic properties.
Methods: 100 bacterial conjunctivitis patients were prescribed topical pefloxacin 0.3% ophthalmological drops monotherapy, 2 drops in each eye after every 3 hours for 2 days, and 2 drops in each eye after every 6 hours for next 5 days. The overall recovery of the patients was clinically examined and assessed. The patients who did not recover completely with 0.3% pefloxacin monotherapy ophthalmological drops, were administered topical pefloxacin 0.3% ophthalmological drops, 2 drops in each eye after every 6 hours for the next 3 days, as combination therapy, with other required ophthalmological eye drops, depending on the prognostic follow-up, on days 0, 3, 5, 7, 10, 15, 30, and on further follow-ups. The evidence-based rational pharmacotherapeutic patient percentage topical application requirements of 0.3% pefloxacin ophthalmological drops monotherapy and subsequent combination therapy for complete recovery from bacterial conjunctivitis was thoroughly analysed and assessed.
Results: In this study, the patient percentage topical application requirements of pefloxacin 0.3% ophthalmological drops monotherapy and combination therapy in bacterial conjunctivitis patients showed that 93% patients had completely recovered with pefloxacin monotherapy, and 7% patients required pefloxacin combination therapy for complete recovery. The evidence-based rational pharmacotherapeutics of newer quinolones, in global multi-centre tertiary care hospitals, was also well characterized and analytically described.
Conclusions: Therefore, 93% patients had completely recovered with the ocular antibiotic pefloxacin 0.3% ophthalmological drops monotherapy, and 7% patients required pefloxacin combination therapy for complete recovery. The evidence-based rational pharmacotherapeutics of newer quinolones was also distinctly delineated.

Keywords: Rational pharmacotherapeutics, Pefloxacin, Newer quinolones, Bacterial conjunctivitis

INTRODUCTION

The topical pharmaco-prophylactic and pharmacotherapeutic ophthalmological drops, like pefloxacin, demonstrate augmented levels of drug safety, norfloxacin, ciprofloxacin and ofloxacin. Although pefloxacin primarily possess oral and parenteral uses, it also has potential topical ophthalmological utility to treat ocular infections, like pseudomonal conjunctivitis.[1-16]

This study was conducted to supplement the existing medical research analyses on pefloxacin treatment in bacterial conjunctivitis. The rationality of the ophthalmological pharmacotherapeutic 0.3% pefloxacin drops, as a monotherapy as well as a combination therapy, was thoroughly appraised. Pefloxacin is a newer broad-spectrum bactericidal fluoroquinolone antibiotic, with superior antibacterial activity *in vivo* against pathogenic ocular gram-negative and anaerobic microorganisms and better pharmacokinetic properties as compared to other quinolones.[1-6]

Objectives

The objective of this clinical pharmacological experimental research was to analyse the evidence-based rational pharmacotherapeutic patient percentage topical application requirements of 0.3% pefloxacin ophthalmological drops monotherapy and combination therapy for complete recovery in bacterial conjunctivitis as well as the evidence-based rational pharmacotherapeutics of newer quinolones, in global multi-centre tertiary care hospitals.

METHODS

Study type

This was a global, multi-centre, prospective, open-labelled as well as analytical evidence-based rational pharmacotherapeutics research study.

Study place

This study, including the entire research study and the compilation of the study literature, was completed in the Departments of Pharmacology, Clinical Pharmacology, Rational Pharmacotherapeutics, Pharmacoepidemiology, Pharmacovigilance, Pathology, Clinical Pathology, Ophthalmology, Clinical Research and Evidence-Based Medicine, in the global multi-centre tertiary care hospitals, like, Dr. Moumita Hazra's Polyclinic And Diagnostic Centre, Hazra Nursing Home, Hazra Polyclinic And Diagnostic Centre, Mamata Medical College, Mamata Hospitals, Narayana Medical College, Narayana Hospitals, 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, Hi-Tech Medical College and Hospital, Shri Ramkrishna Institute of Medical Sciences and Sanaka Hospitals, J. J. M. Medical College and Hospital, Chigateri General Hospital, Dr. B. R. Ambedkar Medical College and Hospital, K. C. General Hospital, and Global Institute of Stem Cell Therapy And Research, Institute of Regenerative Medicine University Institutes, Hospitals and Laboratories.

Study period

The study period was 1 year 7 months, from May 2015 to September 2015; from January 2016 to February 2016; from December 2017 to January 2018; from September 2020 to December 2020; and from June 2021 to November 2022.

Selection criteria of the study patients

The inclusion criteria of the patients were as follows: patients of any gender, patients within 21 and 34 years, patients suffering from bacterial conjunctivitis, with a baseline antibiotic susceptibility testing result confirming sensitivity to pefloxacin, co-operative and conscious patients, patients willing to undergo all pre and post-treatment investigations and willing to complete the entire course of treatment, patients who have given consent and are willing to go for a follow-up, and patients not taking any previously started or any concomitant medication.

The exclusion criteria of the patients were as follows: unco-operative or unconscious patients, patients below 21 and above 34 years, patients presenting with any disease other than bacterial conjunctivitis, patients with a history of hypersensitivity to the study drug, patients with high risk diseases, cardiac, renal or any other associated complications or co-morbidities, patients with any chronic disease intervening with the study data, pregnant or lactating women, paediatric or geriatric patients, any associated medical disease or disorder having impact on study results, and female patients using hormonal contraceptives.

Study participants

The study participants consisted of 100 bacterial conjunctivitis patients. The sample size calculation was done by the 'rule of thumb'.

Study procedure

In this study, 100 patients suffering from bacterial conjunctivitis, were selected. These patients were prescribed the topical instillation of pefloxacin 0.3% ophthalmological drops monotherapy, 2 drops in each eye after every 3 hours for 2 days, and 2 drops in each eye after every 6 hours for next 5 days. The overall recovery of the patients was clinically examined and assessed. The patients who did not recover completely with 0.3% pefloxacin monotherapy ophthalmological drops, were administered topical pefloxacin 0.3% ophthalmological drops, 2 drops in each eye after every 6 hours for the next

3 days, as combination therapy, with other required ophthalmological eye drops, depending on the prognostic follow-up, on days 0, 3, 5, 7, 10, 15, 30, and on further follow-ups.

From the 100 bacterial conjunctivitis patients, thorough patients' history with complete examination details, before and after the administration of the study drug treatment were obtained with the study proforma, thoroughly analysed and the following details were recorded: the patients' participation assessment and adherence to treatment, including patients who completed the study thoroughly, drop-out patients due to adverse effects, lost to follow-up patients, and patients who withdrew voluntarily; the demographic characteristics, including age, gender, race, duration of symptoms of bacterial conjunctivitis, severity of the symptoms, present controller medications, the patients' present and past history, ophthalmological history including infection and immunological history, history of any previous injury, abnormality, or surgery, history of usage of contact lens, spectacles or any other ophthalmological technology accessory, past investigations and treatment history, drug susceptibility testing results, history of co-morbidities and concomitant medications, surgical history, family history, personal history, socio-economic history, reproductive history, and the symptomatic effect of ophthalmological treatment. Details of complete general physical examination, and systemic examination, including special senses neurological examination findings like, ophthalmological examination findings as well as general neurological examination findings, were recorded.

The grading of conjunctivitis and confirmation of diagnosis was done with conjunctival swabs taken from the patients and sent for the confirmation of *P. aeruginosa*, or *Staphylococci* as the causative microorganism. An ophthalmological examination was performed to thoroughly evaluate the different parameters of conjunctivitis, like redness, lacrimal secretion, mucoid discharge, response to ocular therapy and swelling of eyelid.

The parameters of conjunctivitis were graded as follows.

The redness of the mucous membrane of the eye was observed visually and the grades were given from 0 to 4, that is, 0=absent, 1=mild, 2=moderate, 3=severe, 4=extensive. The lacrimal secretion was graded from 0 to 3, as 0=normal, 1=slightly more than normal, 2=more than normal, and 3=severe. The mucoidal discharge was observed for whitish to yellowish white semi-solid discharge if any was noted and recorded as a grade of 0 to 3, in which 0=absent, 1=little, 2=more and 3=extensive. The response to ocular stimulus was assessed by throwing torch light on the eye from a particular distance and noticing the response to this stimulus. It was graded from 0 to 2, as 0=normal; 1=fast; and 2=very fast. The swelling of eye lid was graded from 0 to 2, as 0=absent, 1=slight, and 2=prominent.

The pharmacovigilance safety assessment was done by the monitoring of adverse drug reactions, like transient ocular burning or discomfort, ocular irritation, redness, stinging, pruritis, photophobia, ocular watering, and dryness, in the 100 patients, receiving pefloxacin 0.3% ophthalmological drops treatment, and recording the findings in the adverse event case report forms, on days 0, 3, 5, 7, 10, 15, 30, and on further follow-ups.[1,6]

Finally, the evidence-based rational pharmacotherapeutic patient percentage topical application requirements of 0.3% pefloxacin ophthalmological drops monotherapy and subsequent combination therapy for complete recovery from bacterial conjunctivitis was thoroughly analysed and assessed, for obtaining the patient percentage of complete recovery with pefloxacin 0.3% ophthalmological drops monotherapy and the subsequent patient percentage of complete recovery with pefloxacin 0.3% ophthalmological drops combination therapy.

Clinical pharmacological experimental research was also performed to analyse the various dimensions of evidence-based rational pharmacotherapeutics of newer quinolones, in global multi-centre tertiary care hospitals.

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 the ICH-E17), and in the 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.

Statistical analysis

The statistical analysis was done with percentages and subsequent graphical illustration of the research study findings.

RESULTS

The clinical demographic data of the patients were comparable.

In this research study, the patient percentage topical application requirements of pefloxacin 0.3% ophthalmological drops monotherapy and combination therapy in bacterial conjunctivitis patients showed that 93% patients had completely recovered with pefloxacin monotherapy, and 7% patients required pefloxacin combination therapy for complete recovery, as depicted in Figure 1.

The evidence-based rational pharmacotherapeutics of newer quinolones, in global multi-centre tertiary care

hospitals, was also well characterized and analytically described.

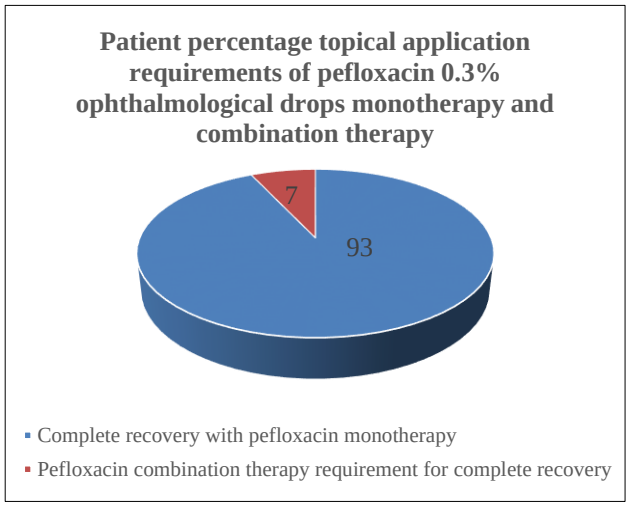

Figure 1: Patient percentage topical application requirements of pefloxacin 0.3% ophthalmological drops monotherapy and combination therapy in bacterial conjunctivitis patients.

DISCUSSION

The clinical demographic data of the patients were comparable.

In this research study, the patient percentage topical application requirements of pefloxacin 0.3% ophthalmological drops monotherapy and combination therapy in bacterial conjunctivitis patients showed that 93% patients had completely recovered with pefloxacin monotherapy, and 7% patients required pefloxacin combination therapy for complete recovery.

From the evidence-based rational pharmacotherapeutics of newer quinolones, it was found that newer quinolones are characterized by advantageous pharmacokinetic properties, broad-spectrum bactericidal activity, excellent oral bioavailability, good tissue penetration and favourable safety and tolerability profiles.

Quinolones possess an ever-expanding spectrum of clinical indications like multiple, multi-resistant, concurrent and recurrent infections, including drug-resistant tuberculosis, drug-resistant leprosy and coronaviridae – 19; refractory inflammations; diabetes and obesity; malignancies; anti-cancer radiotherapy; immune disorders and complicated and refractory diseases and disorders, due to their profound bactericidal, anti-viral, anti-fungal, anti-protozoal, comedolytic and anti-comedogenic, anti-inflammatory, anti-diabetic, anti-obesity, radioprotective, immunomodulatory (transcription factors - like NFB/NFAT/AP1- mediated, and on regulation of cyclic AMP or phosphodiesterases), 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, and inhibition of cell colony formation), anti-metastatic (migration, invasion and metastasis – MET inhibitor), and cancer stemness regulator potential.

The dual inhibitory activity of fluoroquinolones against the bacterial replication enzymes, DNA gyrase and topoisomerase IV, protects them from development of resistance.[1-13,17-23]

Delafloxacin, a new fourth generation broad-spectrum anionic fluoroquinolone, is used in the treatment of acute bacterial skin and skin structure infections, community-acquired bacterial pneumonia, polymicrobial diabetic foot infections and osteoarticular infection, bloodstream infections, acting against gram-positive bacteria including methicillin resistant *Staphylococcus aureus*, *Streptococcus* spp. and *Enterococcus* spp. and gram-negative bacteria such as *Pseudomonas aeruginosa*, anaerobes, and atypical infections. Delafloxacin has increased accumulation in bacteria allowing for enhanced bactericidal activity.[11,23-27]

Sitafloxacin, a new oral fluoroquinolone, has a broad spectrum of activity against multi-resistant gram positive pathogens including Staphylococci, Streptococci, Enterobacteriaceae and anaerobes, used for the treatment of Buruli ulcer. Oral sitafloxacin demonstrated high high clinical pharmacotherapeutic efficacy, in the treatment of acute complicated urinary tract infection and pyelonephritis.[28,29]

Sparfloxacin, a highly potent third generation fluoroquinolone, is indicated for treating community-acquired lower respiratory tract infections (acute sinusitis, exacerbations of chronic bronchitis, community-acquired pneumonia), complicated tuberculosis and multi drug-resistant tuberculosis. It acts against a wide range of gram positive and gram-negative anaerobes, *Legionella* spp., *Mycoplasma* spp., *Chlamydia* spp., and *Mycobacteria* spp. including multi-resistant strains.[30]

Zabofloxacin, an investigational novel fluoronaphthyridone quinolone antibiotic, is implicated in the treatment of acute bacterial exacerbation of chronic obstructive pulmonary disease, multidrug-resistant infections due to gram-positive bacteria like *Streptococcus aureus*, *Streptococcus pyogenes* and *Streptococcus pneumoniae*, *Neisseria gonorrhoea* causing quinolone-susceptible (QSSP) and quinolone-resistant gonorrhea (QRSP), community-acquired respiratory tract infections, caused by *Haemophilus influenzae* and *Moraxella catarrhalis*, COPD patients with moderate exacerbations, and community-acquired acute respiratory tract infections.[31-33]

Finafloxacin, a broad-spectrum fluoroquinolone antibiotic, is used to treat *Pseudomonas aeruginosa* and *Staphylococcus aureus* causing acute otitis externa, and

possesses activity against both gram-positive and gram-negative bacteria, including *Helicobacter pylori*.[34-36]

Garenoxacin is a newly developed novel des-fluoro (6) quinolone, which demonstrates wide spectrum of antibacterial activity against gram positive, gram negative, atypical and anaerobic pathogens. Its clinical indications are pharyngitis, sinusitis, laryngitis, tonsillitis, otitis media, acute bronchitis, pneumonia and secondary infection in chronic respiratory lesion.[12,37]

Ozenoxacin is a topical novel non-fluorinated quinolone antibiotic, which was shown to be bactericidal against methicillin-susceptible and methicillin-resistant *Staphylococcus aureus*, methicillin-susceptible and methicillin-resistant *Staphylococcus epidermidis*, *Streptococcus pyogenes* and *Streptococcus agalactiae*.[38-40]

Aravofloxacin (JNJ-Q2) is a novel fifth-generation broad-spectrum aminoethylidenylpiperidine fluoroquinolone that has excellent *in vitro* and *in vivo* activity against a variety of gram-positive and gram-negative organisms, being developed for the treatment of acute bacterial skin and skin-structure infections and community-acquired pneumonia and methicillin-resistant *Staphylococcus aureus* (MRSA) infections.[9,41,42]

Merafloxacin is a fluoroquinolone antibacterial that inhibits the pseudoknot formation which is necessary for the frameshift in the SARS-CoV-2 genome. It is a potential drug for SARS-CoV-2.[43,44]

WQ-3810, a newer fluoroquinolone, demonstrated the most potent activity against the multidrug-resistant pathogens, like Mycobacterium tuberculosis. It is a next generation respiratory fluoroquinolone. WQ-3810 is a drug is also used for the treatment of quinolone resistant *Salmonella typhymurium* infection, *Acinetobacter baumannii*, *Streptococcus pneumoniae*, *Staphylococcus aureus*, *Neisseria gonorrhoeae*, *Eschericia coli* and *Mycobacterium leprae*.[13,45,46]

Lascufloxacin is a fluoroquinolone antibiotic drug for the treatment of community-acquired pneumonia, otorhinolaryngological infections, and respiratory tract infections, caused by gram-positive bacteria including *Streptococcus pneumoniae* and *Streptococcus anginosu*.[47-49]

Quinolone antibiotics develop from generations to generations to obtain broader activity spectrum by the addition of different substituents into different positions to the core structure.

Quinolones are quite significantly efficacious, for their bactericidal action, through their: inhibitory action on 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; inhibitory action on 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; inhibitory action on pro-inflammatory cytokines, like interleukins : IL-1α, IL-6, IL-8, and tumour necrosis factor α; and superinducing effect on IL-2.

DNA gyrase and topoisomerase IV are A2B2 heterotetramer enzymes including two pairs of identical GyrA/GyrB and ParC/ParE in gram-negative or GlrA/GlrB in gram-positive species. GyrA and ParC or GlrA contain an active site tyrosine residue, which is involved in the breakage or reunion of the DNA. GyrB and ParE or GlrB contain the ATPase domain and the TOPRIM domain, which are involved in the energy transduction for DNA cleavage and ligation. The differences in the physiological functions between DNA gyrase and topoisomerase IV are due to the difference in the C-terminal region of these enzymes. The C-termini of GyrA and ParC (GrlA) associating with the topological recognition are not well conserved. The addition of a CTD region in the A subunits allows DNA gyrase to generate supercoils in DNA, which cannot be modulated by topoisomerase IV.

In the intracelullar region, quinolones bind to the DNA–enzyme cleavage complex at the cleavage-ligation active site. This binding creates a steady-state concentration of cleavage complexes and disrupts the replication process, which causes collision of the stabilized cleavage complexes with the DNA replication systems (replication fork, transcription complexes, and tracking systems) leading to chromosomal breaks. As a compensatory mechanism, SOS response and other DNA repair pathways are activated, resulting in subsequent action of the SOS system, such as extended cell filaments by expression of LexA repressor and programmed cell death by activation of toxin–antitoxin modules.

Nalidixic acid has antimicrobial spectrum of activity against gram-negative organisms (except *Pseudomonas* species), due to the modification of N at X8 position = naphthyridone, being the first molecule to be discovered in the quinolone class. Enoxacin, norfloxacin and ciprofloxacin are active against all gram-negative pathogens and some atypical pathogens (including *Mycoplasma pneumoniae* and *Chlamydia pneumoniae*), due to the modification caused by the addition of piperazine to C7 position, and –F to C6 position of enoxacin. This improves enoxacin's activity against gram-negative organisms, inhibiting the efflux mechanism. Norfloxacin, by the addition of piperazine to C7 position (quinolone), and –F to C6 position, improves bioavailability and side effects; and improves activity against gram-negative organisms that inhibits the efflux mechanism. Ciprofloxacin, by the addition of piperazine

to C7 position, –F to C6 position, and cyclopropyl at the N1 position, improves anti-gram-negative activity and increases potency. Ofloxacin, its L-isomer=levofloxacin, and lomefloxacin has antibacterial spectrum of activity against all gram-negative pathogens and some gram-positive bacteria (including *Staphylococcus aureus*, except *Streptococcus pneumoniae*) and some atypical organisms, due to the addition of methylated piperazine to C7 position and $–OCH_2$ at C8 position, thereby increasing anti-gram-positive activity, tissue penetration, and half-life, and the L-Isomer becomes 4-fold more active. Lomefloxacin, by the addition of methylated piperazine to C7 position, and –F at C8 position, increases anti-gram-positive activity and increases anti-gram-positive activity, tissue penetration, and half-life. Sparfloxacin, grepafloxacin, clinafloxacin, and gatifloxacin retain the activity of second-generation drugs and possesses expanded gram-positive coverage (penicillin-sensitive and penicillin-resistant *Streptococcus pneumoniae*) and improved activity against atypical pathogens, by the addition of dimethylated piperazine to C7 position, –F at C6 and C8 positions, $–NH_2$ at C5 position, and cyclopropyl ring at N1 position of Sparfloxacin, which increases anti-gram-positive activity, tissue penetration, and half-life, improves activity against gram-positive pathogens, and improves potency of the drug. Grepafloxacin, by the addition of methylated piperazine to C7 position, $–CH_3$ at C5 position, and cyclopropyl ring at N1 position, improves anti-gram-positive activity, improves anti-gram-positive activity compared to ciprofloxacin, and improves potency of the drug. Clinafloxacin, by the addition of 3-aminopyrrolidin-1-yl group to C7 position, –Cl at C8 position, and cyclopropyl ring at N1 position, improves anti-gram-positive activity and overcomes physical disadvantages, improves anti-gram-positive activity, tissue penetration, and half-life, and improves potency of the drug. Gatifloxacin, by the addition of methylated piperazine group to C7 position, methoxy group at C8 position, and cyclopropyl ring at N1 position, improves anti-gram-positive activity, improves anti-gram-positive activity, tissue penetration, and half-life, and improves potency of the drug. Moxifloxacin, gemifloxacin, trovafloxacin and garenoxacin, cover all the activities of third generation drugs and extra anaerobic activity, by the addition of azabicyclo group to C7 position, $–OCH_3$ at C8 position, and cyclopropyl ring at N1 position, which improves anti-gram-positive activity, but may result in low water solubility and oral bioavailability, improves anti-gram-positive activity, tissue penetration, and half-life, and improves potency of moxifloxacin. Gemifloxacin, by the addition of 3-methoximine-4-aminomethyl-pyrrolidin-1-yl group to C7 position and cyclopropyl ring at N1 position, improves anti-gram-positive activity and overcomes the physical disadvantages compared with pyrrolidine group alone, and improves potency of the drug. Trovafloxacin, by the addition of amine-substituted bicyclic pyrrolidin-1-yl group to C7 position and 2,4-difluorophenyl group at N1 position, thus improving anti-gram-positive activity, improving potency and activity against anaerobes. Garenoxacin, by the addition of azabicyclo group to C7 position, cyclopropyl group at N1, and difluoromethyl ether group at C8 position, thereby significantly improving anti-gram-positive activity (lipophilicity and half-lives), improving potency of the drug, and improving anti-gram-positive activity.

With the synthesis of fleroxacin, the quinolones entered their third generation. This generation was improvised by the addition of alkylated piperazine and pyrrolidinyl groups to the R7 position, and $–NH_2$, –OH, and $–CH_3$ groups to the R5 position to the pharmacophore. The cyclopropyl group at the R1 position and the $–OCH_3$ group at position R8 were kept unchanged from the second generation. The third generation also added new substituents, such as a chloro group (Cl) at the R8 position; this was verified to improve the anti-gram-positive activity of the drug. The most significant modification at this position was in 8-methoxyquinolone, in terms of activity and spectrum. The improvement is best exemplified by comparing grepafloxacin and gatifloxacin; the MIC90 of gatifloxacin (8-MeO) improved significantly compared with that of grepafloxacin (8-H). These modifications expanded the gram-positive activity of the third generation, including penicillin-sensitive and penicillin resistant *Streptococcus pneumoniae*, while the activity against atypical bacteria was also increased. The piperazine group in the second generation improved the gram-negative activity. The alkylated form of this group added to the gram-positive activity of the fluoroquinolone compounds. A pyrrolidinyl group in this position showed the same improvement as the alkylated piperazine group. Modification of the group at the R5 position increased the activity against gram-positive organisms. The antibacterial potency improvement due to the substitution at this position was found to increase in the order $–CH_3$, –OH, $–NH_2$, respectively. All the modifications (positions R8, R5, and R7) presented in this third generation were designed to improve the activity against gram-positive bacteria. Among these modifications, manipulation at the R7 has generally been the most effective. The spectrum of activity of fourth-generation compounds covers all the criteria of the third generation with the addition of activity against anaerobic organisms. The presence of nitrogen (N) at the R8 position is responsible for the improved activity against anaerobes, while a 2,4-difluorophenyl group at the N position improves the overall potency of the drug.[7,9,12,13]

There were no limitations in this study.

Therefore, this study further re-emphasized 0.3% pefloxacin ophthalmological drops to be a safe treatment option for pseudomonal or staphylococcal bacterial conjunctivitis. This pharmacovigilance research study has the potential to lead towards the development of better and safer topical ophthalmological drugs for treating bacterial conjunctivitis.

The evidence-based rational pharmacotherapeutics of newer quinolones, in global multi-centre tertiary care hospitals, was also well characterized and analytically

described. Therefore, these novel pharmacotherapeutics, quinolones, would always remain unique, due to the infinite metamorphosis of their extensive spectrum of therapeutic indications, every moment.

CONCLUSION

Therefore, it was concluded from the above-mentioned evidence-based rational pharmacotherapeutic research that 93% patients had completely recovered with the ocular antibiotic pefloxacin 0.3% ophthalmological drops monotherapy, and 7% patients required pefloxacin combination therapy for complete recovery. The evidence-based rational pharmacotherapeutics of newer quinolones was also distinctly delineated.

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