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Original Research Article

A rational pharmacovigilance safety appraisal of topical pefloxacin 0.3% ophthalmological drops in bacterial conjunctivitis, in global multi-centre tertiary care hospitals

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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. The objective of this clinical research study was the rational pharmacovigilance safety appraisal of topical pefloxacin 0.3% ophthalmological drops in bacterial conjunctivitis, in global multi-centre tertiary care hospitals.
Methods: The 43 bacterial conjunctivitis patients were prescribed topical pefloxacin 0.3% ophthalmological drops, 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 pharmacovigilance safety appraisal was performed by monitoring the occurrence of adverse drug reactions, like, transient ocular burning or discomfort, ocular irritation, redness, stinging, pruritis, photophobia, ocular watering and dryness, and recording in Adverse Event Case Report Forms, on days 0, 3, 5, 7, 10, 15, 30, and on further follow-ups.
Results: In this study, the safety assessment showed that only 1 patient had ocular discomfort in the eye. The occurrence of adverse effects was statistically non-significant. Thus, 0.3% pefloxacin ophthalmological drops treatment was safe and tolerable, among all 43 patients.
Conclusions: Therefore, pefloxacin is a safe ocular antibiotic for treating bacterial conjunctivitis, with adequate drug tolerability exhibited by the patients.

Keywords: Pharmacovigilance, Fluoroquinolones, Pefloxacin, Bacterial conjunctivitis, Topical pharmacotherapy

INTRODUCTION

The topical pharmaco-prophylactic and pharmacotherapeutic ophthalmological drops, like pefloxacin, demonstrate augmented levels of drug safety, with minimalisation of the systemic adverse effects. 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, including

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. In this study, the adverse drug reactions listed by MedDRA system organ class and preferred term were taken into consideration, along with emphasis on the adverse reactions, within each system organ class, under frequency categories of very common (≥1/10), common (≥1/100 to <1/10), uncommon (.1/1000 to <1/100), rare (.1/10,000 to <1/1,000), very rare (<1/10,000), and not known (cannot be estimated from the available data). The rationality of the ophthalmological pharmacotherapeutic 0.3% pefloxacin drops was thoroughly appraised, with adequate consideration of causality assessment grading and staging. Finally, the pharmacovigilance causality assessment grading and staging scores were also analysed, sequentially, keeping in consideration the different causality assessment score estimation methodologies, like the Naranjo algorithm of adverse drug reactions probability scale, as well as the World Health Organisation and Uppsala Monitoring Centre causality categories. The causality assessment attributes analysed and graded were (i) history of hypersensitivity to the same drug administered; (ii) history of hypersensitivity to the same generic category of drug administered; (iii) history of adverse drug reaction-like symptoms previously; (iv) occurrence of adverse drug reaction after suspected drug administration; (v) improvement of adverse drug effects after discontinuation of drug, modification of drug dose, alternate drug administration, or specific antagonist administration; (vi) appearance of adverse drug effects after re-continuation of drug, reversal to previous drug dose on patient stabilization, reversal to previous drug administration, or discontinuation of antagonist administration; (vii) alternative co-existing sources, like disease or medications, causing adverse drug effect-like reaction; (viii) false adverse drug effect mimicking reactions; (ix) appearance of adverse drug effect with a placebo; (x) detection of suspected drug in body fluids in toxic concentrations; (xi) severity of adverse drug reactions with increase or decrease of drug dose and (xii) occurrence of adverse drug reactions with the suspected drug in a time-variant or place-variant manner, with the grading: Yes=+1, No=-1, and Uncertain=0; and subsequent staging : none, mild, moderate or severe. The causality assessment scoring were derived from the recorded grading and staging, as follows: a) ≥9, severe on average=Definite causality of adverse drug reaction, b) 5-8, moderate-severe on average=probable causality of adverse drug reaction, c) 1-4, mild-moderate on average=possible causality of adverse drug reaction, d) ≤0, mild or none on average=doubtful / unlikely causality of adverse drug reaction, e) ≤0->0, variable, variable on average=conditional / unclassified causality of adverse drug reaction and f) ≥0 variable, variable on average=unassessable/unclassifiable causality of adverse drug reaction.[1-6]

Objectives

The objective of this clinical research study was the rational pharmacovigilance safety appraisal of topical pefloxacin 0.3% ophthalmological drops in bacterial conjunctivitis, in global multi-centre tertiary care 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 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.

Study type

This was a global, multi-centre, prospective, open-labelled pharmacovigilance study.

Study place

The 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, Rama Medical College Hospital and Research Centre, Rama University, Shri Ramkrishna Institute of Medical Sciences and Sanaka Hospitals, J. J. M. Medical College and Hospital and Chigateri General Hospital.

Study period

The study period was 12 months, June 2015; from December 2017 to January 2018 and from July 2021 to May 2022.

Selection criteria of the study patients

The inclusion criteria of the patients were as follows: (i) patients of any gender, (ii) patients within 21 and 34 years, (iii) patients suffering from bacterial conjunctivitis, with a baseline antibiotic susceptibility testing result confirming

sensitivity to pefloxacin, (iv) co-operative and conscious patients, (v) patients willing to undergo all pre and post-treatment investigations and willing to complete the entire course of treatment, (vi) patients who have given consent and are willing to go for a follow-up, and (vii) patients not taking any previously started or any concomitant medication.

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

Study participants

The study population consisted of 43 bacterial conjunctivitis patients. The sample size calculation was done by the 'Rule of Thumb'.

Study procedure

In this study, 43 patients suffering from bacterial conjunctivitis, were selected. These patients were prescribed the topical instillation of pefloxacin 0.3% ophthalmological drops, 2 drops in each eye at every 3 hours interval for the first 2 days, and then 2 drops in each eye at every 6 hours interval for the next 5 days.

From the 43 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, 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; 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 43 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.

The safety assessment for these patients was also done by recording and thoroughly analysing the details of the suspected drug causing adverse effects, drug dose, route of administration, drug frequency, drug starting date, drug stopping date, expiry date of the drug, batch no. / lot no. of the drug, drug manufacturer's name, brand/ generic name of the drug, indications for the usage of the suspected drug, any concomitant medicines, description of adverse reaction : clinical and pharmacological, supporting laboratory investigation results, treatment given for the adverse drug reaction, any specific antagonistic drug given to treat the adverse reactions as well as the clinical outcomes.1, 6

Statistical analysis

The statistical analyses were done with the tabular representation of the study findings, and the subsequent Test of significance, with the calculation of the p values.

RESULTS

In this study, the safety assessment showed that only 1 patient had ocular discomfort in the eye. The occurrence of adverse effects was statistically non-significant. As depicted in Table 1, with pefloxacin 0.3% ophthalmological drops treatment, there was occurrence of transient ocular discomfort in only 1 patient, the first day, which reduced within 24 hours, on drug adaptation with time. Thus, 0.3% pefloxacin ophthalmological drops treatment was safe and tolerable, among all 43 patients.

Table 1: Adverse drug reactions of pefloxacin 0.3% ophthalmological drops treatment.

Adverse drug reactions of pefloxacin 0.3% ophthalmological drops treatment	Patient number of occurrence of adverse drug reactions (n=43)	P value
Ocular discomfort	1	ns
Burning sensation	0	ns
Irritation	0	ns
Itching	0	ns
Bitter taste	0	ns
Redness	0	ns
Swelling	0	ns
Blurred vision	0	ns
Photosensitivity	0	ns

ns=non-significant.

DISCUSSION

In this study, the safety assessment showed that only 1 patient had ocular discomfort in the eye. The occurrence of adverse effects was statistically non-significant. With pefloxacin 0.3% ophthalmological drops treatment, there was occurrence of transient ocular discomfort in only 1 patient, the first day, which reduced within 24 hours, on drug adaptation with time. 0.3% pefloxacin ophthalmological drops treatment was safe and tolerable, among all 43 patients.

Many studies have shown that the poor bioavailability and therapeutic response exhibited by conventional ophthalmic solutions due to rapid precorneal elimination of the drug may be overcome by use of in–situ gel forming system that are instilled as drops into the eye and it undergoes a sol-gel transition in the cul-de-sac. Similar research study literature have demonstrated that pefloxacin, using xanthan gum as a gelling agent in combination with HPMC K15 as viscosity enhancing agent, is used in the treatment of eye infections such as, bacterial conjunctivitis, corneal ulceration and blepharitis, based on the concepts of pH-triggered in-situ gelation, thermo reversible gelation and ion activated system. These studies describe that in situ gelling system of pefloxacin mesylate provides sustained release of drug based on polymeric carriers that undergo sol-to-gel transition upon change in temperature and pH. In a comparative drug evaluation research study, when the pefloxacin formulations were evaluated for clarity, pH measurement, gelling capacity, drug content estimation, rheological evaluation and in vitro release study, it was found that the optimized formulation F6 was stable and provided sustained release up to 92% at the end of 8th hour and this was a viable alternative to conventional eye drops. Often, patient non-compliance is observed A high frequency of ophthalmic solutions instillation is main cause of patient non-compliance. Various ophthalmic vehicles such as inserts, ointments, suspensions, and aqueous gels, and new dosage forms like in situ gel, collagen shield, niosomes, liposomes, dendrimers and implants have been developed in order to lengthen the residence time of instilled dose and enhance the ophthalmic bioavailability. These ocular drug delivery systems, however, have not been used extensively because of some drawbacks such as blurred vision from ointments or low patient compliance from inserts. The ocular bioavailability of the drugs can be improved by prolonging their residence time in the cul-de-sac and by increasing their corneal permeability. In situ gelling system, a more desirable dosage form would be one that can deliver drug in a solution form, create little to no problem of vision and need be dosed no more frequently than once or twice daily. In situ activated gel forming systems are those which are when exposed to physiological conditions will shift to a gel phase. The various approaches that have been attempted to increase the bioavailability and the duration of the therapeutic action of ocular drugs can be divided into two categories. The first one is based on the use of sustained drug delivery systems, which provide the controlled and continuous delivery of ophthalmic drugs. The second involves maximizing corneal drug absorption and minimizing precorneal drug loss. In several comparable studies, fluoroquinolones administered as monotherapy for suspected bacterial keratitis reemphasized their broad spectrum of activity, low toxicity, good corneal penetration, and their efficacy at the usual available strength. In another comparative research study, on the use of a topical fluoroquinolone, both the efficacy and potency against the bacterial pathogen, as well as its concomitant toxicity to the cornea were explored, by using an in vitro assay of 3H-thymidine uptake of rabbit corneal epithelial cells to determine the cytotoxicity of fluoroquinolones. In this study, it was found that the relative toxicities of the fluoroquinolones on corneal epithelial cells from greatest to least were pefloxacin, ofloxacin, norfloxacin, temafloxacin, and ciprofloxacin. In another similar pharmacovigilance study, the adverse drug reactions occurrence, like transient ocular burning or discomfort, ocular irritation, redness, stinging, pruritis, photophobia, ocular watering and dryness was observed after 0.3% ofloxacin ophthalmological drops treatment, on treatment days 0, 3, 5, 7, 10, 15, 30, and on follow-ups, with causality assessment scores, from adverse drug reactions grading and staging. It was found that the occurrence of adverse effects were statistically non-significant, with causality assessment scoring of -11, none on average = Unlikely

causality. Thus, it was concluded that topical ofloxacin ophthalmological drops treatment was safe and tolerable, with nil causality of association of adverse drug reactions. On comparison of these studies to this present study, it was found that in this study, only 1 patient had ocular discomfort in the eye. The occurrence of adverse effects was statistically non-significant, and therefore, 0.3% pefloxacin ophthalmological drops treatment was safe and tolerable among all the patients. In yet another study, the clinical efficacy and safety of 0.3% pefloxacin drops were evaluated as the sole antibiotic used to treat culture gram-smear positive bacterial corneal ulcers, caused mostly by Staphylococcus aureus and coagulase negative Staphylococci. Resolution of corneal ulcer was achieved in 96.9%, with a mean duration of 9.3±0.3 days. Best corrected visual acuity of 20/200 or better was achieved in 65.6% at 4 weeks post resolution. Corneal deposits were observed in 1 case, which disappeared 8 days following discontinuation of therapy. In this study, the topical pefloxacin was found to be effective as a single antibiotic agent in treating bacterial keratitis.[14-16]

The main advantage of this study included an evidence-based pharmacovigilance assessment of 0.3% pefloxacin ophthalmological drops safety, with a causal analysis of the occurrence of the adverse drug reactions and subsequent management of the adverse drug reactions, for a safer and quicker patient recovery. There were no significant 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.

CONCLUSION

Therefore, it was concluded from the above-mentioned pharmacovigilance research on the drug safety appraisal during 0.3% pefloxacin ophthalmological drops treatment, that pefloxacin is a safe ocular antibiotic for treating bacterial conjunctivitis, with adequate drug tolerability exhibited by the patients.

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