

**Safety and Efficacy of a topical combination of Ofloxacin, Clotrimazole, Beclomethasone and Lignocaine for management of Mixed Ear Infections : Phase IV Study****Dr. Mayuresh Kiran¹, Ms. Shruthi George², Mr. Lalit Pawaskar³**¹General Manager, Medical Services, Centaur Pharmaceuticals Pvt. Ltd.²Officer, Medical Services, Centaur Pharmaceuticals Pvt. Ltd.³Research Associate, Pharmacovigilance, Centaur Pharmaceuticals Pvt. Ltd.**Correspondence Author: Dr. Mayuresh Kiran**, Address: Centaur Pharmaceuticals Pvt. Ltd., Centaur House, Near Grand Hyatt, Vakola, Santacruz (East), Mumbai – 400055.**Conflicts of interest:** None to Declare**Abstract**

Introduction: Otitis is a general term used for inflammation of the ear which is commonly caused due to bacteria and fungi. It is subdivided into 3 types which are named as otitis externa, otitis media and otitis interna. Out of which otitis media with perforated ear and otitis externa can be topically treated by the combination of Ofloxacin, Clotrimazole, Beclomethasone Dipropionate and Lignocaine.

Methodology: Total 189 patients were enrolled out of which 174 patients completed the study. Efficacy assessment was made by reduction in Visual Analogue Scale (VAS) Score of ear pain, ear discharge and ear itching related to Otitis media and Otitis Externa. Safety assessment was made by analysing the adverse events through the study.

Results: Reduction in mean VAS score was done from 4.12 (baseline) to 2.293 (day 3) to 0.54 (day 5) of ear pain, from 4.011 (baseline) to 1.931 (day 3) to 0.563 (day 5) of ear discharge and from 2.896 (baseline) to 1.31 (day 3) to 0.241 (day 5) of ear itching. Nearly all the patients had >50% reduction in their VAS score at all visits in all the parameters except in visit 2 in ear pain where reduction was 44.34 %. Majority of patients had complete relief

from the symptoms at visit 3. 17 episodes of adverse events were occurred and all of them were of mild intensity.

Conclusion: A combination of Ofloxacin, Clotrimazole, Beclomethasone Dipropionate and Lignocaine is safe and effective in the treatment of Otitis media and Otitis externa.

Keywords: Ofloxacin, Clotrimazole, Beclomethasone Dipropionate, Lignocaine, Otitis media and Otitis externa

Introduction

Ear inflammation is known as otitis is commonly caused by bacteria as well as fungi. Depending on the parts of the ear involved, it can be called as otitis interna (OI), otitis media (OM) and otitis externa (OE).^[1] OE is common inflammatory condition of outer ear usually caused by bacteria or fungi.^[2] OE i.e. infection of canal is primarily caused by a break in normal cerumen protective barrier or skin in the presence of elevated temperature, humidity or both.^[3] Ear pain, discharge, inflammation, itching and hearing loss are the most common symptoms of otitis externa. Topical drug therapy is mostly preferred for the treatment of external ear infection over surgery or oral antibiotics, as the disease is limited to the skin of the ear canal.^[2]

OM is due to infection of middle ear. It may be acute, serous or chronic suppurative. This inflammation often begins when infections of colds, sore throats or other respiratory spread to the middle ear. It present with symptom of ear inflammation, pain and tenderness of soft tissue with a purulent discharge. These are normally fungal and bacterial infections. OM may cause the complication of rupture of tympanic membrane.^[1]

OI is an inflammatory condition of the inner ear structure.^[4] It is commonly treated by systemic or oral antimicrobial drugs.^[4] Where as for the treatment of otitis media upon perforation of tympanic membrane and Otitis Externa are commonly treated by topical otic solution.^[2,3,5]

OE and OM are often mixed infections wherein bacteria as well as fungi are involved as both are commensals of the auditory canal.^[6] So for the topical treatment of mixed ear infections combination of antibiotic as well as antifungal agents are commonly used. The major symptoms of Otitis externa and Otitis media are pain and inflammation in the ear. For symptomatic treatment to reduce the pain and inflammation, topical local anaesthetic agent and anti-inflammatory agents can be used. Complete management of ear infections including otitis media and otitis externa the combination of antibacterial, antifungal, anti-inflammatory and local anaesthetic agent can be used.

Ofloxacin is an antibacterial agent. Ofloxacin has in vitro activity in contradiction of a wide range of gram-positive and gram-negative microorganisms. Ofloxacin inhibits DNA gyrase which is a bacterial topoisomerase and exerts its antibacterial activity. DNA gyrase is an essential enzyme which assists in bacterial DNA repair, replication, transcription, deactivation and controls DNA topology. As per US FDA 0.3% Ofloxacin sterile otic solution can be used for the treatment of chronic suppurative otitis media, acute otitis media and otitis externa, as an anti-infective (anti-bacterial) solution.^[7]

Clotrimazole is an antifungal agent which belongs to imidazole class. Clotrimazole binds to one of the cytochrome P-450 enzymes and inhibits 14- α -demethylation of lanosterol. This leads to reduced concentrations of ergosterol a sterol essential for a normal fungal cytoplasmic membrane and accumulates 14- α -methylsterols. The accumulation of methylsterols inhibits growth of fungi by affecting the electron transport system. As per US FDA, 1 % cream or lotion of Clotrimazole can be used for the treatment of topical fungal infections.^[8]

Beclomethasone Dipropionate is anti-inflammatory agent which belongs to glucocorticoid class. Irrespective of the type of injury, the attending inflammatory response is suppressed by glucocorticoid. The action of Beclomethasone Dipropionate is nonspecific and covers all components and stages of inflammation. This includes reduction of increased capillary permeability, local exudation, cellular infiltration, phagocytic activity and late responses like capillary proliferation, collagen deposition, fibroblastic activity and ultimately scar formation. The action is direct and local-topical use is possible. The cardinal signs of inflammation like heat, redness, pain and swelling are suppressed.^[9]

Lignocaine is a topical anaesthetic, it stabilizes the neuronal membrane by inhibiting the ionic fluxes required for the initiation and conduction of impulses, thereby effecting local anesthetic action.^[10] Rowbotham MC after conducting a clinical trial on patients of Postherpetic Neuralgia stated that Lidocaine gel 5% produces significant reductions in pain intensity and significant pain relief when applied topically.^[11]

Okovityř SV et al^[12] and Karen Koch et al^[2] has emphasized, otitis externa can be topically treated by antibiotics (Fluroquinolones- Ofloxacin or Ciprofloxacin), antifungal agents (Clotrimazole has greatest zone of inhibition for common fungi), anti-inflammatory agents

(Glucocorticoid) and any agent for pain management can be used.

So for the treatment of mixed ear infection in otitis media with perforation and otitis externa the combination of Ofloxacin 0.3% w/v, Clotrimazole 1% w/v, Beclomethasone Dipropionate 0.025 % w/v and Lignocaine 2% w/v can be used. Such combinations are available in the Indian market. This study was conducted to generate the safety and efficacy data of this combination on Indian patients for the said indication.

Materials and Methods

12 ENT centres were selected all over India for conducting Phase IV clinical study. Total 209 patients were recruited for the study out of which 174 patients completed the study. 35 patients were lost to follow-up. This study was conducted from February 2017 to April 2017.

Inclusion and exclusion study

Patients with confirmed diagnosis of Otitis Media with perforation and Otitis Externa were enrolled in the study. Patients of both the genders (male and female) having age between 18 to 75 years were recruited for this study. Finally the patients who were ready to strictly adhere to the protocol and sign informed consent form were recruited for the study.

Patients with hypersensitivity to the individual study drug or to any of its ingredients were excluded from the study. Pregnant or lactating women and mentally ill patients or who were not ready to strictly adhere to the study protocol were excluded from the study.

Study Intervention

Study drug

Ear drops containing combination of Ofloxacin (0.3% w/v), Beclomethasone Dipropionate (0.025 % w/v), Clotrimazole (1% w/v) and Lignocaine Hydrochloride (2% w/v) per ml.

Study dosage and administration

Patients were asked to instil two drops of Ear Drops thrice a day with 8 hrs interval for a study period of 5 days.

Study procedure

The study interval was decided to be kept 5 days to study safety and efficacy of the study drugs combination. Patients of OM and OE who fulfilled decided inclusion and exclusion criteria were engaged in the study. Before starting PMS study a detailed medical history of each patient was obtained by physical examination (including respiratory rate, blood pressure in the sitting position, oral temperature and pulse rate) was conducted by the investigators. The only investigators holding post-graduate degree in ENT speciality were involved for conducting this study. Patients were dispensed with 4 ml study drug combination otic solution in a dropper bottle by investigators and asked to instil one to two drop thrice a day for a study period of 5 days with 8 hrs interval. Patients were asked to maintain a diary to record any adverse events occurring during the study duration.

Three visits were planned for all the patients recruited in this study – V₁ (baseline visit) on day 1 before treating patient with the study medication, V₂ (reevaluation visit) on day 3 and V₃ (last or conclusion visit) on day 5. VAS score and adverse events occurring were noted at each visit along with physical examination and medical history. Patients were instructed to keep a diary of daily symptoms. Investigators were asked to discontinue the study drug in case of severe adverse event and with discretion, clinical experience in case of mild or moderate adverse events.

Concomitant therapy

No Pharmacological intervention and medication was allowed during the study period of 5 days. No other oral or topical otic drug for pain management or treating bacterial

or fungal infection was allowed during study duration of 5 days.

Efficacy assessment

The primary assessment was done to evaluate the reduction in the VAS score for the Ear pain, Ear discharge and Ear itching related to Otitis media and Otitis Externa on an eleven-point scale (0 to 10) where 0 means no symptoms i.e. patients who are completely cured and 10 means maximum tolerated symptoms. The secondary assessment was done to analyse the percentage reduction in mean VAS score of ear pain, ear discharge and ear itching at visit 2 and visit 3 as compared to baseline.

Safety assessment

Patients were asked for any adverse event at each visit and if present were noted in the case record form (CRF) during each visit. These adverse events were classified into serious and non-serious adverse events. Naranjo's scale of probability was used to classify the adverse event as drug related or nondrug related. Adverse events were followed up and also treated if it is found to be necessary.

Regulatory and Ethical matters

This combination is available in India and classified under the category of schedule H drug, which means that it should be sold only if prescription of registered medical practitioners is present with the patient. All the participated patients in the study have read and voluntarily signed the informed consent form (ICF). This study was conducted by following all the rules and guidelines as per schedule Y. The ICF, protocol, CRF, investigators CV, investigators undertaking, ethics committee registration certificates and investigators medical registration

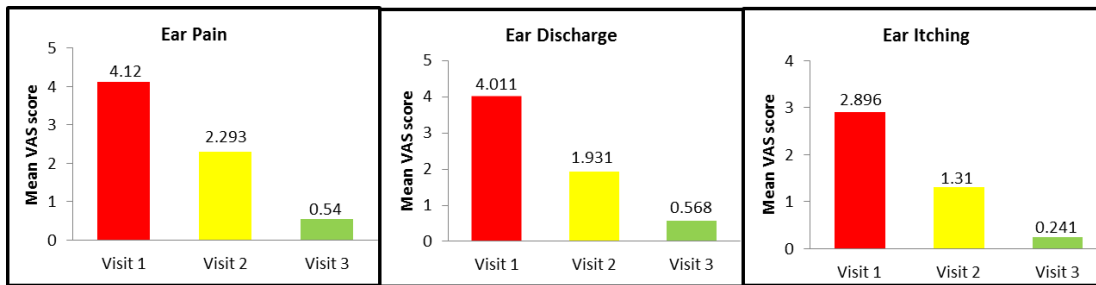
certificates (including post-graduation certificates) were submitted to the office of DCGI (Drug Controller General of India), Central Drugs Standard Control Organization (CDSCO) and are registered under ref. no. 2507/17.

Results

The baseline demographic characteristics are given in Table 1.

Mean Age	32.2 years
Males / Females	82 / 92
Mean BMI	23.4

Mean of VAS score of ear pain, ear discharge and ear itching at each visit was calculated and separately plotted graphically as shown in figure no. 1. Percent reduction in mean VAS score in ear pain, ear discharge and ear itching at visit 2 and visit 3 was calculated and plotted in figure no. 2. At baseline the mean VAS score for ear pain, ear discharge and ear itching was 4.12, 4.011 and 2.896 respectively. On day 3rd (2nd visit) after taking study drug combination, mean VAS score for ear pain, ear discharge and ear itching was reduced to 2.293, 1.931 and 1.31 respectively i.e. there was a reduction of 44.34 %, 51.85 % and 54.76 % in mean VAS score at visit 2. On 5th day (3rd visit) mean VAS score of ear pain, ear discharge and ear itching was reduced to 0.54, 0.568 and 0.241 respectively which means in visit 3, there was a reduction of 86.89%, 85.83% and 91.67% in mean



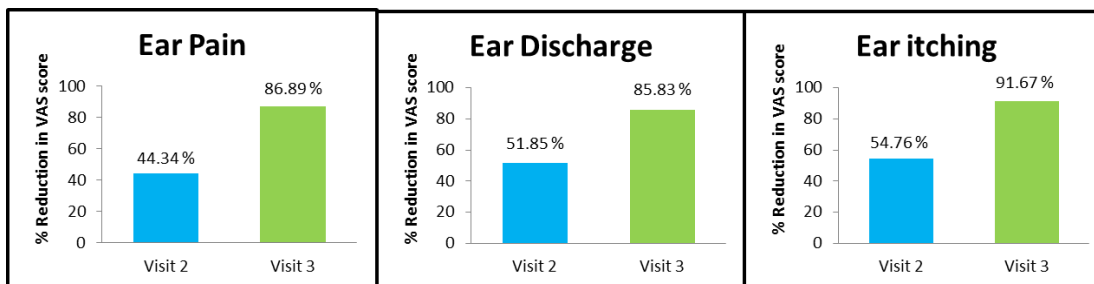
VAS score.

Fig. 1 Reduction in mean VAS score in ear pain, ear discharge and ear itching at each visit

Fig. 2 Percent reduction in mean VAS score in ear pain, ear discharge and ear itching at each visit

Out of total 174 patients 14 patients at day 3 and 55 patients at day 5 had VAS score of 0 in ear pain, ear discharge and ear itching which means 14 and 55 patients were completely cured on day 3 and day 5.

Safety analysis



The overall drug related adverse effects incidences were 17 seen in 12 patients i.e. in 6.89 % of total population. The list of adverse events with the number of patients is mentioned in the Table 2 as below.

Adverse events	No. of episodes	No. of patients	% of total population
Severe burning sensation	14	10	5.74 %
Mild vertigo	3	2	1.15 %
Total	17	12	6.89 %

Discussion

Otitis externa and Otitis media can be best treated with the topical agents. It is not self-limiting and as per American Academy of Paediatrics (AAP) if it is if not properly treated it may lead to several complications such an

infection of the inner ear that causes imbalance and dizziness (labyrinthitis), mastoiditis, meningitis, thickening or scarring of the eardrum, facial paralysis or permanent hearing loss.^[13]

In the best of all the authors knowledge, this is the first clinical study for the otic topical combination of Ofloxacin, Clotrimazole, Beclomethasone Dipropionate and Lignocaine for the treatment of Otitis externa and Otitis media with perforation. Visual Analogue Scale (VAS) was used for analysis of efficacy. VAS has 11 grades for symptom assessment which makes VAS more sensitive. VAS was used for analysing the common and main symptoms of otitis media with perforation and otitis externa which are ear pain, ear discharge and ear itching at all the visits so that we could analyse efficacy of the study drug medication.

In visit 1 before treating patient, mean VAS score of ear pain, ear discharge and ear itching was 4.12, 4.011 and 2.896. After treatment with the study medication at day 3 ear pain, ear discharge and ear itching was decreased to 2.293, 1.931 and 1.31 respectively so VAS score was decreased by 44.34 %, 51.85 % and 54.76 %. Which means at day 3 mean VAS score of ear discharge and ear itching was decreased by more than 50 % except ear pain. At day 5 mean VAS score of ear pain, ear discharge and ear itching was decreased to 0.54, 0.563 and 0.241 respectively. So there was decrease of 86.89 %, 85.83 % and 91.67 % in mean VAS score of ear pain, ear discharge and ear itching which was more than 80 %. Out of total 174 patients 14 patients were having 0 VAS score at day 3 in all the parameters i.e. they were cured at day 3 and similarly 55 patients were completely cured on day 5. Thus study drug medication was found to be efficacious in treating mixed ear infection.

17 adverse events incidences were observed in 12 patients i.e. in 6.89% of patients. The adverse events observed were of mild intensity including burning sensation (in 5.74% of patients) and mild vertigo (in 1.15% of patients) which need not to be treated separately or patients were not needed to be withdrawn from the study.

Ronald N. Jones et al. ^[14] conducted a randomized, evaluator-blind, multicentre clinical trial of Ofloxacin and Cortisporin (combination of neomycin sulfate, hydrocortisone and polymyxin sulfate) otic solution for Treatment of OE in childrens and adults. The study was conducted on 247 adults (12 years and older) and 227 children (younger than 12 years). Children and adults who were treated with Ofloxacin were to receive 5 drops and 10 drops, respectively, of 0.3% Ofloxacin otic solution. If randomized to Cortisporin otic solution, children and adults were to receive 3 drops and 4 drops respectively. All the patients were evaluated at 4 visits: day 1 (pre-

therapy visit); days 3-5 (during-therapy visit); days 11-13 (post therapy visit); and days 17-20 (test of cure visit). 82% and 97% of adults and childrens who were treated with ofloxacin were completely cured at post therapy visit and test of cure visit whereas 84% and 95% of adults and children treated with Cortisporin cured at the same visits. So it was concluded that, Ofloxacin is as safe and efficacious as combination of neomycin sulfate, hydrocortisone and polymyxin sulfate given 4 times daily for otitis externa.

The similar study was conducted by Joseph Dohar et al^[15] for 0.3% otic solution of Ofloxacin in children with tympanostomy tubes. Children younger than 12 years and diagnosed with acute purulent otorrhea of presumed bacterial origin and tympanostomy tubes were selected for the study. All the patients were treated with 0.3% otic solution of ofloxacin, 0.25 mL, twice daily for 10 days. And 84 out of 141 i.e. 59.57 % patients were cured in 10 days and no serious ADR were observed. So it was concluded that Ofloxacin is safe and efficacious in the treatment of acute purulent otorrhea in children with tympanostomy tubes.

Prasanna V et al. ^[16] conducted a clinical study of 1% Clotrimazole otic solution on 75 patients diagnosed with otomycosis (superficial fungal infection in deeper ear canal skin and tympanic membrane). 83 ears were treated by 1% Clotrimazole ear drops after through clearance of ear canal by suction. All the patients were evaluated clinically at the end of 4 weeks. 80 out of 83 (i.e. 98.36%) ears were cured at the end of study. Which concludes that 1% clotrimazole is effective in achieving complete mycological cure in otomycosis.

As per US FDA topical combination of anti-fungal (Clotrimazole) and corticosteroids (Betamethasone Dipropionate) have vasoconstrictor potencies in a range that is equivalent to high potency topical corticosteroids.

The combination of Clotrimazole and Betamethasone is also available in the US market as a US FDA approved product for the topical treatment of fungal inflammatory diseases.^[8]

Michael C. Rowbotham et al.^[11] conducted a study on 47 subjects for testing topical pain relief efficacy of Lidocaine. It was found that in 39 out of 47 patients intensity of pain was reduced. So it was concluded that local topical application of lidocaine is efficacious in reducing the topical pain intensity.

pH of otic solution plays an important role in the acceptance of ear drops as it should be 6.5 ± 0.5 . pH of test otic solution is 6 because of what 14 episodes of burning sensation were observed in 10 patients i.e. in 5.74% of patients.

Conclusion

A combination of Ofloxacin 0.3% w/v, Clotrimazole 1% w/v, Beclomethasone Dipropionate 0.025 % w/v, Lignocaine Hydrochloride IP 2% w/v provides optimum antibacterial, antifungal and symptomatic relief and it is safe in the treatment of Otitis media with perforation and otitis externa.

Acknowledgement

We would like to acknowledge who were the co-investigators in this study Dr. D. Harish Swami (Nizamabad), Dr. Ranbeer Singh (Hyderabad), Dr. S. Prabhakar Singari (vijaywada), Dr. Rajeev Bnagale (Mumbai), Dr. Chandrakant S Shewale (Mumbai), Dr. Anagha A. Joshi (Mumbai), Dr. Jayesh Patel (Mumbai), Dr. C. R. Das (Bhubaneshwar), Dr. Satyajit Mishra (Bhubaneshwar), Dr. Satchidananda Panda (Bhubaneshwar)

Disclosure

Dr. Mayuresh Kiran, Study Director and Mr. Lalit Pawaskar, Research Associate of this study are employees of Centaur Pharmaceuticals Pvt. Ltd. This study was

conducted as a part of Pharmacovigilance activity for Otiflox Ear Drops manufactured and marketed by Centaur Pharmaceuticals Pvt. Ltd. in accordance with Pharmacovigilance Program of India (PvPI).

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