Treatment of chronic resistant otitis externa with Fluticasone propionate (Flixonase®): initial experience

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May 5, 2020

Abstract

Objective: Cases of chronic otitis externa (OE) resistant to conventional treatment remain a significant challenge. This paper describes our experience of utilising fluticasone propionate (Flixonase®) drops in the treatment of such cases. Methods: We included a series of patients with resistant chronic OE that were referred to ENT consultant clinic between 2012 and 2014, all of whom failed to respond to the conventional treatments. The patients were prescribed 200 micrograms of Flixonase® once daily and followed up in the clinic to assess response to the treatment. The case notes were reviewed retrospectively. Results: Total of 25 patients identified over 2 years. Patients reported itching as the most common symptom (83%), and skin changes were the most common sign identified under examination (72%). The combination of steroid and antibiotic drops had been the most common treatment modality prescribed. Fluticasone propionate was started a median of 5 months after the diagnosis (range: 0-54 months) with a median treatment duration of 3 months (range: 1-18 months). All 17 patients who attended the follow-up clinic were classified as having been cured. Conclusions: Our findings suggest fluticasone propionate as an exciting and potentially important modality in the treatment of chronic OE cases, especially where all other treatment options have been exhausted.

Introduction

Otitis externa is a diffuse inflammatory condition of the external auditory canal. It can be divided into sub-categories including acute (less than six weeks), recurrent acute and chronic. Otitis externa that lasts more than three months, or more than four attack of otitis externa per year, are defined as chronic otitis externa.(1)

Acute otitis externa has a rapid onset, significant morbidity and lifetime incidence of up to 10%, this condition is regularly encountered by clinicians in both primary and secondary care. The majority of acute cases (98%) are bacterial infections, with*Pseudomonas aeruginosa* (38%), *Staphylococcus epidermis*(9%), and *Staphylococcus aureus* (8%) being the most prevalent pathogens. Several other gram-positive and gram-negative pathogens have also been reported in literature which account for less than 3% of cases. (2) Fungal infection is less common, with increased prevalence in chronic otitis externa resistant to topical antibacterial treatment, and is often referred to secondary care.(3)

The aetiology of otitis externa may be multifactorial and break down of the skin-cerumen barrier is thought to be the first step in pathogenesis of the condition. Curamen creates an acidic environment, which inhibits bacterial growth. Water exposure during swimming, trauma (such as excessive cleaning), foreign bodies including hearing aids and dermatological conditions disrupt the thin layer of skin in ear canal, alter the quality and the amount of cerumen produce. This will disrupt epithelial migration, increases the pH in the

ear canal, creating an environment ideal for growth of microorganisms in the ear canal. Alkaline pH in the ear canal is a known risk factor for progression of acute otitis externa into chronic otitis externa. [4]Swimming and water exposure is also a well-documented risk factor.[5,6] The pathogenic organisms are present in most swimming pools and hot tubs and specific preventative measures to limit water accumulation for those who are habitually in water and engage in water sports have shown to reduce recurrence significantly.[6]

The majority of cases of acute otitis externa are mild and can be managed with topical antibiotics in primary care. Nevertheless, a significant proportion of patients still require input by otolaryngologists as the inflammation can persist for weeks or even months despite intensive treatment. [7]

The concerns over ototoxicity of eardrops and a lack of national guidelines on the management of otitis externa has been reported as a cause of confusion over the use of topical and oral antibiotics among general practices (GPs) in the UK. [8] Inappropriate use of oral antibiotics is associated with increased disease persistence and recurrence. [8,9] The antimicrobial agents like β-lactamases inhibitors which are often reported to be prescribed in otitis externa cases are not effective against *S. aureus* and*P. aeruginosa* as they are widely distributed throughout the body and there is a rising incidence of antibiotic resistance particularly against *P. aeruginosa* in both community and hospital settings.[10] Topical antibiotics however deliver a high local concentration and shown to be beneficial for eradicating organism resistant to oral antibiotics. [11] The diversity of interventions used in general practices has been reflected in data provided by the General Practice Research Database (GPRD) where oral antibiotics were used in 21% of patients with otitis externa.[9] Another prospective observational study that analysed first-line treatment used by GPs in the UK found 44% of patients referred to secondary care have been prescribed oral antibiotics. [8]

The collective set of data indicates that chronic otitis externa is commonly encountered by clinicians in primary care and it also accounts for a considerable proportion of workload in emergency and otolaryngology departments. [6,7]

Chronic otitis externa may result from inadequately treated acute otitis externa. In these cases, presence of skin disease such as psoriasis and atopic dermatitis are common.

The goal of treatment is to reduce the chronic inflammation, promote the production of cerumen and to restore normal skin flora of the ear canal. Any underlying skin disease should be managed, with input from dermatologists if required. All the (potential) irritants should identified and be avoided during the treatment period and the patient should be advised to keep the ear canal dry.

Itch and conductive hearing loss are the most common symptoms in chronic cases while ear pain is less common. Clinically, these cases present in two main forms, seborrheic and eczematous. In seborrheic form, the ear canal appears dry, shiny or scaly whereas in the eczematous form the canal appears moist and erythematous. [12]

Chronic and recurrent cases require repeated visits for management such as microsuction. The costs and healthcare burden are substantial, with resolution in these cases challenging. At a certain point, clinicians will often have used a majority of conventional treatments without resolution of the infection. Treatment for this is typically poor.

Fluticasone propionate (Flixonase®) are synthetic corticosteroids with potent anti-inflammatory activity that are regularly used intranasally for treatment of nasal polyps and management of allergic or non-allergic rhinitis. [13]

This article presents our experience of using fluticasone propionate drops in managing patients with chronic resistant otitis externa, referred to the ENT department of a tertiary centre.

Methodology

The study was performed at the University Hospital Birmingham. A retrospective case note review was conducted of all consecutive patients with resistant otitis externa, present for over 3 months, treated with

fluticasone propionate (Flixonase®) by the senior author (CC) between October 2012 and October 2014. We did not have any exclusion criteria. The initial assessment was performed by CC, with recorded data regarding symptoms and signs available in the documentation. All patients were treated with half a capsule of fluticasone propionate (200 micrograms equivalent to approximately 6 drops) once daily for the affected ear. There were no modifications of treatment dosage during the length of the study.

Follow up was between two and eighteen months for all patients. Patients details recorded from the notes included gender, age at the time of diagnosis, previous treatment modalities, length of fluticasone propionate treatment, pre- and post-treatment symptoms including otalgia, tenderness, otorrhoea and itching, as well as signs of oedema and inflammation, and eventual outcome of treatment. The definition of cure was to be symptom-free with a normal endoscopic view of the external auditory canal.

Results and analysis

Data were available for a total of 25 patients, with a median age of 55±15 years, and of whom the majority were female (84%). The most common signs and symptoms were itching (83%), skin changes (73%) and otorrhoea (65%). Prior to treatment with fluticasone propionate, 44% had tried combination of antibiotic and steroid drops, 28% had taken steroid drops, 16% have been on antibiotic only drops and 12% had tried other medications, namely oral antibiotics. The treatment modalities used by the cohort is displayed in chart I. The fluticasone propionate treatment was started at a median of 5 months after diagnosis (range: 0-54), with a median treatment duration of 3 months (range: 1-18).

(Chart I)

(Chart II)

After treatment, 17 patients returned for a follow up appointment. Of the remainder, six patients did not attend the planned appointment and records were unavailable in two patients. At the follow up appointment, none of the 17 patients reported otalgia, tenderness, oedema or skin changes, and only one patient had itching. All 17 patients that attended the follow up appointment were classified as having been cured.

Table 1 – (Appendix – to be inserted here)

Discussion

Otitis externa is a common otological problem encountered regularly by clinicians in primary and secondary care. The data from more than 40 emergency departments in 2007, revealed 2.4 million visits for acute otitis externa (8.1 visits per 1000 population), affecting nearly 1 in 123 across the population of the United States. The lifetime incidence has been reported to be up to 10%. [(11)]

Studies from other countries also support this observation. A survey performed in a general hospital in Spain over 12 months, reported otitis externa to be accounted for 14.8% of referrals to otolaryngologist from emergencies, becoming the second most common aetiology referred to otolaryngologists following epistaxis (16.8%). (14)

The direct costs of managing otitis externa have been estimated at around half a billion dollars annually in the United States. This figure only covers the costs of hospital visits and treatment prescriptions. (15) Indirect costs are likely to be substantial due to the disabling effect of the disease. In one study published in the Netherlands, the condition found to cause a discontinuation of daily activity and bed rest for 36% (35/98) of patients, for a median of four days, and 21% (21/98) required bed rest and time off work for a median of 3 days. (16)

The magnitude of resistant chronic cases was demonstrated well in a national epidemiological survey published in 2001, which investigated the prevalence and treatment regimen used in primary care to treat otitis externa in the UK. The data derived from the General Practice Research Database (GPRD) which analysed

GP visits related to 40,661 episodes of otitis externa in more than thirty thousand patients, revealed 21% of patients suffered from more than one episode and a further 7% visited their GP three or more times for persistence and/or recurrence of otitis externa over a one-year period. In addition, 3% of patients had to be referred to ENT specialists for further treatment and expert opinion. [(9)] It is likely that resolving chronic otitis externa will decrease the episodes of acute otitis externa a patient sustains.

Many otolaryngology departments across the National Health Service (NHS) in the UK have now established 'casualty' or 'emergency' clinics which are commonly led by junior trainees and receives referrals from General Practices and Emergency Departments (ED). The high prevalence of otitis externa in these clinics have been demonstrated previously. Data from a tertiary hospital in the UK, indicates that between 16-20% of new referrals and almost 30% of daily follow-ups are related to otitis externa.(17)

Further analysis of findings demonstrates that otitis externa is the most common condition seen more than twice in a single clinical episode. The data obtained from ENT emergency clinic in St. George's Hospital in London shows that 80% of such repeated visits are related to cases of otitis externa not responding to treatments offered in the initial visit, required further follow up and input by senior clinicians. (18)

Similar challenging cases of otitis externa has been encountered in our centre, where they have been referred to the senior author of this paper, by which time most conventional treatments have been exhausted. There is no guideline in the United Kingdom for the management of chronic otitis extern. Although there have been few randomized controlled trial involving chronic cases along with acute otitis externa, no single recommendations can be derived for the treatment of chronic otitis externa as a separate clinical disorder.[(1)]

Other than the conventional combination of topical steroids, topical and oral antibiotics, two novel approaches have been taken recently for treatment of chronic otitis externa, including use of Tacrolimus and Fluocinolone acetonide solution.

Tacrolimus ointment is a nonsteroidal topical immunomodulator that was formulated specifically for the treatment of atopic dermatitis.(19) The ointment effectiveness has been evaluated in a German prospective study, for management of 33 patients with chronic otitis externa. The medication was applied topically for a period of 6 to 9 days and the results showed 13 out of 33 patients (39%) with complete healing (follow up 10-22 months). Total of 15 cases were recorded to have relapse within the same period. (20)

A randomized controlled trial (RCT) looked into the safety and efficacy of fluocinolone acetonide 0.025% solution (a low-to-medium corticosteroid) in treatment of otic eczema, which is often a chronic and relapsing condition difficult to manage.

This RCT measured changes in symptoms including itching and otoscopic signs after administration of fluocinolone acetonide 0.025% solution twice daily for 7 days and compared it with a placebo-treated group. Results indicated that patients treated fluocinolone acetonide solutions (n= 58), compared with the placebo-treated group (n= 63), had significantly higher reduction in itching ($P < 0.001$) and improvement in otoscopic signs ($P < 0.001$). (21)

We have investigated the option of using Flixonase®topically in 25 resistant cases. As presented in the section above, all cases who returned to follow up were classified as being cured and symptoms free. When applied topically, fluticasone propionate, a potent corticosteroid, relieves pruritic and inflammatory symptoms through binding and activation of glucocorticoid receptors. This trigger a cascade of reactions involved in the synthesis of prostaglandins. The results include alteration of protein synthesis, decreased fibroblast proliferation, reduction in the release of leukocyte acid, reduced capillary membrane permeability, less collagen deposition, inhibition of histamine and kinin release and prevention of macrophage accumulation. (22,23)

It should be noted that more than 70% of our patients used treatment modalities which contained corticosteroids, with Sofradex® and Gentisone HC ear drops being the most common ones. A comparison between the steroid concentration of all three drops, shows that daily dosage of fluticasone propionate contains significantly higher concentration of corticosteroids, compare to the other two ear drops. Sofradex® ear drop (0.5% w/v of Framycetin, Sulphate 0.005% w/v of Gramicidin and 0.050% w/v of Dexamethasone) contains

50 micrograms of corticosteroid per 100 ml; when applied topically, it will deliver 0.3 micrograms of corticosteroid to the external ear canal. * Gentisone HC ear drops (Gentamicin 0.3% w/v and Hydrocortisone acetate 1% w/v Ear Drops) contains 1000 micrograms of corticosteroid per 100 ml; which is equivalent to 8 micrograms of steroid per day. **Given that 200micrograms/day fluticasone propionate was prescribed, the significant difference in the amount of highly potent corticosteroid delivered to the external ear canal could explain the successful response observed in cure rate of resistant cases with a course of Flixonase® alone.

* Maximum dosage of Sofradex® is 3 drops, QDS, assuming each drop containing 0.05 ml, the total daily volume of Sofradex® delivered topically equals 0.6 ml

** Maximum dosage of Gentisone HC is 4 drops QDS, assuming each drop containing 0.05 ml, the total daily volume of Gentisone HC delivered topically equals 0.8 ml

A study done to compare systemic exposure of intranasal steroids confirmed that delivery of therapeutic dose of 2400 micrograms of fluticasone propionate daily will result in very low systemic bioavailability, estimated to be 0.06% (24). Given the fact that Flixonase was prescribed topically to the skin, not mucosa, the systemic bioavailability is likely to be lower than the figure cited above ($< 0.06\%$). Hence, it can be concluded that fluticasone propionate is likely to produce very small systemic exposures to steroids, and have a low potential for systemic side effects when administered topically to ears at the recommended doses.

There are however some limitations to our work. The first is the variable length of treatment for each patient. This can be attributed to more difficult cases, or to potentially concurrent skin conditions such as psoriasis or eczema which can attribute to recurrent disease. The second limitation is the restricted number of patients and those lost to follow up. Although, a small cohort size this treatment modality does show promise within a domain notoriously difficult to treat.

Conclusion

Chronic otitis externa is often a recalcitrant problem and a challenge for the attending doctor. A successful management requires investigation of underlying cause and a strategy equipped with mixture of old and new therapies. We present a study analysing the potential benefit of Flixonase® in resistant chronic otitis externa cases. All patients (100%) who returned to follow up showed cure, having previously failed with a multitude of conventional management options. We did have some limitations which we hope could be analysed further with a more robustly designed study, however the use of fluticasone propionate is an exciting and potentially important tool in the arsenal of the otolaryngologist.

Full informed consent was obtained from all patients prior to data collection. All patient data was anonymised prior to data analysis

Funding

None of the authors has a financial interest or commercial association to declare in relation to the content of this article.

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Tables and Charts

Chart I: Treatment modalities used before the Flixonase

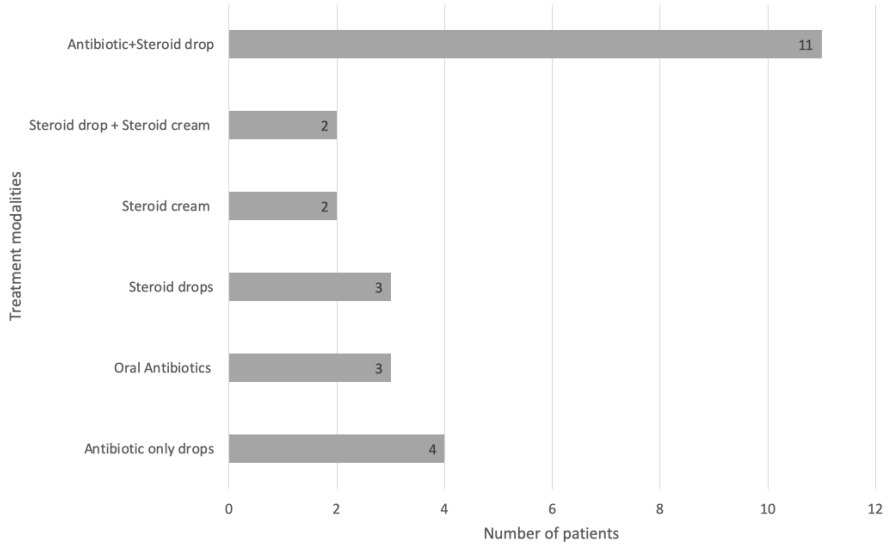

Chart II: Treatment duration

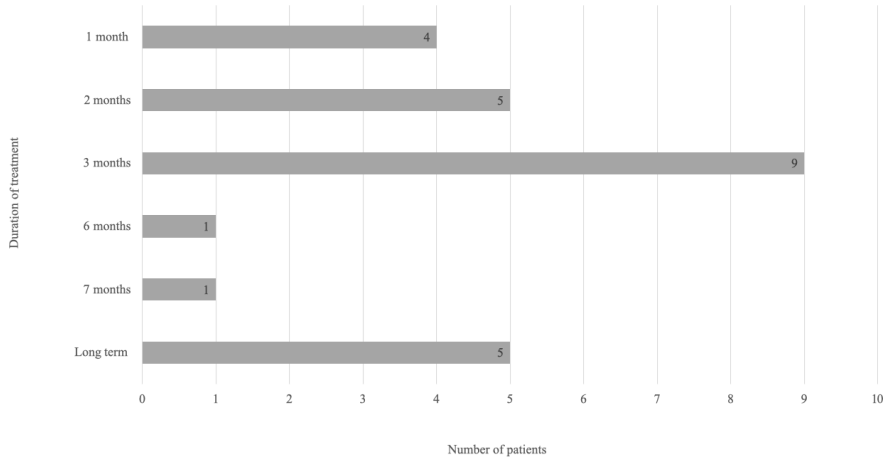

TABLE I Results

	Valid N	Statistic
Patient Demographics and Treatment	Patient Demographics and Treatment	Patient Demographics and Treatment
Age	25	55 ± 15
Gender (Female)	25	21 (84%)
Number of Antibiotics Tried	25	
0		13 (52%)
1		6 (24%)
2		4 (16%)
3		2 (8%)
Steroids Tried	25	6 (24%)
Others Medications Tried	25	2 (8%)
Diagnosis to Flixonase (Months)	22	5 (0 - 54)
Treatment Length (Months)	23	3 (1 - 18)
Pre-Flixonase Signs/Symptoms	Pre-Flixonase Signs/Symptoms	Pre-Flixonase Signs/Symptoms
Otalgia	23	6 (26%)
Tenderness	22	2 (9%)
Otorrhoea	23	15 (65%)
Itching	24	20 (83%)
Oedema	22	5 (23%)
Mucosal Changes	22	16 (73%)
Post-Flixonase Signs/Symptoms	Post-Flixonase Signs/Symptoms	Post-Flixonase Signs/Symptoms
Returned for FU	25	17 (68%)
Otalgia	17	0 (0%)
Tenderness	17	0 (0%)
Itching	17	1 (7%)
Oedema	17	0 (0%)
Mucosal Changes	17	0 (0%)
Cure	17	14 (100%)

Data are reported as N (%), mean±SD, or median (range), as applicable. Valid N: the number of patients for whom data for the stated variable were recorded.

Bullet Point Summary

- **Otitis externa is a common condition encountered by clinicians both in primary and secondary care.**
- Literature reflects continued variation in managing cases with otitis externa.
- Chronic cases, resistant to conventional treatments incur a substantial healthcare burden, with resolution in these cases challenging.
- Fluticasone propionate was utilised in treatment of resistant chronic cases in our clinic which resulted in 100% cure for all patients attending the follow up clinic.

- Despite the limitations in our study, our findings suggest fluticasone propionate as an exciting and potentially important tool in the arsenal of the otolaryngologist.