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Is Besifloxacin Ophthalmic Suspension 0.6% Safe and Effective for the Treatment of Bacterial Conjunctivitis?

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ABSTRACT

OBJECTIVE: The objective of this systematic review is to determine whether or not besifloxacin ophthalmic suspension 0.6% is safe and effective for the treatment of bacterial conjunctivitis.

STUDY DESIGN: Review of three trials in the English language, all published in 2009.

DATA SOURCES: Randomized, double masked, multicenter parallel group studies comparing besifloxacin to a vehicle suspension or moxifloxacin were found using Ovid MEDLINE, and Cochrane databases.

OUTCOME MEASURED: Resolution of bacterial conjunctivitis through reduced or eliminated signs or symptoms, the microbial eradication of the bacteria responsible for the disease, and the safety of the medication used in terms of adverse events while treating bacterial conjunctivitis with besifloxacin.

RESULTS: All three double blinded RCTs demonstrated that besifloxacin was more safe and effective in treating bacterial conjunctivitis when compared with a vehicle suspension. When besifloxacin was compared with moxifloxacin, it was concluded that besifloxacin is not inferior to moxifloxacin for the treatment of bacterial conjunctivitis.

CONCLUSIONS: The results of the RCTs demonstrate that besifloxacin for the treatment of bacterial conjunctivitis is safe and effective. More studies are needed comparing other drug treatments, different strengths, the safety and efficacy in children versus adults and the duration of the medicine adminitaration. Future studies will help to determine the best medicinal option in treating bacterial conjunctivitis safely and effectively.

KEY WORDS: Besifloxacin, Bacterial Conjunctivitis

Introduction

Bacterial conjunctivitis, whether acute or chronic is the most common eye disorder that nearly everyone will face at least once in their lifetime. Bacterial conjunctivitis is a disease that is symptomatically defined by a copious purulent discharge, mild eye discomfort due to sticky eyelids, redness and ocular irritation. The most common organisms to cause bacterial conjunctivitis are *Staphylococci*, *Streptococci*, *Haemophilus*, *Pseudomonas*, and *Moraxella*. In many cases, bacterial conjunctivitis is obtained from upper respiratory infections that have spread to the eye, although there are other ways of transmitting the disease. Many bacterial conjunctivitis cases are also due to transmission from an infected person to another through infected areas and close personal contact. Moreover, conjunctivitis can also exist due to viruses. Viral conjunctivitis is distinguished from bacterial conjunctivitis due to its characteristic clear discharge.[1]

This eye disease is of great importance to primary care patients due to the high prevalence of the disease. Due to its ability to affect anyone in all age groups, bacterial conjunctivitis is important to treat and prevent. Although it is a self limiting disease in most cases, the use of antibiotics for its treatment has ultimately led to reduced transmission, quicker recovery time, shorter duration of the disease and reduced complications from long standing disease.[2] Prevention of bacterial conjunctivitis is also possible through management of associated diseases such as acute otitis media and bacterial pneumonia, which can result in bacterial conjunctivitis if untreated.[1]

Currently, methods that are used to treat bacterial conjunctivitis include topical antibiotics such as sulfacetamide 10%, polymixin-bacitracin-neomycin, and trimethoprim-polymixin. Broad spectrum topical antibiotics are sufficient to treat the disease and cultures of

the ocular discharge are done to determine antibiotic resistance or in cases refractory to medicinal treatment. The total direct and indirect cost of treating bacterial conjunctivitis in the United States in 2005 was estimated to be $589 million.[2] Costs include primary care visits and the cost of medicinal treatment, primarily topical broad spectrum antibiotics.

Besifloxacin is another topical antibiotic that can be used as an option to treat those who have been affected by bacterial conjunctivitis. Besifloxaxin is a fluoroquinolone that has fairly good broad spectrum antibiotic activity. It is an FDA approved drug for the treatment of bacterial conjunctivitis, that has shown success in treating bacterial conjunctivitis as well as preventing complications and reducing transmission as well as duration of the disease.

Objective

The goal of this review is to determine whether or not besifloxacin ophthalmic suspension 0.6% is safe and effective for the treatment of bacterial conjunctivitis. Previous randomized controlled trials that have been published on besifloxacin ophthalmic suspension 0.6% for the treatment of bacterial conjunctivitis have shown that besifloxaxin is a safe and effective treatment and can be used as an alternative to other topical antibiotics for the treatment of bacterial conjunctivitis.

Methods

The studies that were obtained for this analysis were RCT's that included patients over the age of 1 who were adequately diagnosed with bacterial conjunctivitis based on criteria set forth by the studies' authors. The intervention that was utilized in each of these RCT's was besifloxacin ophthalmic suspension 0.6%. Comparisons to this intervention included moxifloxaxin ophthalmic suspension 0.5%, another fluoroquinolone in the treatment of bacterial

conjunctivitis and a vehicle suspension that did not include besifloxacin. To gather information on these studies, databases such as the Cochrane Database of Systematic Reviews, MEDLINE, and the Ovid interface were used. All articles that were chosen were selected based on their importance of the outcomes to patients. Inclusion criteria that were placed for the selection of the studies were: 1) studies that were published in 1996 or later. 2) Studies associated with POEMS. 3) Studies published in the English language. 4) Studies that were randomized controlled trials. 4) Studies that were not previously used in meta-analyses or systematic reviews. Searching for randomized controlled studies in English using the keywords "besifloxacin," and "bacterial conjunctivitis" helped to selectively limit articles that were necessary and were of importance to the study. The studies that were finalized and chosen were: 1) Randomized, prospective, double masked, vehicle controlled trial comparing besifloxacin suspension 0.6% to a vehicle formulation without besifloxacin. 2) Multicenter, randomized, double masked, parallel group study comparing besifloxacin ophthalmic suspension 0.6% to moxifloxacin ophthalmic solution 0.5%. and 3) Randomized, multicenter, double-masked, vehicle controlled study that compared besifloxacin ophthalmic suspension 0.6% to a vehicle suspension without besifloxacin.

The characteristics of all the studies that were used in this analysis are displayed in **Table 1.** The three RCT's are similar in inclusion and exclusion criteria. Interventions are also similar in all the trials. The number of participants in each study varies greatly, as well as the number of withdrawals from the trials.

Table 1. Characteristics of Studies Included in the Systematic Review of Besifloxacin Ophthalmic Suspension 0.6% for the Treatment of Bacterial Conjunctivitis

Study	Type	# Pts.	Age (yrs)	Inclusion Criteria	Exclusion Criteria	W/D	Intervention
Karpecki, et.al., 2009	RCT, double masked	269	1+	Minimum grade 1 for purulent conjunctival discharge, minimum grade 1 for either bulbar or palpebral conjunctival injection, pinhole visual acuity ≥ 20/200, negative pregnancy test	Hypersensitivity to fluroquinolones, besifloxacin, or any other ingredient used in the study, if a topical medication was used within 48 hours before or during study, if Abx were used w/in 72 hrs of the start of study, dx of viral/allergic conjunctivitis, hx of iritis, corneal erosion syndrome, ulcerative keratitis	13	Besifloxacin ophthalmic suspension 0.6% given 3 times daily for 5 days
McDonald ,et al., 2009	RCT, double masked	1161	1+	Healthy pts, grade 1 or more purulent discharge and injection, visual acuity of ≥ 20/200, agreement to d/c Abx agents, negative pregnancy test	Use of ophthalmic solutions, ocular surgery within 6 weeks of start of study, viral/allergic conjunctivitis, ulcerative keratitis, corneal erosion syndrome, hypersensitivity to drug/drug class	52	Besifloxacin ophthalmic suspension 0.6% given 3 times daily for 5 days
Tepedino, et al., 2009	RCT, double masked	957	1+	Visual acuity ≥ 20/200, method of contraception or negative pregnancy test, discontinued use of contact lenses	Use of systemic or topical Abx within 72 hrs, topical soln within 2 hours, anti-inflamm. agent within 48 hrs before or during the study, pregnant or nursing females, viral/allergic conjunctivitis, corneal erosion syndrome, ulcerative keratitis, immunocompromised, hypersensitivity to drug/drug class	26	Besifloxacin ophthalmic suspension 0.6% applied 3 times daily for 5 days

Outcomes that were measured were POEMS such as the resolution of bacterial conjunctivitis through reduced or eliminated signs or symptoms, the microbial eradication of the bacteria that was the cause of the disease, and the safety of the medication used in treating bacterial conjunctivitis. Outcomes were measured using Cochran-Mantel-Haenszel (CMH), Pearson X^2 test, Fisher exact test, individual safety outcomes assessments based on grading scales. Karpecki, DePaolis, Hunter, White, et al used 4 point scales for ocular discharge, bulbar conjunctival injection, where 0= absent, 1= mild, 2= moderate, and 3=severe. The clinical outcomes were then counted for each patient, and an overall score was determined. In the overall score, 0= scores for ocular discharge and bulbar conjunctival injection are 0, 1= improvement, current score less than day-1 score, 2= no change from baseline score, 3= worse, current score greater than day-1 score. In the study done by McDonald, Protzko, Brunner, Morris, et al, the investigators used a scale to determine global assessment of changes in clinical signs and symptoms where 0= cured, 1= improved, 2= no change from pretreatment, and 3= worse. Investigators Tepedino, Heller, Usner and Brunner, et al also used the same 0-3 rating scale for clinical outcomes where 0= resolution or cure, 1=improvement, 2= no change, and 3= worse.

In all three RCT's, microbial eradication was measured through microscopy. Safety was measured in all studies using visual acuity and biomicroscopy for lids, limbus, conjunctiva, cornea, anterior chamber, lens and vitreous.

Results

Two RCT's compared besifloxacin with a vehicle suspension while another RCT compared besifloxacin with moxifloxacin, another topical ophthalmic antibiotic in the same drug class. Inclusion and exclusion criteria for each of the studies was fairly similar. Each study chose

participants who were above the age of 1 and healthy, non pregnant patients. The participants also had to have a minimum grade 1 for purulent ocular discharge and a minimum grade 1 for bulbar or palpebral conjunctival injection along with a pinhole visual acuity of greater than 20/200. The study excluded participants who had a hypersensitivity to fluoroquinolones, if the patients had used any topical medication on the eye within 48 hours of the start of the study, if antibiotics were used within 72 hours of the study or if the patient had a diagnosis of viral or allergic conjunctivitis. Patients with a history of corneal erosion syndrome, ulcerative keratitis, or iritis were also excluded from the studies.

The results of the primary outcome, the treatment of bacterial conjunctivitis were presented in the articles as dichotomous data. All data from the studies were analyzed with the intention to treat, excluding those who were excluded from the study.

In the investigation done by Karpecki et al, the clinical resolution of bacterial conjunctivitis was 43.1% and 73.3% in the control and besifloxacin groups respectively. The relative benefit increase (RBI) was 70.0%, and the absolute benefit increase (ABI) was 30.2%. The number needed to treat (NNT) was 4 patients. The difference in the control and experimental groups is statistically significant with the p-value less than 0.001.[3]

In the study done by McDonald et al, the clinical resolution of bacterial conjunctivitis was 84% in the moxifloxacin group, and 84.5% in the besifloxacin group. The relative benefit increase and absolute benefit increase was 0.60% and 0.5% respectively. The number needed to treat was 200 patients. All data was included in a 95% confidence interval for RBI and ABI.[4]

The investigation done by Tepedino et al in comparing a vehicle suspension with besifloxacin ophthalmic suspension 0.6% yielded a clinical resolution and microbial eradication

of bacterial conjunctivitis of 69.1% in the control group, and 84.4% in the besifloxacin group. The relative risk benefit and absolute benefit increase is 22% and 15.3% respectively. The number needed to treat was 7 patients. All data was statistically significant with a p-value of 0.0011.[5] **Table 2** shows a summary of all three studies and the results for the clinical resolution of bacterial conjunctivitis in each study.

Table 2. Clinical Resolution of Bacterial Conjunctivitis with Besifloxacin Suspension 0.6%

Study	Besifloxacin group resolution of illness	Control group resolution of illness	p-value	Odds Ratio (95% CI)	RBI	ABI	NNT
Karpecki, 2009	73.3%	43.1%	<0.0001	NR	70.0%	30.2%	4*
McDonald, 2009	84.5%	84%	NR	(-5.6%-6.75%)	0.60%	0.5%	200*
Tepedino, 2009	84.4%	69.1%	0.0011	NR	22%	15.3%	7*

CI= Confidence Interval, RBI= Relative Benefit Increase, ABI= Absolute Benefit Increase, NNT= Number Needed to Treat, NR= Not Reported

* The outcome that was measured was the clinical resolution of bacterial conjunctivitis. The NNT means that for every 4/200/7 patients who participated and received besifloxacin treatment, there was one more resolution of bacterial conjunctivitis than in the group of patients taking the vehicle suspension or the moxifloxacin suspension.

Each study also calculated the incidence of adverse effects in terms of safety of besifloxacin ophthalmic suspension 0.6%. In the study done by Karpecki et al, the incidence of adverse events for besifloxacin group was 50.4%, and was 53% for the control group. The relative risk increase (RRI) was -4.9%, and the absolute risk increase (ARI) was -3.0%. The number needed to harm is -34 patients.

In the study completed by McDonald et al, the incidence of ocular adverse events was 12% in the besifloxacin group and 14% in the control group with moxifloxacin. The relative risk increase was -14.3% and the absolute risk increase was -2.0%. The number needed to harm was

-50 patients.[4]

Tepedino et al completed a study between a vehicle suspension and besifloxacin ophthalmic suspension 0.6% in which the incidence of adverse events for the besifloxacin group was 9.2% and the adverse events for the control group, or the vehicle suspension without besifloxacin was 13.9%. The relative risk increase was calculated to be 33.8% and the absolute risk increase was calculated as -4.7%. The number needed to harm in this study was -22 patients. The data in this study was statistically significant with a p-value of 0.0047. **Table 3** shows a summary of the incidence of adverse events in patients with besifloxacin and in the control group for each study performed.[5]

Table 3- Incidence of Adverse Events of Besifloxacin and Control Groups

Study	Besifloxacin Incidence of Adverse Events	Control Group Incidence of Adverse Events	p-value	RRI	ARI	NNH
Karpecki, 2009	50.4%	53%	NR	-4.9%	-3.0%	-34*
McDonald, 2009	12%	14%	NR	-14.3%	-2.0%	-50*
Tepedino, 2009	9.2%	13.9%	0.0047	-33.8%	-4.7%	-22*

RRI= Relative Risk Increase, ARI= Absolute Risk Increase, NNH= Number Needed to Harm, NR= Not Reported

* Since the outcome measured were adverse events in those participants receiving besifloxacin ophthalmic suspension 0.6%, the values mean that for every -34/-50/-22 patients treated with besifloxacin, there was one fewer incidence of adverse events experienced than in the group receiving the vehicle solution.

In all three studies performed with besifloxacin, the most common adverse event that was reported was ocular irritation. Patients reported itching of the eyes or irritation after administration of the medication. However, in all three studies, the incidence of adverse events

in the besifloxacin group were significantly lower than the incidence of adverse events in the control group, whether it be a vehicle suspension without besifloxacin or moxifloxacin. The most common adverse events that were reported in each of the studies was eye irritation, blurred vision and ocular pruritis. Karpecki and associated analyzed ocular adverse events in the experimental and control groups. They determined that the overall ocular adverse event rate in the eyes that were treated with besifloxacin was 34.7%, whereas the ocular adverse event rate in the eyes that were treated with vehicle suspension not containing besifloxacin was 38.8%. **Table 3** displays the results of the ocular adverse events that occurred during the Karpecki et al study on besifloxacin.[3]

Table 3. Incidence of Ocular Adverse Events in Besifloxacin and Vehicle Suspension Groups

Ocular Adverse Event	Besifloxacin (n=190)	Vehicle (n=188)
Eye Pain	20 (10.5%)	13 (6.9%)
Blurred Vision	20 (10.5%)	22 (11.7%)
Eye Irritation	14 (7.4%)	23 (12.2%)

n= number of participants

Discussion

In the double masked RCT that was conducted by Karpecki and associates, the results displayed success for the besifloxacin intervention. The clinical resolution of bacterial conjunctivitis was 73.3% for the besifloxacin experimental group whereas the resolution of bacterial conjunctivitis was 43.1% for the vehicle suspension group. Both interventions were administered similarly 3 times a day for 5 days.[3] McDonald et al determined in their double blinded RCT that moxifloxacin and besifloxacin were similar in efficacy due to their similar properties. The clinical resolution for besifloxacin and moxifloxacin was 58.3% and 59.4% respectively. The solutions were also used three times daily for a total of 5 days. The study also

noted that the 95% Confidence Interval of the clinical resolution rates showed that besifloxacin was not inferior to moxifloxacin despite a difference in their success rates.[4] The administration of besifloxacin and a vehicle suspension for three times daily for five days in the Tepedino et al double blinded study also yielded results in favor of the besifloxacin intervention. The clinical resolution of bacterial conjunctivitis in the besifloxacin group and in the vehicle group without besifloxacin was 45.2% and 33.0% respectively.[5]

All three of the RCTs included a patient population over the age of 1. However, there is no information on the results of clinical resolution and adverse events of besifloxacin between children and adults. More information is needed on the efficacy of the medication between the two groups as well as the strength and the administration of the medication that can be given to children versus adults. This information will likely allow primary care providers to determine if besifloxacin is safe and effective for children also.

Authors of the RCT also mentioned that besifloxacin, a fluoroquinolone was effective in eradicating the bacteria that are the most likely causes for bacterial conjunctivitis. Fluroquinolones cover Gram positive bacteria as well as Gram negative bacteria, and the efficacy of besifloxacin in the microbial resolution of the bacterial conjunctivitis is vital information on treating most cases of bacterial conjunctivitis.

A limitation of each study was the comparison of clinical resolution rates between treating bacterial conjunctivitis symptomatically with no medication and using besifloxacin for treating bacterial conjunctivitis from Day 1. There is no information on how the outcome of the disease would have been in regards to duration of the disease if besifloxacin was not used for five days to treat the illness. A study comparing the duration of the disease in using besifloxacin

versus no medication would be helpful to determine if bacterial conjunctivitis is a disease to be treated with medications or not.

Conclusions

The trials that were reviewed established that besifloxacin is safe and effective in treating bacterial conjunctivitis. Since besifloxacin suspension was only studied using one strength, 0.6%, there was a limitation in knowing the efficacy at different strengths of the medication. Future studies should be designed to include different classes of drugs that can be used to treat bacterial conjunctivitis. The length of the administration of the medication should also vary to determine the recommended duration of treatment. The results of these future studies will help to determine the best medicinal option in the treatment of bacterial conjunctivitis.

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