Original Research Article

Comparison between bepotastinebesilate 1.5% eye drop versus olopatadine hydrochloride 0.2% eye drop in cases of allergic conjunctivitis

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Abstract

Background: Allergic conjunctivitis is an increasingly prevalent allergic reaction having clinical gravity similar to asthma and allergic rhinitis. **Aims and Objectives:** To study Comparison between bepotastinebesilate 1.5% eye drop versus olopatadine hydrochloride 0.2% eye drop in cases of allergic conjunctivitis. **Methodology:** forty consecutive patients presenting from March 2018 to July 2018 in Eye OPD at Saraswathi institute of medical sciences Hapur, with symptoms of ocular itching associated with allergic conjunctivitis a were enrolled in this study. Here, Group A (1st drug B and 2nd drug O) (n=20), Group B(1st drug O and 2nd drug B) (n=20), where Bepotastinebesilate 1.5% eye drop, O Olopatadine hydrochloride 0.2% eye drop. 1stvisit done after 1st day of starting the drug, 2nd visit (day 16) after use of first medication, 3rd Visit (day 39) after use of second medication. The itching symptoms and all Ocular allergy symptoms were graded on 5 points scale. The statistical analysis done by unpaired t-test and calculated by SPSS 19 version software. **Result:** the majority of the patient were in the age group of 40-50 i.e. 60% followed by 30-40-17.5%, 20-30 were 12.5%, 50-60 were 10%. The mean age was (Mean ±SD) 41.68 ± 8.51. The majority of the patients were females 65% and males were 35%. At first visit the symptoms itching were comparable with each other as Ocular itching grading on 5 point scale was 4.2 ± 0.52 and 4.35 ± 0.49 in group A and B respectively (t=0.94 df=38,p>0.05) ; on2nd visit (day 16)after use of first medication the relief score in ocular itching was significantly higher in Group A i.e. 3.9± 0.79 versus 2.85 ± 0.67 in group B (t=4.9 df=38,P<0.0001), 3rd Visit (day 39)after use of second medication the score was significantly higher in Group B i.e. 3.7±0.47 as compared to 2.65 ±0.81in group A (t=5.0 df=38, P<0.0001). At 2nd visit (day 16) after use of first medication the relief score in all ocular allergy symptoms was significantly higher in Group A i.e. 3.55± 0.69 as compared to2.65± 0.75 in group B (t=5.23, df=38, p<0.0001) , at 3rd Visit (day 39)after use of second medication the score was significantly higher in Group B i.e. 3.2±0.70 as compared to 2.3±0.73in group A (t=4.92 , df=38,p<0.0001). **Conclusion:** at the baseline both the drugs were comparable with each other, at second visit the score was variable but at the end the response with respect to score and patients preference the bepotastinebesilate 1.5% was found superior to olopatadine hydrochloride 0.2% with respect to treatment of allergic conjunctivitis.

Key Word: bepotastinebesilate 1.5% ,olopatadinehydrochloride 0.2% , allergic conjunctivitis

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INTRODUCTION

Allergic conjunctivitis is an increasingly prevalent allergic reaction having clinical gravity similar to asthma and allergic rhinitis. Currently around, 40% of global population is suffering from allergic conjunctivitis (Azari and Barney, 2013)[1]. Exposure to particulate matter less than 2.5 µm can lead to allergic reactions. Studies have reflected impact of high PM2.5 levels on increasing prevalence of allergic conjunctivitis among countries like Japan (Mimura et al, 2014)[2]. Among the case countries, 40% of the population in Japan is suffering from conjunctivitis and the prevalence is increasing rapidly

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(Rosario andBielory, 2011)[3]. This is due to change in lifestyle and environmental factors. Further, in case of Africa, the prevalence was found to be 32% and was found most prevalent among children aged between 1-16 years (38.4%) (Malu, 2014)[4]. On the other hand in USA and Australia it was found to be 20%. Similarly in case of UK it was found to be 17.5% (Perkin, Bader, Rudnicka, Strachan, and Owen, 2015)[5]. In comparison the prevalence in India is on higher side with 25.5% population affected by this allergy (Puri, Ashat, Singh Sarpal, Kaur, and Kumar, 2013). High level of allergy in India is because of high pollution levels in the country. Critical review of the situation reflects that the prevalence is common among children studying in government schools due to poor hygiene. Further, in India, consequence of allergic conjunctivitis is blindness (prevalent among 1.84%) and corneal blindness (prevalent among 8.6%) (Dandona and Dandona, 2001, adii, C. (2016))6,7. So with such a significant health problem of allergic conjunctivitis in India, we have studied whether bepotastinebesilate 1.5% eye drop or olopatadine hydrochloride 0.2% eye drop in cases of allergic conjunctivitis is superior in the management of Allergic conjunctivitis as perceived by the patients

METHODOLOGY

forty consecutive patients presenting from March 2018 to July 2018 in Eye OPD at Saraswathi institute of medical sciences Hapur, with symptoms of ocular itching associated with allergic conjunctivitis were enrolled in this study. Patients with age more than 18 years, had a diagnosis of allergic conjunctivitis with no concurrent unrelated ocular diseases, had no plans to undergo ocular surgery during the study period were included into the study while patients who had a known hypersensitivity to either agent, history of alcohol or drug abuse, positive history of an ocular herpetic infection, an active ocular infection, or any significant illness , Patients who were actively taking steroids or antihistamines within 7 days prior to enrollment, pregnant, planning to become pregnant, or nursing/lactating were excluded. The enrolled patients were assigned sequentially according to a computer-generated randomization list to receive bepotastinebesilate 1.5% or olopatadine hydrochloride 0.2% in a 1:1 ratio. Patients instilled either bepotastinebesilate 1.5% twice daily (at approximately 8 am and 5 pm) or olopatadine hydrochloride 0.2% once daily (at approximately 8 am) for 16 days. Following a 7-day washout period during which only preservative-free artificial tears were used twice daily, patients were crossed-over to the other treatment for 16days. Each treatment was provided in the packaging originally approved by the Food and Drug Administration, but the single investigator was masked as to which treatment the patient was currently using. Patients were instructed to use gentle eye lid closure for at least two minutes after dosing and to repeat instillation of a single drop if there was uncertainty as to whether successful instillation of the treatment had occurred In addition, patients wearing contact lenses were encouraged to use glasses during the study period. Patients completed an office questionnaire at visit 1 (baseline, day 0), visit 2 (day 16), and visit 3 (day39). During visit 1, prior to dispensing the treatment, patients were asked to rate the following items on a five-point scale: ocular itching associated with allergies; and satisfaction with over-the-counter allergy medication. During visit 2, a different survey questionnaire was administered. Prior to dispensing the second medication, the patients were asked to rate the following items on a five-point scale: ocular itching prior to dosing in the morning; how well the eye drop relieved ocular itching during the day,and the comfort of the drop. The patients were assessed for adverse events. Following the questionnaire, the patients received preservative-free artificial tear drops and were instructed to use the drops twice daily for one week prior to starting the second treatment. On day 23, patients were informed to discontinue using the artificial tear drops and to start using the new treatment for 16days. During visits 2 and 3, the patients were assessed for adverse events. In addition, a final summary questionnaire was given at visit 3. The patients were asked to choose which eye drop provided better all-day relief of ocular itching and was more comfortable. Lastly, the patients were asked to choose which medication they would like to have as a prescription to continue treating their allergic conjunctivitis. During the study period the treatment relieved their ocular itch (graded on a 1–5 scale, with 5 being completely relieved) and how well the treatment relieved all of their ocular allergy symptoms (graded on a 1–5 scale, with 5 being completely relieved). Ocular allergy symptoms included ocular itch, epiphora, conjunctival chemosis, hyperemia, and eye lid edema. Here Group A (1^{st} drug B and 2^{nd} drug O) (n=20), Group B(1^{st} drug O and 2^{nd} drug B) (n=20), where B→Bepotastinebesilate 1.5% eye drop, O→ Olopatadine hydrochloride 0.2% eye drop . 1^{st}visit done (0 day) of starting the drug, 2^{nd} visit (day 16) after use of first medication, 3^{rd} Visit (day 39)after use of second medication. The itching symptoms and all Ocular allergy symptoms was graded on 5 point scale. The statistical analysis done by unpaired t-test and calculated by SPSS 19 version software.

RESULT

Table 1: Distribution of the patients as per the age

Age	No.	Percentage (%)
20-30	5	12.5
30-40	7	17.5
40-50	24	60
50-60	4	10
Total	40	100
Mean ±SD	41.68 ± 8.51	

The majority of the patient were in the age group of 40-50 i.e. 60% followed by 30-40-17.5%,20-30 were12.5%, 50-60 were 10%. The mean age was (Mean ±SD) 41.68 ± 8.5

Table 2: Distribution of the patients as per the sex

Sex	No.	Percentage (%)
Male	14	35
Female	26	65
Total	40	100

The majority of the patients were females 65% and males were 35%.

Table 3: Distribution of the patients with respect to symptoms itching on subsequent visits

Ocular itching grading on 5 point scale	Group A (1st drug B and 2nd drug O) (n=20)	Group B(1st drug O and 2nd drug B) (n=20)	p-value
1st visit	4.2 ± 0.52	4.35 ± 0.49	t=0.94 df=38 p>0.05
2nd visit (day 16)after use of first medication	3.9± 0.79	2.85 ± 0.67	t=4.9 df=38 P<0.0001
3rd Visit (day 39)after use of second medication	2.65 ±0.81	3.7±0.47	t=5.0 df=38 P<0.0001

At first visit the symptoms of itching were comparable with each other as Ocular itching grading on 5 point scale was 4.2 ± 0.52 and 4.35 ± 0.49 in group A and B respectively (t=0.94 df=38,p>0.05) ; on2nd visit (day 16)after use of first medication the relief score in ocular itching was significantly higher in Group Ai. e. 3.9± 0.79 versus 2.85 ± 0.67 in group B (t=4.9 df=38, P<0.0001), 3rd Visit (day 39) after use of second medication the relief score in ocular itching was significantly higher in Group B i.e. 3.7±0.47 as compared to 2.65 ±0.81 in group A (t=5.0 df=38, P<0.0001)

Table 4: Distribution of the patients with respect to all ocular allergy symptoms on subsequent visits

All Ocular allergy symptoms (grading on 5 point scale)	Group A (1st drug B and 2nd drug O) (n=20)	Group B(1st drug O and 2nd drug B) (n=20)	p-value
2nd visit (day 16)after use of first medication	3.55± 0.69	2.65± 0.75	t=5.23 , df=38 P<0.0001
3rd Visit (day 39)after use of second medication	2.3±0.73	3.2±0.70	t=4.92 , df=38 p<0.0001

At 2nd visit (day 16) after use of first medication the relief score in all ocular allergy symptoms was significantly higher in Group A i.e. 3.55± 0.69 vs 2.65± 0.75in group B (t=5.23, df=38, p<0.0001), at 3rd Visit (day 39)after use of second medication the relief score in all ocular allergy symptoms was significantly higher in Group B i.e. 3.2±0.70 as compared to 2.3±0.73 in group A (t=4.92 , df=38, p<0.0001).

DISCUSSION

Bepotastine is an H_1-antihistamine and an inhibitor of histamine release from mast cells.[9] It is a piperidine derivative, similar to fexofenadine, ebastine, and loratidine.[10] Multiple anti-inflammatory effects have been demonstrated, possibly as downstream mediators of the antihistamine activity. For example, in vitro studies suggest that bepotastine specifically suppresses proinflammatory cytokine production by keratinocytes, including inhibition of CD54 expression.[11] Recent work on guinea pigs showed that bepotastine, along with several other H_1-antihistamines, reduces vascular hyper-permeability in both antigen-induced and histamine-induced hyperpermeability models.[12] This work also showed that bepotastine inhibits in vitro eosinophil chemotaxis induced by leukotriene B_4, and pretreatment with bepotastine limits conjunctival eosinophil infiltration after topical platelet-activating factor instillation.[12] The pharmacokinetic properties of bepotastine as an ophthalmic solution are described in Phase I trial data from Japan, and these will be described as reported in the FDA Office of Clinical Pharmacology review of the Japanese data.[8] First, a repeated instillation study was performed, testing four-times-a day dosing in both eyes

for 7 days in 12 healthy adult male subjects, half of whom instilled bepotastinebesilate 1.0% and half instilled the 1.5% formulation. Venous blood samples were measured by high-performance liquid chromatography and demonstrated a bepotastine plasma concentration peak 1–2 hours postinstillation. The mean maximum concentration (Cmax) for the 1.5% group was 7.3 ±1.9 ng/mL, which was much lower than the Cmax seen in the Phase I single oral dose trial, even at the lowest tested oral dose (Cmax was 22.4 ± 2.1 ng/mL for the 2.5 mg oral dose). At the clinically relevant, approved Japanese oral dose of 10 mg, the Cmax was 101.3 ± 3.5 ng/mL, which is over 13 times higher than the Cmax seen in the repeated ophthalmic dosing trial. Thus, although there is systemic absorption of the ophthalmic drop, the plasma concentrations are quite low, minimizing the likelihood of systemic adverse effects. Furthermore, plasma concentrations at 24 hours postinstallation were below the quantifiable limit of 2 ng/mL in 11 of 12 subjects. In the oral single-dose study, 75%–90% of the administered dose was secreted in the urine as unchanged drug by 24 hours after administration within the 2.5–40 mg dose range. An additional Phase I study addressed the metabolism of bepotastine by liver microsomes, showing that there was minimal metabolism by CYP3A4, CYP2C9, and CYP2C19, again as reported by the FDA Office of Clinical Pharmacology review of the Japanese data9. Within the relevant concentration range, it was concluded that bepotastine would likely have no effects on concomitantly metabolized drugs involving these enzymes. Finally, a protein-binding Phase I study was performed, demonstrating 55.4% mean plasma protein binding of the drug 1–2 hours after a 10 mg oral dose.[8] This binding level was independent of plasma drug concentration. In our study we have found the majority of the patient were in the age group of 40-50 i.e. 60% followed by 30-40-17.5%, 20-30 were 12.5%, 50-60 were 10%. The mean age was (Mean ±SD) 41.68 ± 8.51. The majority of the patients were females 65% and males were 35%. At first visit the symptoms of itching were comparable with each other as Ocular itching grading on 5 point scale was 4.2 ± 0.52 and 4.35 ± 0.49 in group A and B respectively (t=0.94 df=38,p>0.05) ; on2nd visit (day 16)after use of first medication the relief score in ocular itching was significantly higher in Group A i.e. 3.9± 0.79 versus 2.85 ± 0.67in group B (t=4.9 df=38,P<0.0001), 3rd Visit (day 39)after use of second medication the relief score in ocular itching was significantly higher in Group B i.e. 3.7±0.47 as compared to 2.65 ±0.81 in group A (t=5.0 df=38, P<0.0001). At 2nd visit (day 16)after use of first medication the relief score in all ocular allergy symptoms was significantly higher in Group A i.e. 3.55± 0.69 as compared to 2.65± 0.75 in group B (t=5.23 , df=38,p<0.0001) , at 3rd Visit (day 39)after use of second medication the relief score in all ocular allergy symptoms was significantly higher in Group B i.e. 3.2±0.70 as compared to 2.3±0.73 in group A (t=4.92, df=38,p<0.0001). Craig F McCabe[13] found at study end, 63.3% and 66.7% of patients preferred bepotastinebesilate 1.5% for all-day relief of ocular itching and all-day relief of itchy/runny nose, respectively. At study end, there was no significant difference in the number of patients preferring one treatment over the other for comfort. Overall, 66.7% of patients stated that they would prefer to treat their allergic conjunctivitis with bepotastinebesilate 1.5% over olopatadine hydrochloride 0.2%. Conclusion: Based on their evaluation of therapeutic performance, patients preferred bepotastinebesilate 1.5% over olopatadine hydrochloride 0.2% by two-to-one for the treatment of allergic conjunctivitis.

CONCLUSION

at the baseline both the drugs were comparable with each other , at second visit the score was variable but at the end the response with respect to score and patients preference ,the bepotastinebesilate 1.5% was found superior to olopatadine hydrochloride 0.2% with respect to treatment of allergic conjunctivitis.

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