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Randomized Controlled Study Comparing the Efficacy and Tolerance of Bepotastine, a New 2nd Generation Antihistamine, to Fexofenadine, in Symptomatic Relief of Patients with Pruritic Cutaneous Disorders

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Abstract

Bepotastine besilate is a selective histamine H1-receptor antagonist and a second-generation non-sedating antihistamine approved for relief from pruritis in various dermatological disorders.

Aim: To study the efficacy and tolerance of Bepotastine in providing symptom relief in patients with cutaneous disorders associated with pruritus and other symptoms, in comparison to Fexofenadine.

Methodology: Adult patients presenting clinically with cutaneous conditions associated with pruritis like eczemas, psoriasis, urticaria and fungal infections were randomized to receive either Bepotastine 10 mg twice daily or Fexofenadine 120 mg once daily. Patients were evaluated every week for a maximum period of four weeks. Primary end points were weekly change in patients' pruritis, wheal (where applicable) and overall VAS symptom scores. Secondary end points included number of patients attaining complete relief from symptoms at each visit, Global Investigator's rating at end of study and adverse effects seen

Results: Significant decrease in patients' pruritis and overall VAS symptom score was seen from the first week itself in both groups, with no significant difference between the two groups at any visit. Wheal score in urticaria patients also showed reduction in both groups with no significant difference between the groups. The number of patients achieving complete relief was seen to be significantly more in the Bepotastine group at week 3 (P=0.01). The global investigator rating at end of study was significantly better for Bepotastine than Fexofenadine (P=0.0045). Treatment was well tolerated in both groups and no adverse events were spontaneously reported in both groups.

Conclusion: Bepotastine 20 mg/day is as effective and well tolerated as compared to Fexofenadine 120 mg/day in patients presenting with cutaneous disorders associated with pruritis and other symptoms.

Keywords: Bepotastine; Fexofenadine; Pruritis; Urticaria; Antihistamine; Eczema

Introduction

Pruritis is a common symptom, of many skin conditions like chronic urticaria, eczema, atopic dermatitis, psoriasis, as well as skin infections which can greatly impair the patient's day to day functioning [1]. Itching maybe associated with redness (erythema), and in case of urticaria, also wheals and sometimes angioedema [2,3]. Bepotastine besilate is a new selective histamine H1-receptor antagonist and a second-generation minimally-sedating antihistamine. It has been extensively studied to also have additional actions like mast cell stabilization, inhibition of eosinophilic infiltration, Inhibition of leukotriene B4, IL-5, PAF and Substance P all of which may contribute to its anti-pruritic effects [4,5]. Bepotastine 10 mg tablet was approved in Japan for use in the treatment of allergic rhinitis and uriticaria/ pruritus in the year 2000 and 2002, respectively and in India in 2017, for the treatment of allergic rhinitis and itching associated with cutaneous disorders in adult patients.

This is the first randomized clinical study which compares the symptomatic relief obtained (using standardized scoring and VAS), by Bepotastine *vs.* Fexofenadine, which is another minimally sedative, second generation antihistamine approved and established for treatment of Urticaria.

Methodology

60 adult patients presenting clinically in the Dermatologist's out-patient department, with cutaneous disorders associated mainly with pruritus along with other symptoms like wheal, and redness were randomized to receive Bepotastine 10 mg twice daily or Fexofenadine 120 mg once daily. No other oral concomitant medication was permitted under study protocol, however patients could apply topical antifungal or moisturizer as appropriately prescribed. The patients were followed up weekly for total treatment duration of 4 weeks.

Primary end points evaluated were the change in score from baseline at every week for pruritis, wheal (applicable in urticaria patients) and overall VAS symptom score. Pruritis and wheal scores were evaluated in accordance with the Urticaria Activity Score (UAS) on a 4-point defined rating scale [6]. The VAS score was a standardized 10-point scale progressing from complete relief (0) to increasing symptom severity. Secondary end points were total number of patients achieving complete relief from symptoms at every visit (0 for all scores), improvement in quality of life at 4 weeks (assessed by the standardized Dermatology Life Quality Index-DLQI questionnaire consisting of 10 questions scored from 0-3 with higher scores indicating higher Quality of Life impairment), investigator's global rating at end of treatment on a 4-point scale of Excellent, Good, Satisfactory and Poor, and the development of adverse events [7]. The study was initiated post institutional ethics committee approval and all data was obtained in accordance with ethical principles and with patient consent.

Results

In each of the study groups comprising of 30 patients, the baseline diagnostic distribution of cutaneous disorders is given in Figure 1. The duration of symptoms was similar in both groups (P=0.975). Both groups showed significant improvements (decrease) in pruritis scores as well as overall VAS symptom score as compared to baseline starting from end of the first week visit (Figures 2 and 3). There was no significant difference between the improvement in the pruritis and overall VAS symptom scores between the Bepotastine and the Fexofenadine patient groups. There was also improvement (decrease) in wheal scores in urticaria patients however due to small sample size, significance could not be estimated, and however no difference was observed between the groups. The average pruritus and VAS score reduced to '0' in Bepotastine group by the 3rd week itself, compared to Fexofenadine.

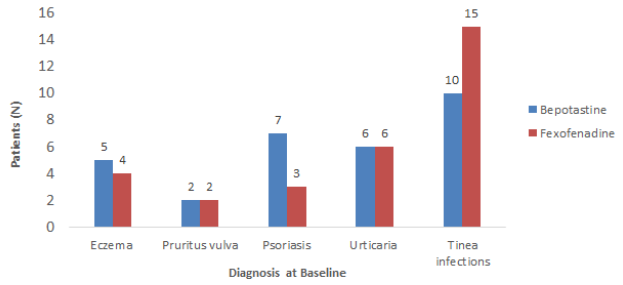

Figure 1: Diagnostic distribution of patients.

The number of patients who achieved complete relief in the two groups was not significantly different at the first and second week but was significantly better for Bepotastine at the third week as compared to Fexofenadine (30 *vs.* 22 patients: P=0.01). The mean total DLQI score at baseline for Bepotastine and Fexofenadine groups was 17.67 and 18.4 respectively (P=0.53). The decrease in mean total DLQI score signifying improved Quality of Life at weeks was significant and similar in both groups (-17.67 in Bepotastine group *vs.* -17.94 in Fexofenadine group; P=0.82). The mean total DLQI scores at 4 weeks for Bepotastine and Fexofenadine was 0 and 0.46 respectively. Global investigator's rating of Excellent was for 100% patients in the Bepotastine group as compared to 73% in the Fexofenadine group at the end of study (P=0.0045). None of the study groups spontaneously reported any adverse events. On further enquiry of specific side effects, no headache or psychomotor impairment was reported at any visit. Mild drowsiness was seen transiently only in the first week in both groups with no significant difference observed between the groups (P=0.088).

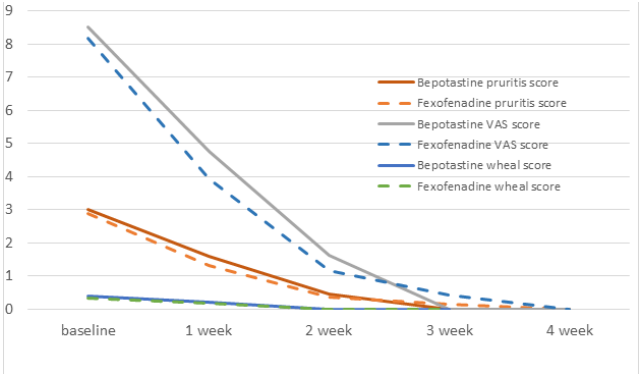

Figure 2: Change in weekly symptom scores of pruritis, wheal and overall symptom VAS score.

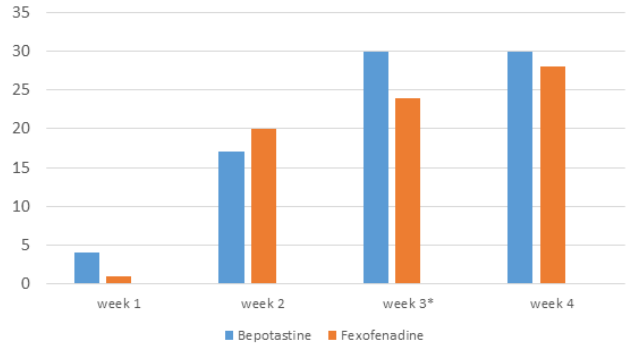

Figure 3: Number of patients achieving complete symptomatic relief.

Discussion

Oral Bepotastine is a highly selective second-generation histamine H1 receptor antagonist and has shown long-lasting, dose-dependent antihistaminic and antiallergic activity *in vitro* and *in vivo* [4,5]. Bepotastine has been seen to exhibit mast cell stabilization, decrease in PAF and Leukotriene B4 inhibition which contribute to its anti-pruritic and anti-inflammatory actions. Bepotastine suppresses production of pro-inflammatory cytokines like interleukin-5 and interleukin-1a and may suppress nitric oxide production in vascular endothelial cell, which attenuates itch induced by substance P. Bepotastine's action on inhibition of intercellular adhesion molecule-1 (ICAM-1) expression in human epidermal keratinocytes and vascular endothelial cells can contribute to reducing recruitment and infiltration of inflammatory cells. Bepotastine is rapidly absorbed after oral administration, not much affected by food, with onset of action within half hour and T max of 1.2 h [4,8]. Due to high membrane permeability and absorption of Bepotastine in the upper small

intestine, (where P-gp expression is minimal), almost complete absorption takes place here which is unaffected by intestinal P-gp, however this restricts entry of Bepotastine across the blood brain barrier [9]. It has minimal hepatic metabolism which is not CYP dependent (80% renally excreted unchanged) with an elimination half-life of 2-3. Bepotastine does not appear to accumulate in the body due to stable elimination half-life with repeated dosing studied upto 40 mg/day.

Short and long-term clinical and post marketing studies have shown 10 mg twice-daily Bepotastine to be effective and well tolerated in the treatment of allergic rhinitis, chronic urticaria or pruritus associated with skin conditions (eczema/dermatitis, prurigo or pruritus cutaneus) [2]. A 1-week phase 3 trial versus placebo with Bepotastine 20 mg/day showed higher efficacy than placebo in improving the level of itching on a 5-point itching scale and improving the level of eruption on a 4-point eruption scale, ($p<0.0001$ for both) [10]. Global improvement ratings were significantly better with Bepotastine versus placebo with no significant difference seen in adverse event rate. Bepotastine has been compared to Terfenadine in a study for treatment of chronic urticaria (final global improvement rating of moderate or greater: 77.1% *vs.* 73.0%) with comparable adverse event rate (12.4% *vs.* 16.1%) [11]. Similar number of Bepotastine and Terfenadine recipients had an improvement from baseline of two or more grades in itching (74.0% *vs.* 73.7%) or eruption (69.5% *vs.* 68.6%), based on a 5-grade scale while patient perception of treatment utility was 74.2% with Bepotastine 20 mg/day and 68.6% with Terfenadine 120 mg/day.

Though, till date to our knowledge there is no published study which compares the clinical symptomatic improvement of Bepotastine in patients with cutaneous pruritic disorders to Fexofenadine, the following comparative studies with Fexofenadine are available. The first compares Bepotastine to Fexofenadine to evaluate the attenuation of histamine induced itch at 30 min after the administration of each drug and thereafter until 6 h. Bepotastine suppressed flare formation after only 30 min following drug administration which was sooner than Fexofenadine [12]. A double-blind, placebo-controlled, crossover study to compare the inhibitory effects of Bepotastine, Cetirizine, Fexofenadine, and Olopatadine yielded significant reduction of histamine-induced wheal-and flare response compared to placebo ($P<0.01$) with the strongest suppression with Olopatadine. Among the drugs, Olopatadine, Fexofenadine, and Cetirizine showed a significant systemic sedative effect and psychomotor impairment in this order with Bepotastine showing the least sedative effect [13]. In a long-term study in Chronic urticaria, efficacy of Bepotastine efficacy was maintained up to 12 weeks with final global improvement rating of moderate or greater in 87.3% receiving Bepotastine 20 mg/day (increasing over time from 71.8% at week 2 to 90.0% at week 12) [14].

A 2-week trial to study the efficacy of Bepotastine 20 mg/day in adult patients with pruritus associated with skin disease: eczema/dermatitis, prurigo, and pruritus cutaneous, showed a final global improvement rating of moderate or greater in 64.7% (63.1%, 73.2%, and 60.0% in eczema/dermatitis, prurigo and pruritus cutaneous respectively) [15]. Patient perception of treatment utility of extremely useful or useful was in 62.2%. Severity of pruritus from moderate or severe at baseline in all patients improved to mild, slight or no symptoms in 70%-81% of patients. In a post-marketing surveillance study of the efficacy of Bepotastine in the treatment of skin conditions, rating of satisfactory or almost satisfactory was reported by 84.3% (N=549) of Chronic urticaria and 92.7% (N=1101) of patients with pruritus associated with skin disease [16]. In a real world in clinic data capture and study done by us, 3415 adult Indian patients, presenting clinically with pruritis, redness, wheal or angioedema symptoms associated with skin conditions, were evaluated to record patient's end of treatment perception of improvement in the presenting symptoms, as well as tolerance to treatment, in response to Bepotastine 10 mg twice a day [17]. Overall for each symptom, complete or significant relief was obtained by >80% patients ($P<0.001$). Average treatment duration was 21 days or less in 80% patients. Patients achieved complete relief was max between 14-21 days. The adverse event rate was low at 0.3%. In a 4 week study in patients of Atopic Dermatitis, chronic eczema, chronic urticaria and cutaneous pruritis, significant improvement was seen in VAS scores (27.3 ± 26 *vs.* 60.7 ± 20.1) and HRQoL at 4 weeks versus baseline [18].

Conclusion

The results of our study have shown that Bepotastine and Fexofenadine are comparable in efficacy and safety in relieving symptoms of pruritic cutaneous conditions. The overall sample size is small therefore this was intended as a proof of concept study across various pruritic skin conditions. Bepotastine is a new second generation minimally sedative antihistamine with multiprong action available in the clinical armamentarium to manage pruritic cutaneous conditions, and it has shown real world efficacy and safety as well as comparative efficacy and tolerance to Fexofenadine in pruritic skin conditions.

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