

Real-World Efficacy and Safety of Novel Second-Generation Antihistamine “Bepotastine” in Management of Pruritus Associated With Skin Disorders

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Abstract

Introduction: Pruritus is one of the most common symptoms of skin diseases affecting quality of life. H1 antihistamines are most commonly used drugs for pruritus management. Bepotastine, a novel second-generation antihistamine with antagonistic effect on leukotriene B4 and substance P, was recently approved in India. We conducted this observational survey to assess effectiveness and safety of bepotastine in the management of pruritus in real-world setting.

Materials and Methods: Prevalidated survey booklets were given to select dermatologists to collect information on the efficacy and safety of bepotastine. Data were collected regarding demographic details, pruritus score, medication effectiveness, and sedation potential of bepotastine. Clinical assessment was done by analyzing the change in pruritus score at day 7–14. Patient satisfaction was assessed by analyzing medication effectiveness and sedation on Likert scale.

Results: A total of 50 dermatologists completed the survey involving 500 patients. 440 completed survey questionnaire forms were included for further evaluation. There was a significant reduction in mean pruritus score from 2.93 at baseline to 1.49 ($P < 0.05$) at day 7 and 0.56 at day 14 ($P < 0.05$). On analyzing the severity of pruritus, 75% and 91% of patients with mild pruritus showed complete relief at days 7 and 14, respectively, whereas 65% and 84% of patients with moderate pruritus showed complete relief at days 7 and 14, respectively. Similarly, in patients with severe pruritus, 48% and 83% of patients showed complete relief at days 7 and 14, respectively. No improvement was seen on day 7 in patients with very severe pruritus; however, 73% of patients showed complete relief by day 14. All the patients were highly satisfied with treatment as reflected by medication effectiveness score and sedation score. 4.7% of the patients complained of mild drowsiness.

Conclusion: This real-world data indicate that bepotastine was efficacious and safe in the management of pruritus associated with skin diseases.

Key words: Bepotastine, Pruritus, Real world

INTRODUCTION

Pruritus is an unpleasant sensation associated with desire to scratch. Pruritus is most frequent symptom associated with multiple dermatological disorders.^[1] Even though not life threatening, pruritus has a significant impact on

patient's quality of life (QoL), leading to disturbance in sleep, anxiety, attention, etc. In addition, many systemic diseases are also known to be associated with pruritus and further incapacitating nature of this condition.^[1]

Histamine plays a very significant role in pathogenesis of pruritus associated with skin diseases.^[1,2] Histamine through H1 receptors acts on blood vessels and sensory nerves to produce a flare and wheal response that contributes to pruritus and modulates inflammatory conditions.^[3,4] Due to significant role of histamine, H1 antihistamines are mainstay of therapy in the management of pruritus associated with skin diseases.^[5] The use of non-sedating

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second-generation H1 antihistamines is preferred to that of older, first-generation H1 antihistamines, due to lack of adverse effects such as sedation and anticholinergic effects that are commonly seen with the older agents.^[5]

Even though antihistamines are mainstay therapy in the management of pruritus, their effectiveness is limited in many patients.^[6] Furthermore, not every patient with pruritus shows characteristic histaminic response of wheal and flare.^[6,7] This points toward the important role of mediators other than histamine in pathogenesis of pruritus. Multiple studies have shown that, in addition to histamine, mediators such as leukotriene B4, platelet-activating factor (PAF), and substance P also play an important role in pathogenesis of pruritus.^[8-14]

Due to these reasons, antihistamine that also suppresses the other mediators may be of benefit in the management of pruritus;^[15] hence, there was a need of novel antihistamine. Bepotastine besilate is one of such novel second-generation, non-sedating antihistamine.^[15,16] Along with selective action on H1-receptor, bepotastine also has multiple additional actions such as mast cell stabilization, inhibition of eosinophilic infiltration, inhibition of leukotriene B4, IL-5, PAF, and substance P, all of which may contribute to its antipruritic effects.^[15-21]

Even though bepotastine was approved in Japan, in 2002, for the management of pruritus and urticaria, it was recently approved in India, in 2017; hence, there is a need of data of the effectiveness and safety of bepotastine in Indian patients in real-world setting. We conducted this retrospective survey to evaluate the effectiveness and safety of bepotastine in the management of pruritus associated with skin disorders in real-world setting.

MATERIALS AND METHODS

This was a multicenter, open-label, observational, retrospective questionnaire-based survey designed primarily to assess the efficacy and safety of bepotastine in the management of pruritus associated with skin diseases. The survey was conducted in compliance with the Declaration of Helsinki and current good clinical practice guidelines.

Dermatologists involved in the management of pruritus were identified through “SCRIP intelligence” database. Among these, 50 doctors who were maintaining the patients’ clinical record were selected across four zones (east, south, west, and north) each by convenient sampling to have uniform representation of population across country.

Each dermatologist was given prevalidated survey questionnaire booklet containing survey forms to evaluate the effectiveness and safety of bepotastine. The questionnaire’s booklets were collected after the end of survey period and data from all the patients were assessed to evaluate the medication effectiveness and sedation potential of bepotastine. Each patient was given bepotastine 10 mg twice daily and evaluated at baseline (day 0), day 7, and day 14. The total survey period was from July 2017 to September 2017.

Patients >18 years of age with presenting with pruritus, redness, or wheals due to any dermatological condition and keeping regular follow-up with dermatologists were included in the survey. Patients with severe dermatological conditions and patients who changed their therapy or who underwent any dermatological procedures during survey period were excluded from final analysis.

Effectiveness Evaluation

Effectiveness assessment was done by analyzing the responses from both patients (patients’ satisfaction) and investigator at baseline, day 7, and day 14. Investigator assessment was done by analyzing pruritus activity score on 5-point pruritus activity scale ranging from complete absence of pruritus to very severe pruritus. Similarly, patients’ satisfaction with the treatment was assessed by analyzing medication effectiveness score and sedation score. Effectiveness of bepotastine in reducing patients’ pruritus was analyzed on 5-point Likert scale ranging from complete improvement in symptoms to no improvement at all. Sedation profile of the drug was evaluated by the assessment of the degree of sleepiness on visual analog scale (VAS) ranging from no sleepiness (0) to extreme sleepiness (10).

Safety Evaluation

Safety assessment was done by analyzing all the reported adverse events during the survey period.

RESULTS

A total of 500 survey forms were collected from 50 dermatologists at the end of 3 months. Of 500, 60 forms were incomplete and, hence, were not considered for further evaluation. Data from 440 patients were considered for final assessment. The average age of the patients was 36.6 years, of total 440 patients evaluated, 62.95% ($n = 277$) were female while 37.05% ($n = 163$) were male patients. In this survey, 27 (6%) patients were having mild pruritus, 114 (26%) patients were having moderate pruritus, 167 (38%) patients were suffering severe pruritus, and remaining 132 (30%) patients were complaining of very severe degree of pruritus.

After treatment with bepotastine 10 mg twice daily, there was a significant reduction in mean pruritus score from 2.93 at baseline to 1.49 ($P < 0.05$) at day 7 and 0.56 at day 14 ($P < 0.05$) [Figure 1].

On further analyzing the data with respect to severity of pruritus, similar results were observed. In patients with mild pruritus, 75% ($n = 20$) and 91% ($n = 25$) of patients showed complete relief at days 7 and 14, respectively. In patients with moderate pruritus, 65% ($n = 74$) achieved complete relief on day 7 while 84% ($n = 96$) of patients achieved complete relief from pruritus on day 14. Similarly, in patients with severe pruritus, 48% ($n = 80$) and 83% ($n = 139$) of patients showed complete relief at days 7 and 14, respectively. In patients complaining of very severe pruritus, no improvement in symptoms was seen on day 7; however, 73% ($n = 96$) of patients showed complete relief by day 14 [Figure 2].

Patients were highly satisfied with the treatment as reflected by their medication effectiveness score and sedation profile. On day 7, 31% ($n = 136$) of patients showed complete or significant improvement in their pruritus symptoms. Duration of treatment was seen to have an effect on symptomatic relief obtained, with 82% ($n = 361$) of patients showing complete or significant improvement in their pruritus on day 14. In this survey, mild sedation on sedation scale was reported by 4.7% ($n = 21$) of patients due to bepotastine. Gastrointestinal upset or nausea was seen in 15 patients while two patients complained of headache. All

adverse events were mild, resolved spontaneously and did not require bepotastine discontinuation or any additional treatment.

DISCUSSION

Pruritus is one of the most common symptoms associated with various dermatological disorders with significant impact on patient's QoL that causes various problems related to sleep, anxiety, attention, etc.^[1] Histamine plays a very significant role in pathogenesis of pruritus associated with skin diseases.^[1,2] Hence, antihistamines, especially the second-generation antihistamines due to their better safety profile, are mainstay of therapy in the management of pruritus.^[5]

Even though antihistamines are mainstay therapy in the management of pruritus, their effectiveness is limited in many patients. Multiple studies have shown that in addition to histamine mediators such as leukotriene B4, PAF, and substance P also play an important role in pathogenesis of pruritus. This further limits the effectiveness of antihistamines. Hence, there was a need of novel antihistamine which along with histamines also has additional effect on other mediators responsible for pruritus.^[6-14]

Oral bepotastine is a highly selective second-generation histamine H1 receptor antagonist. In multiple *in vitro* and *in vivo* studies, it has shown long-lasting, dose-dependent antihistaminic and antiallergic activity.^[15] Along with antihistaminic activity, bepotastine has been associated with mast cell stabilization, leukotriene B4 inhibition, and suppression of nitric oxide production induced by substance P which may contribute to its antipruritic and anti-inflammatory actions.^[15-17] In addition, bepotastine is also associated with decrease in levels of PAF and antigen-induced eosinophilic infiltration as well as suppression of various pro-inflammatory cytokines such as interleukin-5 and interleukin-1a which may further contribute to its antipruritic activity.^[18-21]

Kawashima *et al.* in their Phase 3 trial with bepotastine 20 mg/day showed significant improvement in itching and cutaneous eruption on day 7 compared to placebo. No significant difference in adverse event rate between bepotastine and placebo was reported by the authors.^[22]

Ishibashi *et al.* in their Phase 3 study reported that bepotastine was as effective as terfenadine in the management of patients with chronic urticaria. 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%).^[23]

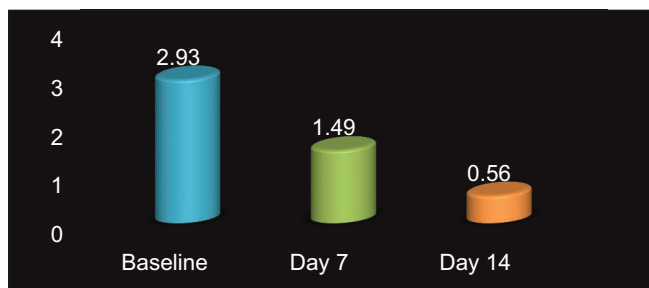


Figure 1: Change in mean pruritus score with bepotastine 10 mg twice daily

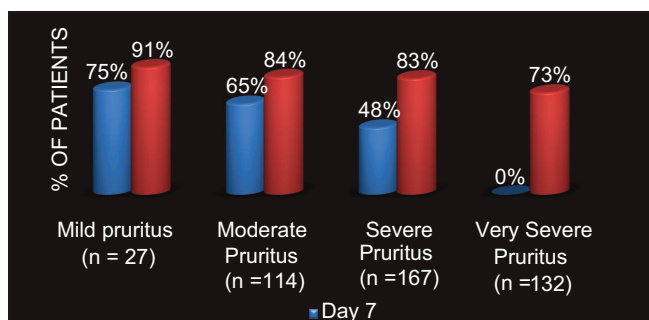


Figure 2: Percentage of patients with complete relief from pruritus according to the intensity of pruritus

Narayan *et al.* in their study on 3415 patients reported significant improvement in symptoms of pruritus, erythema, or wheals in >80% of patients with bepotastine 20 mg/day.^[24]

In post-marketing surveillance study, Kawashima *et al.* reported satisfactory or almost satisfactory rating in 84.3% ($n = 549$) of patients with chronic urticaria and 92.7% ($n = 1101$) of patients with pruritus associated with skin diseases.^[25]

In a 2-week trial in patients with pruritus associated with skin diseases, Ishibashi *et al.* reported global improvement rating of moderate or greater in 64.7% of patients. In the same study, 62.2% of patients reported treatment utility of extremely useful or useful. 70–80% of patients reported significant improvement in intensity of pruritus from moderate or severe at baseline to mild, slight, or no symptoms.^[26]

Horikawa *et al.* and Takahashi and Iizuka in two separate studies reported significant reduction in VAS score for pruritus and scratch mark after 2 weeks in patients of senile pruritus or pruritic skin conditions.^[27,28]

The results of the current survey are in accordance with published studies as described above,^[22-28] establishing real-world efficacy and safety of bepotastine in the management of pruritus associated with skin disorders. In our survey, there was significant improvement in mean pruritus score compared to baseline on day 7 as well as day 14. Similarly, more than 80% of patients showing complete or significant improvement in their symptoms profile. Sedation of mild degree was seen in only 4.7% of patients in our survey which is in accordance with published literature.^[22-28] Overall, adverse event rate has been very low showing good real-world tolerance for bepotastine.

This survey has certain limitations. Due to the observational and retrospective design of the survey, the possibility of selection bias cannot be ruled out. Coprescribed drugs were not taken into consideration which may have impacted the final outcome. Long-term, comparative, control studies to address the shortcomings of the present study are warranted.

CONCLUSION

Bepotastine is a new non-sedative and effective treatment option for patients having cutaneous conditions with pruritus and other symptoms such as erythema, wheal, and angioedema. Adverse event rates are low and if present, are mild, without usually needing treatment discontinuation. This real-world data indicate that bepotastine was

efficacious and safe in the management of pruritus associated with skin diseases.

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REFERENCES

1. Rajagopalan M, Saraswat A, Godse K, Shankar DS, Kandhari S, Shenoi SD, *et al.* Diagnosis and management of chronic pruritus: An expert consensus review. *Indian J Dermatol* 2017;62:7-17.
2. Zuberbier T, Iffländer J, Semmler C, Henz BM. Acute urticaria: Clinical aspects and therapeutic responsiveness. *Acta Derm Venereol* 1996;76:295-7.
3. Tanizaki H, Ikoma A, Fukuoka M, Miyachi Y, Kabashima K. Effects of bepotastine and fexofenadine on histamine-induced flare, wheal and itch. *Int Arch Allergy Immunol* 2012;158:191-5.
4. Bielory L, Duttachoudhury S, McMunn A. Bepotastine besilate for the treatment of pruritus. *Expert Opin Pharmacother* 2013;14:2553-69.
5. Zuberbier T, Aberer W, Asero R, Abdul Latiff AH, Baker D, Ballmer-Weber B, *et al.* The EAACI/GA²LEN/EDF/WAO guideline for the definition, classification, diagnosis and management of urticaria. *Allergy* 2018;73:1393-414.
6. Garibyan L, Rheingold CG, Lerner EA. Understanding the pathophysiology of itch. *Dermatol Ther* 2013;26:84-91.
7. Klein PA, Clark RA. An evidence-based review of the efficacy of antihistamines in relieving pruritus in atopic dermatitis. *Arch Dermatol* 1999;135:1522-5.
8. Andoh T, Saito A, Kuraishi Y. Leukotriene B(4) mediates sphingosylphosphorylcholine-induced itch-associated responses in mouse skin. *J Invest Dermatol* 2009;129:2854-60.
9. Camp RD, Coutts AA, Greaves MW, Kay AB, Walport MJ. Responses of human skin to intradermal injection of leukotrienes C4, D4 and B4. *Br J Pharmacol* 1983;80:497-502.
10. Amaty B, Nordlind K, Wahlgren CF. Responses to intradermal injections of substance P in psoriasis patients with pruritus. *Skin Pharmacol Physiol* 2010;23:133-8.
11. Weidner C, Klede M, Rukwied R, Lischetzki G, Neisius U, Skov PS, *et al.* Acute effects of substance P and calcitonin gene-related peptide in human skin – a microdialysis study. *J Invest Dermatol* 2000;115:1015-20.
12. Andoh T, Kuraishi Y. Lipid mediators and itch. In: Carstens E, Akiyama T, editors. *Itch: Mechanisms and Treatment*. Ch. 15. Boca Raton (FL): CRC Press/Taylor & Francis; 2014. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK200912/>. [Last assessed on 2019 Jan 2].
13. Abeck D, Andersson T, Grosshans E, Jablonska S, Kragballe K, Vahlquist A, *et al.* Topical application of a platelet-activating factor (PAF) antagonist in atopic dermatitis. *Acta Derm Venereol* 1997;77:449-51.
14. Fjellner B, Hägermark O. Pruritus in polycythemia vera: Treatment with aspirin and possibility of platelet involvement. *Acta Derm Venereol* 1979;59:505-12.
15. Lyseng-Williamson KA. Oral bepotastine: In allergic disorders. *Drugs* 2010;70:1579-91.
16. Godse K, Kumari N. Bepotastine besilate: A novel anti-histamine. *Indian J Drugs Dermatol* 2017;3:64-8.
17. Andoh T, Kuraishi Y. Suppression by bepotastine besilate of substance P-induced itch-associated responses through the inhibition of the leukotriene B4 action in mice. *Eur J Pharmacol* 2006;547:59-64.
18. Ueno M, Inagaki N, Nagai H, Koda A. Antiallergic action of betotastine besilate (TAU-284) in animal models: A comparison with ketotifen. *Pharmacology* 1998;57:206-14.
19. Sakai A, Kikuchi M, Yato N, Kikkawa S, Saito N, Narita H, *et al.* Inhibitory effect of betotastine besilate on antigen-induced airway eosinophil infiltration and peripheral blood eosinophilia in mice. *Arzneimittelforschung* 1997;47:954-8.

20. Kaminuma O, Ogawa K, Kikkawa H, Kikuchi M, Naito K, Ikezawa K, *et al.* A novel anti-allergic drug, betotastine besilate, suppresses interleukin-5 production by human peripheral blood mononuclear cells. *Biol Pharm Bull* 1998;21:411-3.
21. Kobayashi M, Kabashima K, Nakamura M, Tokura Y. Downmodulatory effects of the antihistaminic drug bepotastine on cytokine/chemokine production and CD54 expression in human keratinocytes. *Skin Pharmacol Physiol* 2009;22:45-8.
22. Kawashima M, Harada S, Nakashima M. Phase III study of TAU-284 (bepotastine besilate) on chronic urticaria: A multicenter double-blind comparative study with placebo. *Rinsho Iyaku* 2002;18:501-19.
23. Ishibashi Y, Harada S, Niimura M. A multicenter double-blind comparative study; clinical evaluation of TAU-284 (betotastine besilate) on chronic urticaria using terfenadine as a control drug. *Rinsho Iyaku* 1997;13:1287-306.
24. Narayanan V, Bhargava A, Mane A. Real world Efficacy and Tolerance of bepotastine, a new 2nd generation antihistamine, in pruritis and other symptoms associated with cutaneous disorders (BEREAL study). *J Med Pract Rev* 2018;2:101-5.
25. Kawashima M. Post-marketing surveillance of Talion tablets (bepotastine besilate) in patients with urticaria and pruritus associated with skin disease (eczema/dermatitis, prurigo, and cutaneous pruritus). *J New Rem Clin* 2007;56:93-107.
26. Ishibashi Y, Harada S, Niimura M. Clinical evaluation of TAU-284 (betotastine besilate) on eczema/dermatitis, prurigo, and pruritus cutaneous. *Rinsho Iyaku* 1997;13:1383-400.
27. Horikawa T, Ueda M, Nishigori C. Efficacy of bepotastine besilate in the management of senile pruritic diseases. *Skin Res* 2005;4:475-80.
28. Takahashi H, Iizuka H. Usefulness and safety of bepotastine besilate for pruritic skin disorders. *Nishinohon J Dermatol* 2006;68:284-7.

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