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Original Article

Evaluation of Effectiveness and Safety of Oral Bepotastine in the Management of Chronic Urticaria

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Abstract

Introduction: Nearly 20% of the total population suffer from urticaria for a minimum of one episode during the entire lifetime. Second-generation antihistamines are preferred in majority cases of urticaria.

Objective: The present survey was undertaken in pursuit of analyzing the effectiveness and safety of bepotastine in the treatment of chronic urticaria (CU).

Materials and Methods: This was a retrospective questionnaire-based survey. Doctors were identified from four directional zones of the country, and each was given prevalidated questionnaire booklets. Clinical response was evaluated by urticaria activity score (UAS) at baseline (D0), day 14 (D14), and day 28 (D28). All the adverse effects were monitored for severity. Specifically, sedation was closely monitored for its occurrence and severity.

Results: A total of 50 doctors completed the survey involving 226 patients. The mean UAS score at D0/baseline was 3.47 which reduced to 1.71 at D14 and 0.73 at D28. 78 patients were having UAS score in the range of 1–2, 89 patients in 3–4, and 59 patients in the range of 5–6 at D0. 59 patients were encountered in Grade 5–6 at D0, which reduced to 45 patients at D14 and 29 patients at D28, while 89 patients in score range 3–4 at D0 reduced to 68 at D14 and 38 at D28. Sedation was reported in only 15 patients (6.6%) that too majority had mild sedation, rated in sedation scale range of 0–5.

Conclusion: The present survey indicates that bepotastine is efficacious and safe in the management of CU.

Key words: Bepotastine, Chronic Urticaria, Retrospective survey, Urticaria activity score

INTRODUCTION

Nearly one-fifth of the total population suffer from urticaria for a minimum of one episode during the entire lifetime. The highest number of sufferers of urticaria are encountered in young adult age group.[1] Clinically, urticaria manifests in the form of wheals/hives and angioedema. There are three emblematic features of wheals in the form of reflex redness surrounding the area of swelling, connotation with itching, and evanescent in nature.[2] Depending on the periodicity of lesions, urticaria can be acute or chronic. If urticaria is <6 weeks, it is labelled as acute urticaria, while >6 weeks it is known as chronic urticaria (CU). Prevalence of CU shows sex variations with predilection toward female sex and male: female ratio of prevalence of 1:2.

Despite exhaustive laboratory investigations, half of the cases of CU remain idiopathic; although a host of factors have been identified to trigger the development of CU, like certain foods and food additives, drugs, etc. The pathogenesis of CU is mainly driven by mast cells. The activated mast cells release histamine and other inflammatory cytokines which lead to chemotaxis, vasodilation, and exudation of plasma into surrounding tissues.[3]

CU is known to impair the quality of life (QOL) significantly. This impairment is akin to that found in other chronic skin diseases such as psoriasis and atopic

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dermatitis.[4] QOL is endorsed by the European Academy of Allergy and Clinical Immunology guidelines on the management of CU, as a target for management.[5-7]

Conventionally, management of CU is done by non-pharmacological and pharmacological options. Non-pharmacological options include removal of aberrant factors such as stress, heat, alcohol, and drugs including angiotensin-converting enzyme inhibitors. Pharmacological treatment is mainly comprised of antihistamines. Since antihistamines inhibit the release of critical inflammatory cytokines and histamine, it is usually advocated that antihistamines be prescribed on daily basis instead of need-based approach. This will also help to curb the misapprehension of therapeutic effectiveness failure. Second-generation antihistamines are preferred in majority cases of CU, while first-generation antihistamines are preferred in cases of nocturnal CU. Preference for second-generation antihistamines is due to their multipronged action on the suppression of inflammatory cytokines, chemotaxis, leucocyte adhesion to vascular endothelium, release of histamine, etc.[8]

Bepotastine is a methoxypiperidine derivative, non-sedating second-generation antihistamine, which was first approved in Japan in 2002, as an oral drug for the treatment of allergic rhinitis.[9-11] Later, it was approved for the treatment of urticaria and pruritus associated with allergic skin diseases.[12,13] Bepotastine has twin mode of action in the form of inhibition of eosinophil chemotaxis to inflamed tissue and stabilization of mast cells.[9,14] Apart from these, peculiar feature of bepotastine lies in the fact that it has negligible sedation action, which is major hurdle for the use of conventional antihistamines. Impairment of psychomotor functions is another drawback of conventional antihistamines, which is negligible in the case of bepotastine.[8]

Since second-generation antihistamines are the mainstay of treatment in majority of CU cases, it was dire need of the hour for newer drug in this class, which would overcome major adverse effects of conventional agents but with analogous effectiveness. The present survey was undertaken in pursuit of analyzing the effectiveness and safety of bepotastine in the treatment of CU.

MATERIALS AND METHODS

A pre-validated questionnaire to analyze the safety and effectiveness and safety of bepotastine 10 mg in the treatment idiopathic CU was used to conduct the survey. The total duration of survey was from July to December 2017. Using the SCRIP database, we initially identified physicians and dermatologists who were treating patients of CU. In pursuit of taking representation of each zone in the country, we refined our search from the east, west, north, and south zones. Only those doctors were selected who maintained complete patient records. Thus, 50 of 80 doctors were finally selected based on these two criteria. Only those records were included for analysis, whose data were available for complete 28 days.

The prevalidated questionnaire booklet was provided to each of these doctors, and all relevant patient data were extracted and analyzed after collecting these questionnaire booklets at the end of this survey. The methodology adopted for the present survey is depicted in Figure 1.

Effectiveness Analysis

Clinical effectiveness was analyzed using urticaria activity score (UAS). UAS consists of two components - wheals/hives and itching. UAS was recorded at baseline (D0), day 14 (D14), and day 28 (D28). The score ranges from 0 to 6, 0 indicating the absence of disease and 6 indicating severe form of CU [Table 1].[15] We divided UAS into four categories – 0 indicating no disease, 1–2 indicating mild urticaria, 3–4 indicating moderate urticaria, and 5–6 indicating severe urticaria. Adherence to treatment was also analyzed.

Safety Evaluation

All the adverse effects were monitored for severity. Specifically, sedation was closely monitored for its occurrence and severity.

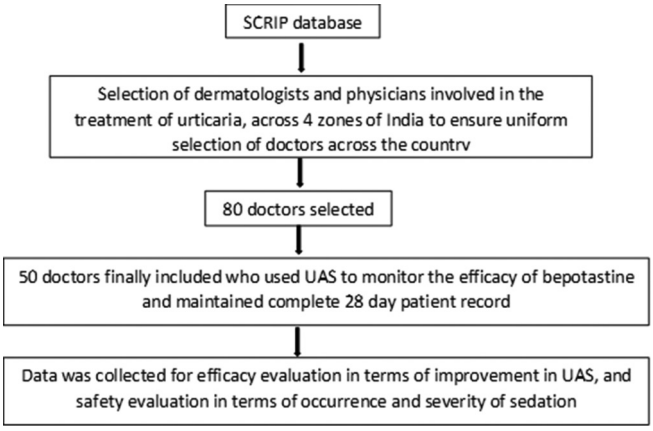

Figure 1: Methodology adopted for the survey

Table 1: Components of UAS (adapted from Jauregui *et al.*)[15]

Score	Wheals/hives	Itching
0	None	None
1	Mild (<20 wheals/24 h)	Mild
2	Moderate (21–50 wheals/24 h)	Moderate
3	Severe (>50 wheals/24 h or large confluent areas of wheals)	Severe/intense

UAS: Urticaria activity score

RESULTS

A total of 50 dermatologists and physicians participated in the survey, and a total of 250 survey questionnaire booklets were collected at the end of the survey. 226 duly filled survey questionnaire booklets were included for further analysis. The demographic characteristics of the patients are depicted in Table 2. Mean age of the patients was 35.1 years. Of 226 patients evaluated, 90 were male (40%) and 136 (60%) were females with male: female ratio of 1:1.5.

Effectiveness Evaluation

The mean UAS score at D0/baseline was 3.47 which reduced to 1.71 at D14 and 0.73 at D28 [Figure 2].

On analyzing a number of patients achieving specific UAS scores, it was found that 78 patients have UAS score in the range of 1–2, 89 patients in 3–4, and 59 patients in the range of 5–6 at D0. A number of patients in Grade 3–4 and 5–6, i.e., moderate and severe urticaria, respectively, decreased consistently at D14 and D28. 59 patients were encountered in Grade 5–6 at D0, which reduced to 45 patients at D14 and 29 patients at D28, while 89 patients in score range 3–4 at D0 reduced to 68 at D14 and 38 at D28. A number of patients in 0 (no urticaria/complete relief) and 1–2 (mild urticaria) increased consistently from baseline through D14 and D28 [Figure 3 and Table 3].

Adherence to bepotastine treatment was found to be excellent in 25%, very good in 33%, and good in 37% patients, i.e., 95% adhered to bepotastine therapy very well [Figure 4].

Safety Evaluation

Sedation was reported in only 15 patients (6.6%) that too majority had mild sedation, rated in sedation scale range of 0–5. Bepotastine therapy was discontinued in only five patients (2%), due to complete relief or due to sedation (in two patients) [Table 4 and Figure 5].

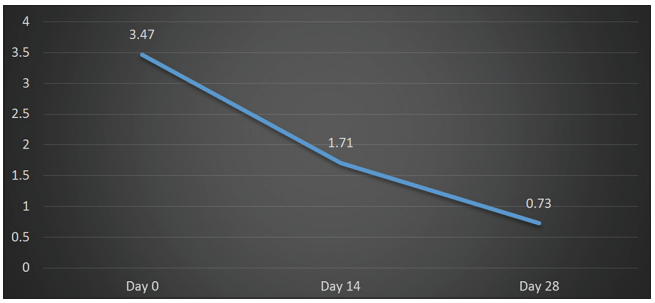

Figure 2: Mean urticaria activity score at D0, D14, and D28

Table 2: Demographic details of patients

Demographic details		
Sr. No.	**Particulars**	**Number of patients (%)**
1	Mean age	35.1 years
2	Total patients	226
3	Male	90 (40)
4	Female	136 (60)

Table 3: Number of patients achieving specific UAS scores at D0, D14, and D28

Day	Number of patients achieving UAS score			
	Complete relief	Mild urticaria	Moderate urticaria	Severe urticaria
D0	0	78	89	59
D14	34	79	68	45
D28	46	113	38	29

UAS: Urticaria activity score

Table 4: Number of patient experiencing sedation and discontinuation of bepotastine therapy

Items	Numer of patients	
	Yes	No
Sedation	15	211
Bepotastine was stopped	5	221

DISCUSSION

About 20% of the global population suffer from at least one episode of urticaria during their lifetime.[1] Second-generation antihistamines are the mainstay of symptomatic management of urticaria in majority of the cases. Bepotastine is one of the effective therapeutic options for the treatment of urticaria with crucial advantage of causing minimal sedation. It has shown consistent effectiveness against urticaria, achieving 65–77% significant clinical improvement.[11,12]

However, conventional second-generation antihistamines, although effective in ameliorating symptoms of urticaria, sedation, and impairment of psychomotor activities, limit their use in the treatment of urticaria.[8] Effectiveness of bepotastine in the present survey was analyzed by UAS score which consistently reduced from 3.47 at D0 to 0.73 at D28. The UAS score takes into account the symptoms of histamine-induced inflammation.[15] Thus, a significant reduction in UAS score indicates potent counteraction of histamine action.

The latest guidelines on the treatment of urticaria laid down by numerous medical societies such as the World Allergy Organization, European Academy of Allergy and Clinical Immunology, Global Allergy and Asthma European Network, and American Academy of Allergy, Asthma, and Immunology recommend UAS score as a

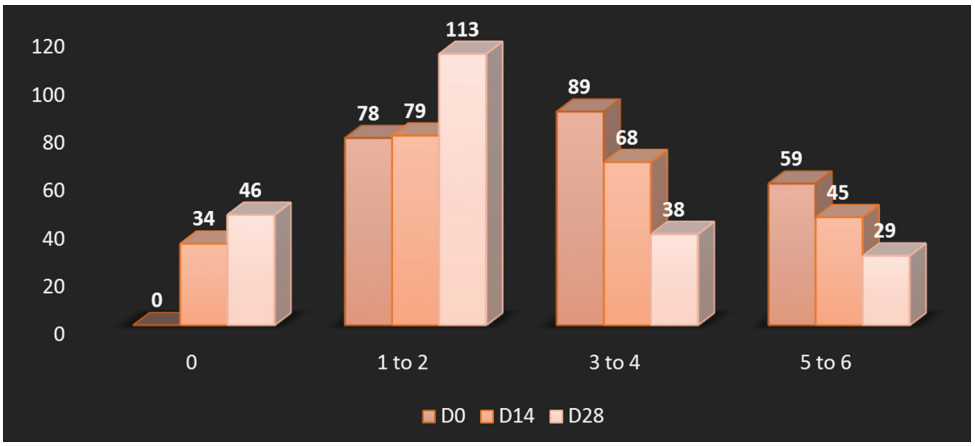

Figure 3: Number of patients achieving specific urticaria activity scores

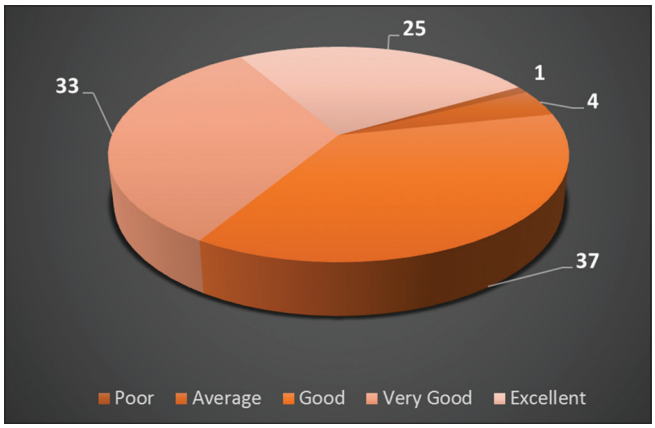

Figure 4: Percentage adherence to bepotastine therapy

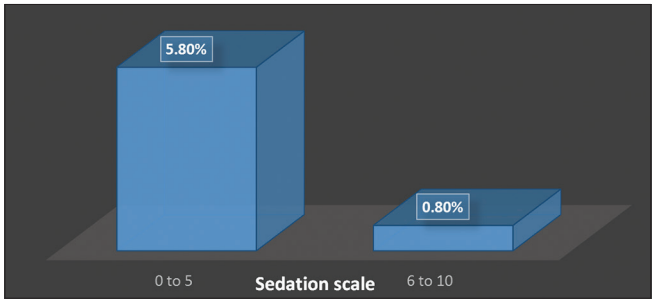

Figure 5: Percentage of patients reporting sedation intensity

target for monitoring effectiveness of antihistamines. This is the reason why UAS scoring is widely used in clinical trials and routine clinical practice in western countries, for monitoring and follow-up of CU.[16]

Number of patients in moderate and severe grades on D0 reduced at D14 and D28 consistently. Similar results have been obtained in placebo-controlled randomized clinical trial of bepotastine.[13] The crucial reduction in a number of patients in moderate and severe UAS scores at D14 and D28 indicates effective antihistaminic action of bepotastine. The increase in a number of mild cases at D14 and D28 was due to improvement in moderate and severe grades, which shifted to mild or completely cured categories. Similar effective improvement rates of around 84% were reported in a post-marketing surveillance done on 549 patients of urticaria associated with skin diseases, who were treated with bepotastine.[17] This effectiveness of bepotastine might be due to multipronged action of counteracting histamine release and action, mast cell stabilization, inhibition of eosinophil chemotaxis, inhibition of allergic inflammatory cytokines like IL-5, platelet activating factor, leukotriene B4 and D4, and substance P which are responsible for antipruritic effect also.[18] In a recently published Indian consensus regarding diagnosis and treatment of urticaria, it was strongly recommended to use modern second-line antihistaminic as a first-line therapy for the management of urticaria.[19]

It has also been studied in head-to-head comparison with conventional terfenadine, and it was found to be as effective as later, in ameliorating the urticaria symptoms as well as global improvement scores.[20] In a clinical study done to evaluate the efficacy of bepotastine and fexofenadine in histamine-induced wheal and flares, it was found that wheal development at the end of 3 h and 6 h was suppressed more significantly in case of bepotastine as compared to fexofenadine.[21] In another clinical study on effects of bepotastine, fexofenadine, olopatadine, and cetirizine on histamine-induced wheal and flare response, sedation, and psychomotor performance, it was found that bepotastine showed significant inhibitory effect on wheals and flare, with maximum response among all the drugs on wheal suppression.[21]

Bepotastine had very negligible sedation in <1% of the patients in the present survey. This was corroborated by the findings of a clinical study, wherein all the conventional second-generation antihistamines such as cetirizine,

fexofenadine, and olopatadine induced significant sedative effect and affected psychomotor performance. In comparison, bepotastine had minimal effect on psychomotor activities and least sedation.[21] This can be attributed to:

1. Very negligible action at receptors associated with sedation such as dopamine, serotonin, and muscarinic receptors.
2. Limited ability to cross the blood–brain barrier.
3. Efflux from brain cells through P-glycoprotein efflux pump.
4. Internalization of H1 receptors.[9]

Most common reason for poor adherence to conventional antihistamines is the induction of sedation and impairment of psychomotor activities.[8] The high adherence rate of 95% in the present survey toward bepotastine can be attributed to negligible sedation and no impairment of psychomotor activities. Thus, complete relief and improvement were seen in >70% of the patients, which is in accordance with other studies establishing the effectiveness of bepotastine.[21]

CONCLUSION

Bepotastine is a newly introduced non-sedating effective therapeutic option for the treatment of urticaria associated with skin diseases with proven effectiveness and very less adverse effects, especially negligible sedation and absence of impairment of psychomotor activities. The findings of the present real-world survey fortify the favorable effectiveness and safety data of clinical trials.

Limitations of the Survey

Due to the retrospective design of the survey, chances of bias cannot be ruled out. Furthermore, the effect of bepotastine on QOL was not studied.

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REFERENCES

1. Greaves MW. Chronic urticaria. N Engl J Med 1995;332:1767-72.
2. Singh M, Kaur S, Kanwar A. Evaluation of the causes of physical urticaria. Indian J Dermatol Venereol Leprol 1990;56:109-11.
3. Yadav S, Uhyapady A, Bajaj A. Chronic urticaria: An overview. Indian J Dermatol 2006:51:171-7.
4. Bernstein JA, Lang DM, Khan DA, Craig T, Dreyfus D, Hsieh F, *et al.* The diagnosis and management of acute and chronic urticaria: 2014 update. J Allergy Clin Immunol 2014;133:1270-7.
5. Baiardini I, Pasquali M, Braido F, Fumagalli F, Guerra L, Compalati E, *et al.* A new tool to evaluate the impact of chronic urticaria on quality of life: Chronic urticaria quality of life questionnaire (CU-qoL). Allergy 2005;60:1073-8.
6. O'Donnell BF, Lawlor F, Simpson J, Morgan M, Greaves MW. The impact of chronic urticaria on the quality of life. Br J Dermatol 1997;136:197-201.
7. Grob JJ, Revuz J, Ortonne JP, Auquier P, Lorette G. Comparative study of the impact of chronic urticaria, psoriasis and atopic dermatitis on the quality of life. Br J Dermatol 2005;152:289-95.
8. Kathuria P. Urticaria and its management. Indian J Allergy Asthma Immunol 2011;25:33-7.
9. Williams JI, Gow JA, Klier SM, McCue SL, Salapatek AM, McNamara TR, *et al.* Non-clinical pharmacology, pharmacokinetics, and safety findings for the antihistamine bepotastine besilate. Curr Med Res Opin 2010;26:2329-38.
10. Baba S, Takasaki T, Baba K. Late phase II clinical study of TAU-284 for perennial allergic rhinitis dose finding study by the double-blind method. J Clin Ther Med 1997;13:1259-86.
11. Baba S, Takasaka T, Baba K. Long-term treatment of TAU-284(betotastine besilate) on perennial allergic rhinitis. J Clin Ther Med 1997;13:1361-82.
12. Ishibashi Y, Harada S, Niimura M. Late phase II study of TAU-284 (bepotastine besilate) on chronic urticaria optimal dose finding study by double-blind technique. J Clin Ther Med 1997;13:1237-57.
13. Kawashima M, Harada S, Kawashima M. Phase III study of TAU284 (bepotastine besilate) on chronic urticaria. A multicenter double blind comparative study with placebo. J Clin Ther Med 2002;18:501-19.
14. Kato M, Nishida A, Aga Y, Kita J, Kudo Y, Narita H, *et al.* Pharmacokinetic and pharmacodynamic evaluation of central effect of the novel antiallergic agent betotastine besilate. Arzneimittelforschung 1997;47:1116-24.
15. Jáuregui I, Ortiz de Frutos FJ, Ferrer M, Giménez-Arnau A, Sastre J, Bartra J, *et al.* Assessment of severity and quality of life in chronic urticaria. J Investig Allergol Clin Immunol 2014;24:80-6.
16. Młynek A, Zalewska-Janowska A, Martus P, Staubach P, Zuberbier T, Maurer M, *et al.* How to assess disease activity in patients with chronic urticaria? Allergy 2008;63:777-80.
17. 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.
18. Lyseng-Williamson KA. Oral bepotastine: In allergic disorders. Drugs 2010;70:1579-91.
19. Godse K, De A, Zawar V, Shah B, Girdhar M, Rajagopalan M, *et al.* Consensus statement for the diagnosis and treatment of urticaria: A 2017 update. Indian J Dermatol 2018;63:2-15.
20. Ishibashi Y, Harada S, Niimura M, Shimao S, Takeda K1, Yamamura H. A multicenter double-blind comparative study; clinical evaluation of TAU-284 (bepotastine besilate) on chronic urticaria using terfenadine as a control drug. Rinsho Iyaku 1997;13:1287-306.
21. 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.

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