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ORIGINAL RESEARCH

Real-World, Non-Interventional, Observational Study of Hydroxyzine Hydrochloride in Chronic Pruritus: a Prospective, Non-Comparative Study

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ABSTRACT

Introduction: Although hydroxyzine is widely used for symptom relief in pruritus, its clinical safety and efficacy data in the Indian setting are scarce. We conducted a study to assess the effectiveness and tolerability of hydroxyzine in the management of Indian patients with chronic pruritus in a real-world setting.

Methods: This was a prospective, observational, patient-reported outcomes (PRO) study in patients with chronic pruritus due to dermatological causes treated with hydroxyzine as per the clinician's discretion for a period of up to 12 weeks. The primary outcome was improvement in quality of life from baseline, assessed using the 10-point Dermatology Quality of Life Index (DLQI) at week 12 of the study period. Secondary outcomes were improvement in the pruritus scores (5-D itch scale) at 12 weeks, improvements in the DLQI and 5-D itch scores at 2, 4 and 8 weeks and safety.

Results: The study included 400 patients (179 males, 221 females) from 7 dermatology centres across India. Of the 400 patients recruited, 391 patients completed at least 2 weeks of treatment. There was significant ($p < 0.0001$) improvement from baseline in the DLQI scores and 5-D itch scores at 2, 4, 8 and 12 weeks; 189/391 (48.34%) patients had symptom relief leading to early termination. Overall, the

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treatment was well tolerated with a total of 11 mild-to-moderate adverse events reported during the study, which included dizziness, constipation, drowsiness, dry mouth and sedation. All events resolved without any intervention. There were no serious adverse events.

Conclusion: This real-world, observational, PRO study demonstrates that hydroxyzine significantly improves symptoms of pruritus and quality of life in patients with chronic pruritus due to dermatological causes over 12 weeks. Despite the sedating potential of the drug, hydroxyzine is well tolerated in real-world settings.

Trial Registration: CTRI/2017/06/008847.

Funding: Dr. Reddy's Laboratories.

Keywords: 5-D itch score; Dermatology Quality of Life Index; DLQI; Hydroxyzine; Pruritus

INTRODUCTION

Pruritus or itch is an unpleasant sensory perception that causes an intense desire to scratch and has a high impact on patients' quality of life (QOL) [1]. Pruritus has a prevalence of about 13.5% in adults and increases to 16.8% in those undergoing cancer screening [2, 3]. The prevalence of chronic pruritus increases with advancing age [4]. It is a symptom of many conditions with a major impact on healthcare costs [5, 6]. It is the most frequent symptom in dermatology and can occur in acute or chronic forms (over 6 weeks in duration) [7, 8]. However, the nature of pruritus may vary in different disorders [9].

H1 antihistamines along with topical corticosteroids are part of the symptomatic therapy in the first step of management of chronic pruritus [1]. Many sedating first-generation antihistamines (Table 1) such as hydroxyzine hydrochloride and pheniramine are used for the management of chronic pruritus and have been shown to be effective in the management of pruritus due to dermatological conditions such as chronic urticaria, atopic dermatitis, contact dermatoses and histamine-mediated pruritus [10]. Of these, hydroxyzine hydrochloride is considered the most potent antihistamine in managing chronic pruritus, which has been demonstrated in in vivo studies [11]. Non-sedating second-generation antihistamines (Table 1) are less sedating, long-acting and have a documented anti-inflammatory activity but are considered less efficacious than sedative first-generation antihistamines for relief from chronic pruritus [1]. However, they do not provide complete symptom control compared with first-generation antihistamines [1, 11]. Moreover, up-dosing of non-sedative second-generation agents may lead to sedative side effects as well [12].

Although hydroxyzine hydrochloride has been one of the preferred drugs for treating

Table 1 Chemical and functional classification of H1 antihistamine agents [25]

	First generation	Second generation
Alkylamines	Chlorpheniramine, pheniramine	Acrivastine
	Clemastine	
	Cyproheptadine	
	Diphenhydramine	
	Promethazine	
Piperazines	Hydroxyzine	Cetirizine, levocetirizine
Piperidines	Cyproheptadine, ketotifen	Astemizole, desloratadine, fexofenadine, loratadine, mizolastine, olopatadine, terfenadine, bilastine
Ethanolamines	Dimenhydrinate, diphenhydramine, doxylamine	–
Phenothiazines	Promethazine	–
Others	Doxepin	Azelastine

chronic pruritus for decades, limited data are available on its role in improving patient-reported outcomes (PROs) as an anti-pruritic agent, especially in India. This study therefore aimed to assess the real-world effectiveness and tolerability of hydroxyzine hydrochloride as an anti-pruritic with a focus on PROs in the overall management of chronic pruritus due to dermatological causes in Indian settings.

Trial registration no.: CTRI/2017/06/008847; registered on: 15/06/2017.

METHODS

This was a real-world, non-interventional, multicentric observational study conducted in dermatology centres across India.

Study Participants

Adult patients of either sex, $\geq$ 18 years of age, suffering from chronic pruritus due to dermatological conditions and for whom the physician had taken a decision to prescribe hydroxyzine hydrochloride were included in study. Those with pruritus due to systemic causes, known hypersensitivity to the study drug, pregnant or lactating women, those receiving any centrally acting medications or those with known neurological conditions were excluded from the study.

Compliance with Ethics Guidelines

The study documents were reviewed and approved by the respective Institutional/Independent Ethics Committees (please see supplementary material for list of Ethics Committees), and the study was conducted in accordance with the principles of the Declaration of Helsinki (World Medical Association) and Good Clinical Practice guidelines issued by the ICMR & DCGI, Government of India. All the patients received explanations about the study details and were provided the opportunity to raise any queries/doubts about the study. Written informed consent was obtained from all patients before enrolment. The study was registered in the clinical trials registry of India (CTRI/2017/06/008847; registered on: 15/06/2017).

Study Treatments

Because of the observational nature of this study, patients who were prescribed oral hydroxyzine hydrochloride (Atarax® 10/25 mg tablets, Dr. Reddy's Laboratories Ltd., India) for a 12-week period at the discretion of the clinician were enrolled. The dosing allowed followed the prescribing information, i.e. up to 25 mg four times daily. Patients were allowed to continue other concomitant medications.

Study Procedures

Detailed medical history was taken and clinical examination was performed at baseline. The patients were followed up as per routine clinical practice. However, clinical assessments were recorded at baseline and after 2, 4, 8 and 12 weeks of starting hydroxyzine hydrochloride treatment. The effect of pruritus on the quality of life was assessed using the Dermatology Life Quality Index (DLQI) questionnaire, which is a ten-item validated questionnaire for assessment of quality of life (QOL) in patients with dermatological disorders [13–15]. The effect of pruritus on the patient's life was interpreted based on the total DLQI scores of ten items: no effect at all on the patient's life (score 0–1), a small effect on the patient's life (scores 2–5), a moderate effect on the patient's life (scores 6–10) and a very large effect on the patient's life (scores 11–20). Pruritus severity was assessed using the 5-D itch scale, which measures pruritus according to five dimensions, i.e. degree, duration, direction, disability and distribution [16, 17]. Single-item domain scores (duration, degree and direction) were marked on a range of 1–5, whereas the disability domain had four items that assess the impact of itching on daily activities: sleep, leisure/social activities, housework/errands and work/school, and for the distribution domain, the number of affected body parts was tallied (potential sum 0–16). The sum for the distribution domain was sorted into five

scoring bins: sum of 0–2 = score 1, sum of 3–5 = score 2, sum of 6–10 = score 3, sum of 11–13 = score 4 and sum of 14–16 = score 5. The score for the disability domain was achieved by taking the highest score on any of the four items. The scores of each of the five domains were arrived at separately and then summed together to obtain a total 5-D itch score, and the total score ranged from 5 (no pruritus) to 25 (most severe pruritus).

Study Outcomes

The primary study outcome was improvement in DLQI scores from baseline at the end of the 12-week study period. Secondary outcomes were improvement in 5-D itch score at the end of 12 weeks and safety. Safety was assessed based on spontaneous reports generated by the clinician.

Statistical Analysis

The estimated sample size for 80% power for this observational study was 400 based on the assumption of 5% error and expecting a response rate of 50% for improvement in the DLQI score. The efficacy analysis was done on the full analysis set (FAS), i.e. those patients who completed the 12-week study period as well as those who left the study early because of being either cured (treatment discontinuation) or lost to follow-up and had at least one follow-up visit completed. Data from all patients enrolled in the study was included for safety analysis, i.e. the intent-to-treat set (ITTS), which included all 400 patients enrolled in the study. Continuous data are summarized as means, standard deviation (SD), median and range. The baseline scores were compared with scores at follow-up visits (pairwise) using the Wilcoxon test, and scores at all visits were analysed using the Friedman test (non-parametric repeat measures ANOVA). The changes from baseline [mean, SD, 95% confidence interval (CI) and percentage change] in the DLQI scores and 5-D itch scores were computed for each follow-up visit (2, 4, 8 and 12 weeks) and were presented as numbers and percentages for the FAS. Since many patients were terminated early at investigator's discretion because they had complete symptomatic relief and there was no further need for antihistamine therapy, cure rates for symptoms were computed at each follow-up visit and are presented as numbers with percentages.

RESULTS

Demographics and Patient Characteristics

Four hundred patients with chronic pruritus due to dermatological causes were enrolled from seven study sites; of these, nine patients did not have a single follow-up visit and were excluded from the full analysis set (FAS, $n = 391$). Amongst the 391 patients completing at least 1 follow-up visit, 25 patients completed 2 weeks, 176 completed 4 weeks, 14 completed 8 weeks and 176 completed 12 weeks of the study period. The demographic profile and vital parameters at baseline for all patients (ITTS) and those in the FAS are presented in Table 2. The primary diagnosis of chronic pruritus recorded included conditions such as allergy, psoriasis, dermatophytosis, acne, urticaria, xerosis and other dermatological conditions. Being an observational study, the dose and dosing schedule were decided by the treating physician based on patient characteristics. The dosing allowed was as per the prescribing information, i.e. up to 25 mg four times daily. While 272 patients received 10 mg, 122 patients received 25 mg. The majority ($n = 313$) of the patients were administered the drug once daily, while others received it up to four times daily (Table 3). Two hundred fourteen patients were on hydroxyzine therapy alone without any concomitant medications (54.31%).

Efficacy Outcomes

Tables 4 and 5 show the descriptive data for DLQI and 5-D itch scores at all visits, respectively. The post-treatment scores for the DLQI and 5-D itch scale were significantly lower than the baseline scores, and there was a significant

Table 2 Demography and baseline data of patients

	ITTS (n = 400)		FAS (n = 391)	
	Mean	SD	Mean	SD
Age (years)	37.66	12.39	37.73	12.44
Weight (kg)	63.94	11.09	63.94	11.05
Height (cm)	158.23	8.76	158.37	8.61
Baseline scores				
DLQI score	11.75	5.40	11.78	5.45
5-D itch score	15.43	2.95	15.44	2.94
	No.	%	No.	%
Gender				
Male	179	44.8	176	45.0
Female	221	55.2	215	55.0
			No.	%
Concomitant therapy received				
Anti-infectives			14	3.5
Topical corticosteroids			23	5.8
Other antihistamines			25	6.3
Antacids			10	2.5
Moisturizer			8	2.0

DLQI dermatology life quality index, *ITTS* intent-to-treat set, *FAS* full analysis set

reduction in the scores at all follow-up visits ($p < 0.0001$). The percentage reductions from baseline in DLQI scores and 5-D itch scores are presented in Figs. 1 and 2, respectively.

DLQI Scores

Based on the DLQI scores at baseline (n = 391), there was a significant effect of pruritus on patient's life with 56.2% patients reporting a 'very large to extremely large effect on their life', 29.9% reporting a 'moderate effect on their life', 13.0% reporting a 'small effect on their life' and only 0.8% reporting 'no effect on their life'. After hydroxyzine hydrochloride therapy, at 12 weeks (n = 176), none of the patients had a 'very large to extremely large effect on their life' and 20.5% patients reported 'no effect on their life'. Only 17.6% patients reported a 'moderate effect on their life' and 61.9% reported a 'small effect on their life'. Significant ($p < 0.0001$)

Table 4 Effect of treatment on DLQI scores over treatment period

Time point	n	DLQI score (mean ± SD)	p value (vs. baseline)
Baseline	391	11.78 ± 5.45	
2 weeks	391	9.08 ± 5.47	< 0.0001
4 weeks	366	5.85 ± 4.62	< 0.0001
8 weeks	190	5.99 ± 2.65	< 0.0001
12 weeks	176	3.35 ± 2.33	< 0.0001

Table 5 Effect of treatment on 5-D itch scores over the treatment period

Time point	n	5-D itch score (mean ± SD)	p value (vs. baseline)
Baseline	391	15.44 ± 2.94	
2 weeks	391	12.72 ± 3.32	< 0.0001
4 weeks	366	10.58 ± 3.26	< 0.0001
8 weeks	190	10.01 ± 2.38	< 0.0001
12 weeks	176	8.05 ± 1.94	< 0.0001

Table 3 Number of patients for each dose and dosing schedule

Hydroxyzine	Once daily	Two times daily	Three times daily	Four times daily	Cumulative
10 mg	255	17	–	–	272
25 mg	58	30	28	6	122
Cumulative	313	47	28	6	394

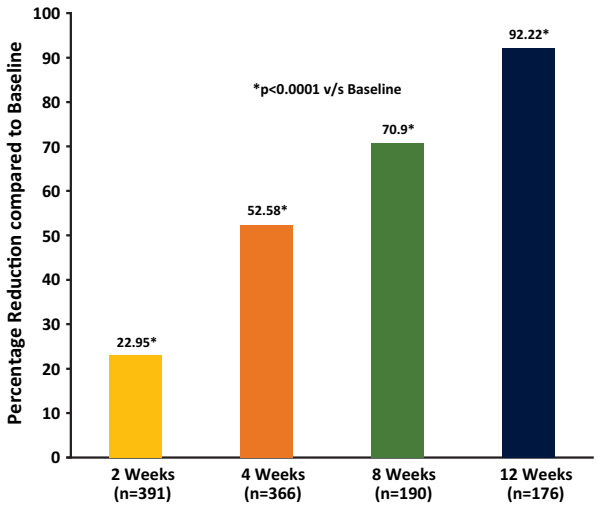

Fig. 1 Percentage reduction in DLQI scores compared with baseline in the study population

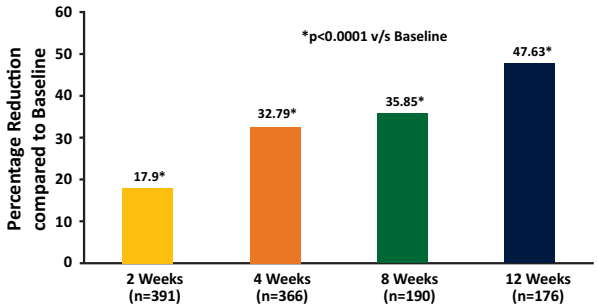

Fig. 2 Percentage reduction in 5-D itch scores compared with baseline in study population

improvement (reduction in mean DLQI scores) was observed over the 12-week period. Significant benefit was observed as early as 2 weeks and further improvement was seen over all subsequent follow-up visits. There was a significant improvement in DLQI score by 2.70 (95% CI 2.39–3.01) at 2 weeks and 10.86 (95% CI 9.95–11.78) at 12 weeks compared with baseline. Furthermore, the improvement in mean DLQI scores was 22.95% at 2 weeks and 92.22% at 12 weeks compared with baseline (Fig. 1).

The 5-D Itch Scores

Significant ($p < 0.0001$) reduction in the mean 5-D itch score was observed over the 12-week period. Significant benefit was seen after 2 weeks and at all subsequent follow-up visits. There was a significant improvement in 5-D score by 2.76 (95% CI 2.48–3.05) at 2 weeks and 7.35 (95% CI 6.88–7.83) at 12 weeks compared with baseline. Furthermore, the improvement in mean 5-D itch scores was 17.90% at 2 weeks and 47.63% at 12 weeks compared with baseline (Fig. 2).

Symptom Elimination

Symptom elimination, defined as no need for further antihistamine therapy (hydroxyzine hydrochloride) during the study period, was observed in 48.34% ($n = 189$) patients. Overall 189 of 391 patients were symptom free after hydroxyzine therapy at some time point during the study. The cumulative symptom elimination rates were 3.58% ($n = 14$), 46.04% ($n = 180$) and 48.34% ($n = 189$) at 2, 4 and 8 weeks, respectively. The symptom elimination rates in males and females were 47.16% and 49.30%, respectively, at 8 weeks. At the end of the 12-week study period, only 35 patients (8–9%) were actually lost to follow-up, given the observational design of this study.

Safety Outcomes

Of 400 patients, only 11 (2.8%) patients reported adverse events. Dizziness was the most common adverse event reported by four patients (1.0%), while constipation was reported by two patients (0.5%), drowsiness by two patients (0.5%), dry mouth by two patients (0.5%) and sedation by one patient (0.3%). All events were of mild-to-moderate severity not requiring any interventions and resolved without sequelae. There was no predilection for any adverse event for any particular age group or sex of the patients. No serious adverse events were reported in this study.

DISCUSSION

Chronic pruritus is a common condition; it has a major impact on patients' quality of life and also has severe psychological implications [1, 18]. Despite the availability of various treatment modalities today, management of pruritus

remains a challenge when it is not associated with a primary skin disease [19]. Antihistamines are the standard therapy for management of chronic pruritus as they are effective in many of these patients. The second-generation agents have been recommended as first-line agents by some guidelines, though up-dosing is generally recommended for improving efficacy if desired. Despite this, large variation in responses to the second-generation agents has been noted. For patients not deriving adequate benefit despite up-dosing of second-generation agents, first-generation antihistaminics are recommended, although their sedative and motor impairment potential is less or not evident with second-generation agents [20]. Amongst the first-generation agents, hydroxyzine hydrochloride has been demonstrated to be equally or more efficacious compared with other antihistaminic drugs [10].

Our study showed significant improvement in the DLQI and 5-D itch scores within 2 weeks of starting therapy with hydroxyzine hydrochloride with progressive improvement seen till the end of the 12-week study period. At the end of 12 weeks compared with baseline, there was a reduction in DLQI scores of 10.86 units or 92.22% (Fig. 1) and reduction in 5-D itch scores of 47.63% (Fig. 2). The symptom elimination rates were 46.04% and 48.34% at the 4th and 8th weeks, respectively. In controlled studies of second-generation antihistaminics in patients with chronic idiopathic urticaria, improvement in DLQI was observed to be 7.3–8.83 units with levocetrizine [21, 22] and 5.5–6.0 units with fexofenadine [23]. Improvement in DLQI scores with hydroxyzine hydrochloride observed in our study is thus similar to or better than that previously reported with second-generation antihistaminics.

Adverse events reported with hydroxyzine are usually mild and transitory in nature with dry mouth and drowsiness as the most common effects [24]. In our study, hydroxyzine was well tolerated with only 11 (2.8%) patients reporting mild-to-moderate adverse events, which included dizziness, constipation, drowsiness, dry mouth and sedation. There was a probable underreporting of adverse events in the study due to observational nature of the study.

The European Guideline on Chronic Pruritus recommends use of hydroxyzine hydrochloride as a first choice in the treatment of itch because of various aetiologies due to its antipruritic, anxiolytic and sedative properties [11]. Also, there is limited evidence of antipruritic efficacy of non-sedating agents especially in pruritus of diverse origin.

Real-world studies are important for ascertaining the effectiveness and safety of a drug in clinical practice beyond the evidence generated in its controlled clinical trials. In this regard, our study is limited by the attributable efficacy of the study medication in a few patients on other concomitant medications and efficacy comparisons between doses for 10 mg and 25 mg and also between commonly observed primary dermatological conditions causing chronic pruritus as these were not the objectives of this study. Future studies could evaluate the efficacy of hydroxyzine for a single dermatological condition. Although our study is limited by its observational and non-comparative design, this study captured data from clinical practice in an Indian setting involving hydroxyzine, which may be be the first report in India, and thus the conclusions could be more representative of general patient populations of interest and may be generalizable to a wider population. Also, our study captured data regarding patient-reported outcomes of hydroxyzine hydrochloride using validated instruments such as the DLQI and 5-D itch scoring, providing evidence of the effectiveness of hydroxyzine hydrochloride in controlling symptoms and improving the quality of life of patients with chronic pruritus caused by dermatological conditions of diverse origin.

CONCLUSIONS

This real-world observational study provides evidence of the good efficacy and tolerability of hydroxyzine hydrochloride including achieving the desired patient-reported outcomes and continues to reinforce its usefulness as an effective and safe option for treatment of chronic pruritus.

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Compliance with Ethics Guidelines. The study documents were reviewed and approved by the respective Institutional/Independent Ethics Committees (please see supplementary material for list of Ethics Committees) and the study was conducted in accordance with the principles of the Declaration of Helsinki (World Medical Association) and Good Clinical Practice guidelines issued by the ICMR and DCGI, Government of India. All the patients received explanations of the study details and were provided the opportunity to raise any queries/doubts about the study. Written informed consent was obtained from all patients before enrolment. The study was registered in the clinical trials registry of India (CTRI/2017/06/008847; registered on: 15/06/2017).

Data Availability. The data sets generated during and/or analyzed during the current study are not publicly available because of unavailability of the online repository at this time but are available from the corresponding author on reasonable request.

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