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Up-dosing of non-sedating antihistamines in chronic urticaria: Need for well-designed clinical trials in India

Abstract

Urticaria is a heterogeneous group of diseases. Chronic urticaria significantly impacts quality-of-life of patients. Second generation, non-sedating antihistamines are recommended as first line treatment for chronic spontaneous urticaria. In patients with inadequate control of symptoms, increase in dosage of non-sedating antihistamines up to four fold has been recommended. This recommendation is based on low cost, good safety and good evidence of efficacy of non-sedating, second generation antihistamines. This article reviewed Indian data on up-dosing of antihistamines in chronic urticaria. There is a need for well-designed clinical trials with up-dosing of individual antihistamines in Indian patients.

Key words: Antihistamines, up-dosing, urticaria

INTRODUCTION

Urticaria is a heterogeneous group of diseases having multiple underlying causes, diversity of eliciting factors and variable clinical presentation.[1] Lifetime prevalence of urticaria is approximately 20% in the general population. Urticaria is usually acute and self-limited, but can be chronic in some cases. Chronic urticaria is usually idiopathic. Pathophysiology includes immunoglobulin E and non-immunoglobulin E mediated mast cell and basophil release of histamine and other inflammatory mediators. Urticaria patients suffer from intense pruritus associated with raised wheals, with or without edema of the deeper cutis.[2] Exact epidemiology of chronic urticaria in India is unknown. World-wide it occurs in 0.1-3% of the population.[3]

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CHRONIC URTICARIA: CONSEQUENCES AND MANAGEMENT WITH ANTIHISTAMINES

Patients suffering from chronic urticaria have impaired quality-of-life (QOL). Negative effects of chronic urticaria on several aspects of QOL are as severe as ischemic heart disease. Chronic urticaira has impact on physical as well as mental health of patient. Hence, prompt diagnosis and initiation of optimal therapy is needed in chronic urticaria.[4]

RATIONALE FOR USE OF ANTIHISTAMINES IN MANAGEMENT OF CHRONIC URTICARIA

Symptoms (wheals, flare and pruritus) in urticaria are mainly caused by the actions of histamine on H1 receptors. For example, wheals are caused by action of histamine on H1 receptors located on endothelial cells while the action of histamine on H1 receptors located on sensory nerves causes flare and pruritus.[1] Hence, there is a rational to use H1-antihistamines in the treatment of urticaria.

Limitations of older first generation antihistamines

Older first generation antihistamines may lead to anticholinergic effects and have sedative actions. Short

action on pruritus, interference with rapid eye moment sleep, interactions with alcohol and some drugs acting on central nervous system, are other limitations for use of older first generation antihistamines.[1]

Dermatology Section of European Academy of Allergology and Clinical Immunology/Global Allergy and Asthma European Network/European Dermatology Forum and World Allergy Organization (EAACI/GA² LEN/EDF/WAO) guideline on management of urticaria have recommended not to use sedating antihistamines for the routine management of chronic urticaria as first line agents except in places where non-sedating antihistamines are not available or where they prove to be more effective or better tolerated than non-sedating H1-antihistamines.[1]

Non-sedating, second generation antihistamines

New generation non-sedating antihistamines do not have these major side-effects and also have long duration of action. Astemizole and terfenadine had shown cardiotoxic effects. Cetirizine, desloratadine, fexofenadine, levocetirizine, acrivastine, ebastine and mizolastine are second generation antihistamines.[1]

Treatment of urticaria also includes avoidance of triggering factors. First-line treatment for acute and chronic urticaria is non-sedating second-generation H1-antihistamines, which can be increased to higher than standard doses.[2]

Second generation antihistamines are considered as the first line symptomatic treatment for urticaria because of their better safety profile compared to first generation antihistamines.[1]

Recommendations for up-dosing of non-sedating antihistamines in chronic urticaria

EAACI/GA²LEN/EDF/WAO guideline on management of urticaria (2009)[1] recommends up-dosing of non-sedating antihistamines (up to 4 times the standard dose) in chronic urticaria patients who do not respond satisfactorily to the standard dose. This recommendation is based on the low cost, good safety profile and good evidence of efficacy of antihistamines in higher doses in chronic urticaria

Consensus statement developed by special interest group-urticaria (Indian Association of Dermatologists, Venereologists and Leprologists)[5] in India, recommends the use of second-generation non-sedating H1 antihistamines as the first-line treatment for management of urticaria. In case of non-responding patients, the dose can be increased up to 4 times.

INDIAN EVIDENCE WITH UP-DOSING OF SECOND GENERATION ANTIHISTAMINES IN CHRONIC URTICARIA

In India, few studies have been carried out with up dosing of different antihistamines in patients suffering from chronic urticaria. A review of literature was carried out through "PubMed" to find out studies with higher doses of antihistamines in Indian patients suffering from chronic urticaria. Three studies with different antihistamines were found in the literature. These are discussed in brief below.

Levocetirizine

Godse,[6] (2010) studied twenty adult patients (12 females and 8 males) with chronic urticaria. All these patients had chronic idiopathic urticaria ranging from 3 months to 2 years. Patients were started with levocetirizine 5 mg tablet at bedtime. Patients were monitored at weekly intervals of 4 weeks. If patient was found to be symptomatic, then levocetirizine dose was doubled to two tablets at bedtime at the end of 1 week and four tablets in two divided doses at the end of 2 weeks. The results of the study showed that at the end of 1 week, eight patients were symptomatic; dose of levocetirizine was increased to 10 mg. At the end of 2 weeks two patients out of eight were symptomatic. In these patients, dose of levocetirizine was doubled to 10 mg twice a day. One patient with 20 mg of levocetirizine complained of mild sedation while another patient with 10 mg of levocetirizine also complained of mild sedation. Twelve, six and two patients became symptom-free with 5, 10 and 20 mg levocetirizine respectively.

Fexofenadine

Godse *et al.*,[7] (2010) studied fexofenadine in chronic spontaneous urticaria in higher doses. They studied 37 adult patients (17 females and 20 males) with chronic spontaneous urticaria for at least 6 weeks. All patients had chronic spontaneous urticaria from 3 months to 2 years. All patients were started with fexofenadine 180 mg tablet once daily. Patients were reviewed at weekly intervals for 4 weeks. Dose of fexofenadine was doubled to 360 mg (two tablets) in two divided doses at the end of 1 week in case of symptomatic patients; and three tablets of fexofenadine (540 mg) in three divided doses at the end of 2 weeks. Elevan, 12 and 13 patients became asymptomatic when administered 180, 360 and 540 mg fexofenadine, respectively.

Ebastine

Godse,[8] (2011) also studied higher doses of ebastine in chronic spontaneous urticaria. Thirty adult patients (16 females and 14 males) with chronic spontaneous urticaria were studied in this study. All patients had chronic spontaneous

urticaria ranging between 3 months and 2 years. All patients were given ebastine 10 mg tablet at bedtime. Patients were reviewed on weekly intervals for 4 weeks. Dose of ebastine was doubled to 20 mg at bedtime at the end of 1 week in case of a symptomatic patient and two tablets of ebastine 20 mg in two divided doses at the end of 2 weeks. Three patients were lost to follow-up at the end of 1 week possibly due to poor response. Seventeen, eight and two patients became symptom-free when administered 10, 20 and 40 mg ebastine, respectively.

NEED OF DOUBLE BLIND STUDIES FOR UP-DOSING OF ANTIHISTAMINES IN INDIA

All of the above discussed studies conducted in small number of Indian patients have proved efficacy and tolerability of higher doses of three different antihistamines i.e. levocetirizine, fexofenadine and ebastine in chronic spontaneous urticaria. All are single arm and non-randomzied studies.

There are no published randomized, double blind studies with up-dosing of antihistamines in India. Hence, there is a need for well-designed clinical trials (randomized, double-blind clinical study with adequate sample size) comparing efficacy and safety of individual non-sedating H1-antihistamines in chronic spontaneous urticaria in Indian patients.

CONCLUSION

Second generation non-sedating antihistamines are recommended as first line therapy in the management of chronic spontaneous urticaria. If standard dose of second generation antihistamine is not found to be effective, higher dose (up to four fold) of non-sedating antihistamines is recommended. In India well-designed clinical trials with up dosing of antihistamines in chronic urticaria are lacking. Hence, there is a need for well-designed clinical trials for individual antihistamines in higher dose in Indian patients.

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