Efficacy of Rupatadine in Treatment of Chronic Idiopathic Urticaria

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Abstract

Introduction: Urticaria is a vascular lesion of the skin characterized by the appearance of well demarcated wheels along with angioedema. In more than 75% of cases, a causative agent can't be established and thus is termed as chronic Idiopathic Urticaria. Treatment of this condition focuses on measures which provide symptomatic relief; 2nd and 3rd generation anti-histaminic drugs are the mainstays now for the treatment of chronic idiopathic urticaria.

Objectives: To determine the efficacy of rupatadine in the treatment of chronic idiopathic urticaria.

Materials and Methods: A clinical trial was conducted on 60 patients who were suffering from chronic idiopathic urticaria from March to August 2015 at Department of Dermatology and Venereology, Combined Military Hospital (CMH), Dhaka. Tab. Rupatadine 5 mg 1 tab daily was given for 6 weeks. Clinical response of treatment and adverse effect was assessed at every two weeks' interval by taking history and clinical examination. Ethical issue was addressed

Results: The patients reported a considerable improvement in overall chronic idiopathic urticaria due to the use of Rupatadine. The mean total symptom score (TSS) value reduced by 83% compared to the base line evaluation at the end of the therapy duration. Total disappearance of symptom was recorded in 25% patients. There were 79% decrease in the score for number of wheals, 81% reduction in the score for size of the wheals, 88% reduction in the pruritus severity score, and 83% reduction in the duration of pruritus score in relation to baseline evaluation.

Conclusion: 5mg of Rupatadine once daily is effective in patients with chronic idiopathic urticaria.

Key-words: Urticaria, Rupatadine, Anti-histamine.

Introduction

Urticaria is a vascular reaction of the skin characterized by the appearance of wheals, well demarcated, superficial erythematous or pale swellings of the dermis, generally surrounded by a red halo or flare and associated with severe itching, stinging and pricking sensations, rarely lasting for longer than 24-48 hours. When the edematous process extends deeper into the dermis and/or the subcutaneous and the submucosal layers, then it is known as angioedema[1,2]. Traditionally, urticaria classified depending on duration into acute and chronic. When urticaria is present daily or almost daily for less than 6 weeks it can be termed as acute urticaria. If urticaria occurs on most days for longer than 06 weeks, it can be categorized as chronic[3]. On the basis of pathogenesis urticaria can be classified into immunologic, non-immunologic and idiopathic type. Several types of urticaria may coexist in the same person.

In 75% cases of chronic urticaria, the causative agent isn't defined and hence termed as idiopathic. However, it may be associated with autoimmune thyroid disease, chronic infections, especially fungal infection (with Candida albicans), parasitic or bacterial infection (e.g. sinus, urinary bladder, dental), viral hepatitis B and C, connective tissue disease (SLE & sjogrens syndrome), malignant disease, physical stimuli and sensitivity to certain drugs or food additives. An association also exists between chronic urticaria and the major histocompatibility complex allele, HLA-DRB1-04. It has been proposed that H. pylori infection may play an indirect role in autoimmune chronic urticaria by molecular mimicry in genetically predisposed individual. Several dermatologic disorders may present with urticaria lesion. These are bullous pemphigoid, dermatitis herpetiformis, vasculitis, systemic lupus erythematosus (SLE), urticaria pigmentosa, erythema multiforme, and morbilli form drug eruption.

Urticaria is due to a degranulation of mast cell and eosinophil. In chronic urticaria IgG autoantibodies cross-link the alfa chain of high affinity receptor for IgE on mast cells (Fc epsilon R1) which results in histamine release. Complement also augments histamine release. Some neuropeptides also play role in the pathogenesis of urticaria. Moreover, urticaria occurs after direct mast cell degranulation and in relation to activation of cellular arachidonic acid metabolic pathway. Treatment of chronic idiopathic urticaria focuses on therapies that give symptomatic relief. In addition to medication, support and reassurance is very much required in the management of urticaria. In some individual it is aspirin and other NSAIDs should be avoided. Antipruritic lotion, ice packs and cool compresses may provide temporary relief. H1- type antihistaminic drugs are the mainstays in the

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treatment of urticaria. Instead of older sedating first generation drugs newer, second and third generation H1-type antihistamines with low sedative and anticholinergic side effects have become initial therapeutic agent of choice. Initially, antihistaminic drugs should be administered at a lower dose and then it should be increased to tolerance. Rather than taking as needed, the drug should be taken on a regular basis. Among the second-generation antihistamines loratidine, cetirizine, acrivastin, fexofenadine are now being used.

Rupatadine is a newer selective non-sedating long-acting H1-antihistamine which was approved for the treatment of allergic rhinitis and Chronic spontaneous urticaria. Along with its antihistaminic property, rupatadine can also antagonize platelet activation factor (PAF) and inhibit the secretion of proinflammatory cytokines by mast cells. This drug has shown effectiveness in the treatment of CSU at a dose of 10 mg/day[4-6]. Rupatadine demonstrated dual activity as an antagonist of the histamine Hi and PAF receptors in a number of in vitro biochemical assays and in vivo animal models[7-9]. The longer term tolerability and cardiac safety of the drug have been assessed according to ICH and EMEA guidance, and rupatadine is the first of the currently available second-generation Hi-receptor antagonists to undergo the ICH 'thorough QT/QTc testing'. This study was done in order to evaluate the efficacy of this new drug in treatment of CIU in light of Bangladesh.

Materials and Methods

A clinical trial was conducted from 1st March 2015 to 31st August 2015 at Department of Dermatology and Venereology, CMH, Dhaka. A total of 60 patients of both sexes, aged from 15 to 50 years and suffering from chronic idiopathic urticaria were selected as study population. However, patients suffering from drug and food induced urticaria, physical urticaria or urticarial vasculitis were excluded. Pregnant and lactating mother or patient with severe renal impairment were also excluded. We sought an informed consent from the patient in order to take part in the study. Ethical issue was addressed. Patients' data were recorded on predesigned record form. Tab. Rupatadine 5 mg 1tab daily was given for 6 weeks. Clinical response of treatment was assessed at every two weeks interval by taking history and clinical examination. Assessment of adverse effect of rupatadine was also carried out. In addition to history and clinical examination, lab investigations like routine blood examination; TC, DC, Hb%, ESR, platelet count, serum IgE, TCEC, urine routine examination, stool routine examination, thyroid function test, thyroid antibody, serum creatinine, blood urea, liver function test were also done.

After giving rupatadine 5mg once daily for 6 weeks all patients were examined clinically at 2nd, 4th and 6th week period. Treatment efficacy was assessed by number and size of wheal, severity and duration of pruritus. Efficacy measures were scored using the following scale: pruritus: 0(no pruritis), 1(mild pruritus), 2(moderate pruritus) and 3 (severe pruritus): duration of pruritus: 0(none), 1(less than 1 hour), 2(1-6 hour), 3(more than 6 hours); number of wheals: 0(none), 1(I- 6 wheals), 2(6-12 wheals), 3(more than 12 wheals); size of wheals (mean diameter): 0(no lesion), 1(<1.3 cm),2(1.3-2.5 cm),3(>2.5cm). The maximum value of the total symptoms score (TSS) was around 12.8.

Results

Among 60 chronic urticaria patients 30 were male and 30 were female. The mean age of the patient was 26.8 years and range 15-49 years. The median duration of disease is 11.7 months. Patients reported that they experienced a significant improvement in overall chronic idiopathic urticaria in all study visits. At the end of the therapy, there was a reduction of 83% of the mean TSS compared to the baseline evaluation. The value was decreased by 43% and 61% at 2nd week & 4th week follow up period respectively (Fig 1). Throughout the trial there was reduction in mean score for pruritus. At the end of the active treatment of 6 weeks a reduction of pruritus severity by 88% was recorded compared with the baseline evaluation. The value was decreased by 50% and 65% at 2nd & 4th week follow up period respectively. Moreover, the mean pruritus severity score was 2.47 at baseline evaluation and it was 1.23 and 0.86 at 2nd and 4th week follow up period. At the end of 6 weeks' treatment it was 0.3 (Table-I).

The duration of pruritus was also significantly shorter. At the end of the active treatment the duration of pruritus was decreased by 83%, compared with baseline evaluation. At 2nd and 4th week follow-up period these reductions were 47% and 60% respectively. The mean duration of pruritus was 1.76 at base line evaluation and it was 0.93, 0.72, and 0.3 at 2nd, 4th and 6th week follow up period respectively (Table-II). There was reduction of the number of wheals score throughout the trail. During the six weeks' treatment period Rupatadine produced a 79% decrease in the scores for number of wheals compared with baseline evaluation. At 2nd and 4th week follow-up period the reductions were 36% and 56% respectively. The mean number of wheal score was 2.1 at baseline and it became 1.33, 0.93 and 0.43 at 2nd, 4th & 6th week follow up period respectively (Table-III). The size of the wheals scores also reduced through the study period. Throughout the whole 6 weeks of active treatment, rupatadine achieved an 81% decline in the scores for the size of wheals compared with baseline evaluation. These reductions were 39% & 61% at 2nd and 4th weeks of treatment follow up period respectively. The mean size of wheals score was 2.4 at baseline

evaluation. And it was 1.47, 0.93, and 0.47 at 2nd, 4th and 6th weeks of follow up period respectively (Table-IV).

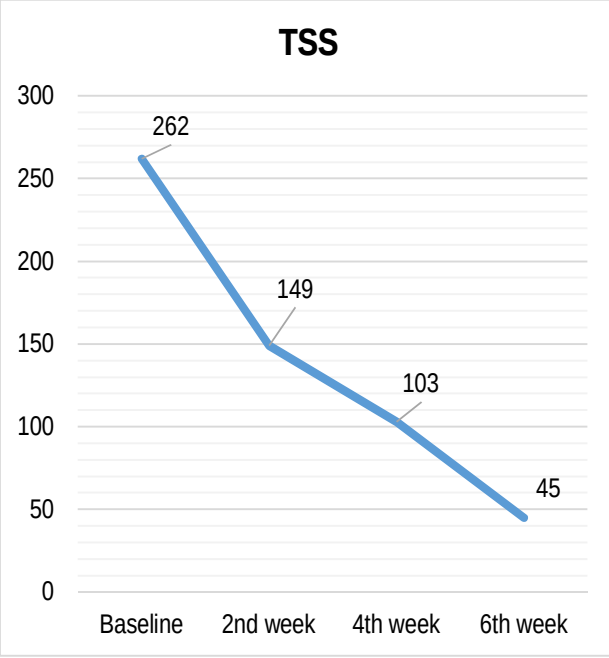

Figure-1: Total symptom score(TSS) of patients' base line to 6 weeks.

Table-I: Therapeutic response by pruritus severity score (n=60)

Pruritus score	Baseline n(%)	2nd week n(%)	4th week n(%)	6th week n(%)
0(None)	0	8(13.3)	22(36.7)	44(73.3)
1(Mild)	4(6.7)	30(50.0)	24(40.0)	14(23.3)
2 (Moderate)	24(40.0)	22(36.7)	14(23.3)	2(3.3)
3 (Severe)	32(53.3)	0	0	0
Total score	74	37	26	09

Table-II: Therapeutic response by duration of pruritus score (n=60)

Duration pruritus score	Baseline n(%)	2nd week n(%)	4th week n(%)	6th week n(%)
0(No pruritus)	0	12	22	44
1 (<1h)	26	40	34	14
2 (1-6h)	22	8	4	2
3 (>6h)	12	0	0	0
Total score	53	28	21	09

Table-III: Therapeutic response by number of wheal score (n=60)

Wheal score	Baseline n(%)	2nd week n(%)	4th week n(%)	6th week n(%)
0(None)	0	6	18	36
1 (1-6)	10	28	28	22
2 (6-12)	34	26	14	2
3 (>12)	16	0	0	0
Total score	63	40	28	13

Table-IV: Therapeutic response by size of wheal score (n=60)

Wheal score	Baseline n(%)	2nd week n(%)	4th week n(%)	6th week n(%)
0-(None)	0	6	14	36
1-(<1.3cm)	6	24	36	20
2-(1.3-2.5cm)	24	26	10	4
3- (>2.5cm)	30	4	0	0
Total score	72	44	28	14

Discussion

The total symptomatic score determines the efficacy of the drug. A reduction in the total score indicates that there is an overall clinical improvement[10]. We found significant reduction in the mean total symptom score (MTSS), Mean score for number of wheals (MNW)and mean score for pruritus severity (MPS). This finding concurs with those of previous studies of rupatadine[11,5]. The etiology of CsU is multifactorial, although it mainly refers to histamine, platelet activating factor, along with a various other cytokine. Platelet activation factor is a mediator of inflammation causing an increase in vascular permeability[12]. It is known that both Platelet activating factor (PAF) and histamine complement and promote the secretion of one another[13]. Both of these are inhibited by Rupatadine. This results in a more inhibitory effect on the vasodilatation, vascular leakage, edema, wheal formation, pruritus, and eosinophil chemotaxis which is normally produced by these mediators[14]. Rupatadine has also shown potent antiallergic activity in vitro (i.e. it inhibits the degranulation of mast cell). It has shown its activity in vivo in several type I

hypersensitivity models as well. Beside these Rupatadine also has anti-inflammatory effects that act directly on H1 receptors. This drug has a high H1 receptor-binding affinity. This allows Rupatadine to inhibit histamine-induced interleukin-6 and interleukin-8 production using concentrations that are below plasma levels at the therapeutic dose[15,16].

This study has also shown 5mg of Rupatadine taken once a day is effective and well tolerated in the therapy of chronic idiopathic urticaria. At the end of the therapy, there was a reduction of 83% of the mean TSS whereas the total disappearance of symptom was recorded in 15 patients (50%). There was a 79% decline in the score for number of wheals, 81% decline in the score for size of the wheal and 88% reduction in the pruritus severity score which correlate with the results achieved of previous studies[11-13,16]. In this study 80% (24) patients were between 15-35 years and the mean age group is 26.8 years which is supportive of other's finding[4]. This occurs with the observation that urticaria is most common in these age groups. In the present study male and female ratio was found equal that is 1:1 with the reflection that urticaria affects both sexes equally which is similar to the study by Dubertret L et al[11].

Conclusion

Treatment of chronic idiopathic urticaria should improve both symptoms & quality of life. 5mg of Rupatadine once a day is an effective treatment choice in patients with chronic idiopathic urticaria, as its action provides a rapid and adequate control of symptoms along with the subjective disease measures.

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