

Study of Effectiveness of Combined Antiallergic Drug Dualler-G

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Abstract: The secretory granules of mast cells contain several mediators, some of which, such as histamine and serotonin, are known to participate in many immune reactions and allergic diseases. Allergic reactions play the leading role in pathogenesis of dermatitis and mechanism of such reactions is based on release of histamine and serotonin. Due to this, the development of drug with both antihistamine and antiserotonine activity was the goal of this study. Drugs with close chemical structure and pharmacological activity were selected from derivatives of quinuclidin carbinols. This difference in pharmacological activity of different compounds makes Dualler-G, a new antiallergic drug with antihistamine and antiserotonine activity. The goal of the study was clinical trial of Dualler-G in patients with allergic dermatosis. Obtained data shows that Dualler-G shows high effectiveness in treatment of different types of dermatosis. The effect of Dualler-G, an original antiallergic drug, was evaluated in patients displaying different kinds of dermatosis (urticaria, eczema). A total of 22 patients diagnosed with dermatosis were randomized to receive in an open fashion 40 mg of Dualler-G per day, for 2 weeks. Efficacy was assessed according to the common improvement of pathological elements on skin or itching as symptom. Clinical course of patients treated with Dualler-G tended to be significantly better than the patients treated with other antiallergic preparations and the symptoms were significantly correlated in the Dualler-G treated group. These data suggest that Dualler-G provides direct efficacy on the symptoms (skin elements and itching) in patients with different kinds of dermatosis.

Key words: New antiallergic drug allergic reaction, dermatosis, histamine, serotonin.

1. Introduction

Histamine is a major mediator in the pathophysiology of the allergic response and, as such, is a primary target for therapeutic intervention. H1-receptor antagonists constitute the therapy of choice for inhibiting the inflammatory effects of histamine release and the inhibition of other proinflammatory activities that occur subsequent to histamine release [1, 2]. Some of the H1-receptor antagonists also have antiallergic effects that do not appear to be mediated through the H1 receptor; these include inhibition of histamine release and the inhibition of the release of such other proinflammatory agents as cytokines, chemokines, and adhesion proteins

[3]. ACD (allergic contact dermatitis) is a common clinical condition leading to considerable morbidity. As demonstrated [4] that ketanserin, a serotonin antagonist, significantly inhibits nickel sulphate-induced ACD. Furthermore, IR (serotonin-immunoreactive) cells have previously been demonstrated in normal human cutaneous melanocytes [5, 6]. In our study the effectiveness of preparation with both antiserotonin and antihistamine activity was the subject of interest.

2. Objective

This experimental study is aimed to investigate the effectiveness of antihistamine quifenadine (H1 blocker) and sequifenadine (H1 and 5HT serotonin receptor antagonist) and their combination in rats.

Clinical trial of Dualler-G, a combined preparation consisting of two quinuclidylcarbinol derivatives

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(quifenadin 10 mg and sequifenadine 10 mg), provides a dual pharmacological-antihistamine and antiserotonin effect.

3. Materials and Methods

Preclinical study in rats (Wistar) was performed by the method of determining the dextral edema of the paws. Fasting rats (12 animals in each group) were injected with 0.05 mL of 0.6% dextran (right foot) or saline vehicle (left foot) 1 hr after receiving methylcellulose vehicle (control group) quifenadine 30 mg/kg (group 1) sequifenadine 30 mg/kg (group2) or mixture of quifenadine 15 mg and sequifenadine 15 mg. After 30 min, the diameters of paws of rats were measured. The dose that resulted in 50% inhibition of edema (ED50) was calculated, and 95% confidence intervals were determined by the linear least-square dose-response method.

Clinical research was carried out at the Department of Dermato-Venerology of (TSMU) according to the protocol approved by the pharmaceutical agency of the Ministry of Health of Georgia on patients with various types of skin-allergic diseases using the drug of comparison was quifenadine. Clinical research was conducted in the department of skin-venereal diseases of TSMU on patients with various types of skin-allergic disease. Approbation of the drug was performed in 30 patients, 22 of them (the group of patients studied) took Dualler-G and 8 (the comparison group) took the drug fencarol. The study group of patients underwent Dualler-G treatment at a dose of 0.02 g per day. A general blood test was performed before and after treatment in the comparison group, phenarol was taken at a dose of 0.025 g per day. The excluding criteria for trial were pathology of the cardiovascular system, liver, stomach and duodenal ulcer, pregnancy and personal refusal to participate in the study.

4. Results

4.1 Results of the Experimental Study

The results of the experimental study are presented

in Table 1 and Fig. 1. As can be seen from the data presented, the simultaneous administration of quifenadine and sequifenadine significantly increases ($p < 0.001$) anti-edema effect of which reaches 80%. The same indicator for separately administered quifenadine and sequifenadine is 20% and 30% respectively.

Twenty-four hours after the administration, a pronounced effect is also observed with the combination of drugs, and sequifenadine whereas the action of quifenadine is completely absent.

4.2 Results of Clinical Trial

According to the results of the treatment (presented in Table 2) in a group of 22 patients (5 cases of neurodermitis, 5-atopic neurodermitis, 5 cases of urticaria, 3 cases of toxoderma, 1 red lichen, 1 eczema, 2 cases of psoriasis). Clinical course of patients treated with Dualler-G tended to be significantly better than the patients treated with drug of comparison "fencarol" (quifenadine). Patients treated with Dualler-G (cases of urticaria, neurodermitis, lichen rubber planus) had superior improvements in their symptoms (elements on skin and itching) compared to controls overall across the 2-week trial, but not in cases of eczema. However, care cases of eczema level of eosinophils was reduced and severity of symptoms as well.

5. Discussion

Our experimental studies indicate the potentiated synergy of the quifenadine and sequifenadine, the effect of the anti-edema action of the combination on the dextran edema of the paws in rats is superior to the effect of quifenadine or sequifenadine by 280-300%, and also exceeds the duration of action of sequifenadine by 24 hours, which is explained by the specific mechanism of action of quinuclidins associated with lowering the level of histamine in tissues by activation of diaminoxidase (the enzyme that metabolizes histamine) [7].

Results of clinical trial shows that patients treated with Dualler-G (cases of urticaria, neurodermitis, lichen

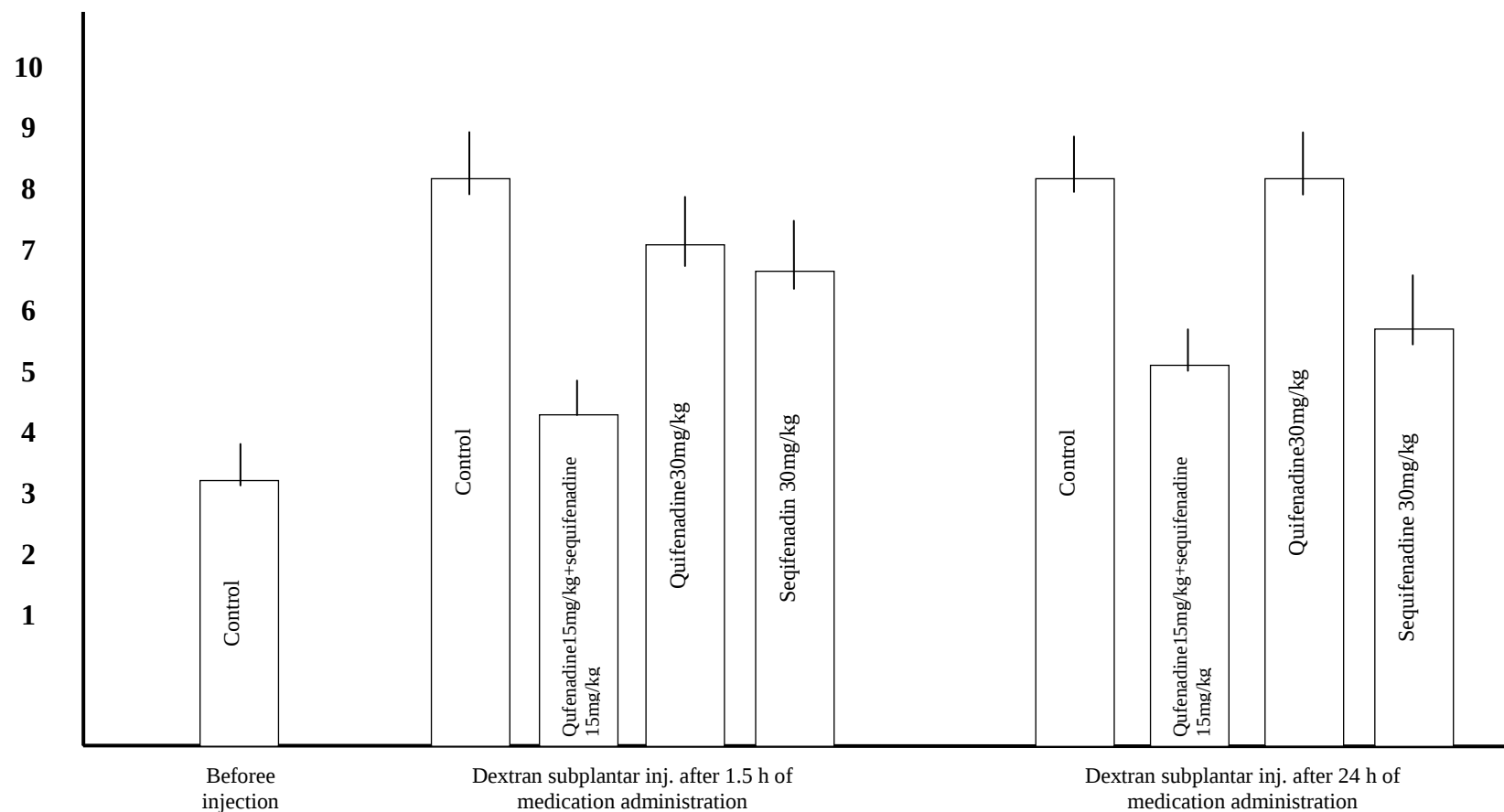


Fig. 1 Effect of drugs and their combination on rat foot diameter (mm) caused by subplantar injection of dextran.

Table 1 Effect of drugs and their combination on rat foot diameter (mm) caused by subplantar injection of dextran.

Time after injection of antihistamines	Control			Quifenadine 30 mg/kg			Sequifenadine 30 mg/kg			Quifenadine(15 mg/kg)+sequifenadine (15 mg/kg)		
	Without dextran	30 min after dextran	Increase of diameter as % of initial	Without dextran	30 min after dextran	Increase of diameter as % of initial	Without dextran	30 min after dextran	Increase of diameter as % Of initial	Without dextran	30 min after dextran	Increase of diameter as % of initial
90 min	3.8 ± 0.1	8.3 ± 0.2	118	4.1 ± 0.23	7.6 ± 0.3	85	3.8 ± 0.1	7.0 ± 0.4	84	3.8 ± 0.08	4.7 ± 0.04	23

Table 2 Results of clinical trial.

Group	Dinamics	Signs eliminated		Significant improvement		Without improvement	
		absolute	%	abs	%	abs	%
1		11	50	9	40.9	2	9
2		-	-	2	25	6	75

rubber planus) had superior improvements in their symptoms (elements on skin and itching) compared to controls overall across the 2-week trail, but not in cases of eczema. Level of eosinophils was reduced and severity of symptoms as well. Clinical course of patients treated with Dualler-G tended to be significantly better than the patients treated with drug of comperison. These data suggest that Dualler-G provides direct high efficacy on the symptoms (skin elements and itching) in patients with different kinds of dermatosis.

It can be explained by combined antiserotonin and antihistamine effects of Dualler-G. As it was noted above [4] serotonin plays important role in pathogenesis of allergic dermatitis.

Clinical course of patients treated with Dualler-G tended to be significantly better than the patients treated with drug of comparison "fencarol". Taking into account the known role of serotonin in allergic reactions of the skin, it is quite logical that the drug with a complex (antihistamine and antiserotonin) effect is more effective in comparison with the drug that is justly antihistamine. When receiving 100 mg of preparation once, no side effects were observed.

6. Conclusions

Potentiated synergism is observed beetwin two antiallergic substances Quifenadine and Sequifenadine in experiments on rats.

Based on this data new antiallergic combined drug Dualler-G was developed. Clinical trials of Dualler-G showed its high therapeutic effectiveness. In 90% subjects, a pronounced therapeutic effect was observed. The results of the study testify that Doualer-G has a

pronounced antiallergic effect, superior to drug of comparison (H-1 blocker qufenadine). It should be noted that the drug is rapidly absorbed, so effect is observed after 15-30 minutes after administration and is maintained for 12-24 hours, depending on the dose. In therapeutic doses (20-40 mg/day) no side effects were observed.

Based on our study, we can argue that the treatment with drugs with antihistamine and antiserotonin properties (like Dualer-G) in some cases can be much more effective than treatment with only antihistamine (H-1 blockers) drugs.

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