

New Progress in Pharmacodynamics and Application of Lupatadine

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Abstract: *Lupatadine has dual antagonistic effect, which can play an obvious antagonistic effect on histamine H1 receptor and platelet activating factor receptor. It is a new type of anti allergic drug, which can effectively inhibit inflammation in all stages of allergic reaction. This drug has the characteristics of rapid onset and long-lasting effect. It is recommended to take orally once a day in clinical application. Clinical studies have shown that oral low-dose of lupalatadine can effectively relieve the symptoms of seasonal and perennial allergic rhinitis. With the deepening of relevant research in recent years, it has been found that lupalatadine has good therapeutic effect on skin diseases such as chronic urticaria, and patients have better tolerance to this drug. In this paper, through the relevant literature review, summarize and analyze the new progress of pharmacodynamics and application of lupalatadine, mainly from the drug effect and clinical application.*

Keywords: *Lupatadine; Pharmacological action; Histamine H1; Chronic urticaria*

1. Introduction

Lupatadine is an antiallergic drug. It is the only drug on the market that can antagonize the activity of platelet activating factor (PAF) as well as diamine resistance. It is widely used in the treatment of seasonal and perennial allergic rhinitis. Histamine contains the most inflammatory mediators, most of which exist in the early stage of allergic reaction or at the beginning of symptoms. Antagonistic platelet activating factor is another important inflammatory mediator in airway inflammation. Lupatadine can block platelet activating factor and histamine at the same time, which shows good effect in clinical application. In this paper, its pharmacodynamics and application progress are summarized as follows.

2. Pharmacological action

The occurrence of early inflammation is related to the release of histamine by mast cells and basophils stimulated by antigen. Platelet activating factor (PAF) is an important inflammatory mediator in the late stage of allergic reaction, and plays an important role in the occurrence of urticaria and allergic rhinitis [1-2]. They can complement each other and release histamine in different tissues. In the past animal experiments, lupalatadine has shown strong antihistamine and platelet activation, and can effectively inhibit the activities of many granulosa cells, and has different degrees of inhibitory effect on the release of some cytokines.

2.1. Inhibition of H1 histamine receptor

In the past, some researchers compared and analyzed the antihistamine activity of lupalatadine and other antihistamines through the ileum function experiment of guinea pigs. The results showed that the antihistamine activity of lupalatadine was stronger than that of other antihistamines. However, no such effect was found in the use of loratadine. Lupatadine significantly inhibited the gene expression of histamine H1 receptor and bradykinin receptor B2 [3-4].

2.2. Inhibition of platelet activating factor receptor

From a number of existing in vitro and animal model experiments, the effect of lupalatadine on platelet activating factor activity is very significant. Studies have shown that the concentration of lupalatadine is set at 2.5 μ Mol / L and 25 μ Mol / L. However, diphenhydramine 25 could significantly inhibit the inhibition of

platelet activating factor induced by human lad2 mast cells and the release of interleukin μ Mol / L does not achieve this effect.

2.3. Other anti-inflammatory effects

Degranulation of mast cells is an important step in the early stage of allergic reaction, and eosinophils are the key cells in the later stage of allergic reaction. From the clinical pharmacological studies of lupatadine, this drug can effectively inhibit mast cell degranulation, effectively reduce the secretion of bioactive substances by these cells, effectively inhibit mast cells to release a variety of pro-inflammatory cytokines, and inhibit the release of other bioactive substances^[5-6]. In addition, lupatadine has a significant inhibitory effect on eosinophil chemotaxis in ovalbumin induced allergic guinea pigs, and can reduce the release of TNF- α from human mast cells, and has a good inhibitory effect on the expression of adhesion molecules in endothelial cells, and can effectively reduce the infiltration reaction of local inflammatory cells.

2.4. Pharmacokinetic characteristics

The absorption rate of lupatadine is faster when used orally, and the plasma concentration can reach the peak in a short time. In practical clinical application, the best effect of single dose of lupatadine is 4 hours after administration, the efficacy of the drug can last for 24 hours, and the half-life of the drug is about 6 hours. Relevant studies have pointed out that lupatadine is mainly metabolized by CYP3A4 in vivo, and no other gene polymorphisms have been found in the process of metabolism. However, the metabolic reaction of lupatadine in human body is mainly completed by liver and gallbladder^[7-8].

3. Clinical application

3.1. Chronic urticaria

The efficacy of loratadine in the treatment of patients with chronic urticaria will be significantly improved by more than 50% of the patients treated with loratadine. However, if desloratadine is used, it requires 4 times the standard dose to achieve this effect^[9-10]. Relevant studies have shown that for patients with chronic spontaneous urticaria, cetirizine and lupatadine were given respectively. The results showed that the clinical symptoms of patients with cetirizine were significantly relieved after 3 weeks of treatment, and the improvement of patients' condition by lupatadine was more significant in the same period.^[11] In addition, after 6 weeks of treatment, the average number, size and erythema of patients treated with lupatadine were significantly relieved, and the treatment effect was significantly better than cetirizine, which indicated that lupatadine was more significant than cetirizine in the treatment of chronic spontaneous urticaria (M21).

In related clinical studies, a total of 100 patients with chronic idiopathic urticaria, 50 patients received levocetirizine 5mg / D, the other 50 patients were treated with lupatadine 10mg / D. The efficacy was evaluated by urticaria activity score and skin disease quality of life score, and the adverse drug reactions were evaluated by critical flicker fusion threshold test and visual analogue scale. The results showed that the score of urticaria activity decreased to 0.10 in levocetirizine group and 0.38 in lupatadine group. Although the symptoms of both groups were improved, the improvement of levocetirizine group was more obvious. The scores of skin disease quality of life decreased in both groups, but the decrease was more obvious in levocetirizine group. Drowsiness was the most common adverse reaction in both groups. Based on the critical flicker fusion threshold test, the levocetirizine group had more obvious psychomotor injury, and the visual analog scale showed that both groups had certain sedative effect. Therefore, clinical research shows that levocetirizine is better than lupatadine in the treatment of chronic idiopathic urticaria, but the two drugs can play a significant role in improving the quality of life and clinical symptoms of patients, and can play a slight sedative effect.

3.2. Cold urticaria

The pathogenesis of the disease is related to the release of histamine and PAF factor. As an antagonist of histamine H1 receptor and PAF receptor, lupatadine can effectively control the symptoms of the disease. In a controlled trial, 21 patients with cold urticaria were treated with lupatadine 20 mg / D and placebo for 1 week. Results the evaluation standard was the critical stimulation time threshold. The skin was exposed to cold environment to observe the wind mass, pruritus, burning and other discomfort. The

results showed that the improvement of symptoms after taking rupatadine was significantly better than that of placebo, and 11 out of 21 patients completely disappeared, including wheeze, itching, burning and other discomfort. The results showed that 20 mg of rupatadine daily could effectively improve the symptoms of cold urticaria, and it was well tolerated.

Studies have shown that for some patients with cold urticaria resistant to other H1 antihistamines, rupatadine can play a better effect, and there is no significant difference between the two doses of 10mg/D and 20mg/d. However, due to the limited number of cases, the conclusion needs to be confirmed by large sample study. In a double center, randomized, double-blind, placebo-controlled clinical study, researchers evaluated the efficacy and safety of increased doses of rupatadine in the treatment of cold urticaria. A total of 23 patients were randomly divided into three groups: placebo, 20 mg / D rupatadine and 40 mg / D rupatadine for 1 week. The results showed that 20 mg / D and 40 mg / D rupatadine could effectively reduce the critical temperature threshold and stimulation time threshold, but the adverse reactions did not increase.

3.3. Mastocytosis

Mastocytosis is a group of heterogeneous diseases in which clonal mast cells gather, distribute and infiltrate in one or more organs in multiple foci or clusters. According to the location and extent of the lesions, such diseases can be divided into cutaneous mastocytosis and systemic mastocytosis. In addition, many patients with tachycardia after treatment with clopidogrel, as well as other symptoms of pruritus, appear in patients with different degrees of pruritus after treatment. However, for patients with intestinal adverse reactions, there was no significant improvement in intestinal symptoms [12-13].

4. Security

Rupatadine is well tolerated in clinical application, it will not have adverse effects on the heart of patients in the process of use, and the overall safety is high, which is also an important reason for its recognition in clinical application [14]. The most common adverse reactions were headache, followed by drowsiness, fatigue, weakness and dry mouth, most of which were mild to moderate adverse reactions. Moreover, the occurrence of these adverse reactions is mostly closely related to the patient's disease itself, not entirely caused by drugs [15-16]. In the course of using rupatadine, it can be found that the drug has high selectivity for peripheral nerve receptor, low affinity for hi receptor in central nervous system, low permeability of blood-brain barrier and no sedative adverse reaction. The combination with lorazepam did not increase the inhibitory effect of central nervous system. Oral administration of 10 mg / D of rupatadine did not affect driving ability. The healthy volunteers were given 10.20.40 and 80 mg of rupatadine and 25 mg of hydroxyzine respectively. Results the cognitive and psychomotor effects of low-dose (10.20 mg) rupatadine were similar to those of placebo. Only high-dose rupatadine (80 mg) and hydroxyzine had obvious central nervous system inhibitory effect.

Through the study of healthy people, it is found that the healthy people can better tolerate 4 times of the recommended dose of rupatadine, but for the erythematous reaction of platelet activating factor and histamine, the curative effect can last about 72 hours. After 40 mg of rupatadine was given to healthy male volunteers, only transient drowsiness was observed. There was no obvious abnormality in supine blood pressure, heart rate and electrocardiogram. Among healthy young volunteers, 20 mg of rupatadine combined with alcohol had more cognitive and mental impairment than drinking alone. However, no significant effect was found when 10 mg of rupatadine was taken with wine. In vitro experiments, more than 400 times of normal blood concentration of 20 mg of rupatadine is required to block the cardiac potassium channel.

Drug induced prolongation of QT interval can increase the risk of ventricular arrhythmia. This problem once plagued the use of antihistamines. In a clinical study of 160 healthy volunteers, the routine clinical trial of arrhythmia induced by the research drug "comprehensive QT / QTc study" was given with 10 mg / D, 100 mg / D and placebo respectively for 5 days. The results showed that there was no significant change in ECG of patients with rupatadine 10 mg / D and 100 mg / d. This study further confirmed that rupatadine has no risk of arrhythmia.

5. Medication for special population

Rupatadine has been shown to be effective and safe in the treatment of adult allergic rhinitis and

urticaria. In recent years, lupatadine has been approved for the treatment of allergic rhinitis in children aged 6-11 years. The efficacy of lupatadine in the treatment of spontaneous urticaria was evaluated in children aged 2 to 11. A total of 199 patients were enrolled, including 63 patients in the lupatadine group (1 mg / ml), 69 in the desloratadine group (0.5 mg / ml), and 67 in the placebo control group. According to the body weight, the corresponding dose of oral liquid medicine was given (10 ~ 25 mg body weight was given to 2.5 ml > 25 kg patients were given 5 ml), the course of treatment was 6 weeks, and the follow-up observation was 6 weeks after the end of treatment. The results showed that compared with the placebo group (- 30.3%), the urticaria activity score was significantly decreased in the lupatadine group (- 55.8%, $P = 0.001$) and the desloratadine group (- 48.4%, $P = 0.013$). In addition, children's skin disease quality of life score was significantly improved in the treatment group, and the incidence of adverse events was similar between the treatment groups. The results showed that lupatadine was safe and effective in the treatment of 2-11 years old children with chronic spontaneous urticaria.

6. Conclusions

Lupatadine is often used in the treatment of urticaria and allergic rhinitis. It has a good inhibitory effect on histamine and platelet activating factor, can effectively inhibit the activity of some granulosa cells, and has certain inhibitory effect on the release of cytokine activity. In terms of anti-inflammatory, lupatadine can effectively reduce the occurrence of local inflammatory cell infiltration reaction, and has certain anti-inflammatory effect. Lupatadine in clinical application, patients for this drug tolerance is generally good, usually, patients will not appear obvious adverse reactions, clinical application safety is high. In addition, lupatadine can inhibit allergic reactions in different links of inflammation, which provides a new choice for drug treatment of allergic diseases. Although the current clinical approved indications for lupatadine mainly include seasonal and perennial allergic rhinitis, according to the mechanism of action of this drug and a large number of clinical studies, lupatadine also has great development potential in the treatment of some allergic diseases such as chronic urticaria, which needs to be further studied in the future, it should be put into clinical application as soon as possible.

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