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A review: Ketotifen in its treatment of allergic rhinitis (AR) and relevant disease

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Abstract. Allergic rhinitis (AR) is a common disease in the world, which causes various adverse effects on quality of life. There are over 1 billion AR patients globally, with over 300 million cases in China alone. AR is closely related to asthma, 70.3% of children with AR can develop to asthma, and 80-95% of asthmatics have AR. To address the correlation between these two diseases, in 2015, the World Health Organization (WHO) put forward the idea of "the same airway, the same disease". Although a relatively low mortality rate, AR confers a significant burden on personal health and society. Ketotifen was an old medicine for asthma and AR etc., invented in 1970. In experiments with rat models and rat peritoneal mast cells, Ketotifen has been demonstrated to effectively inhibit histamine release induced by substances like 48/80. Ketotifen has been proven effective in treating AR and relevant diseases in clinics. We will review the mechanisms of ketotifen in treating AR for further study.

Keywords: Allergic rhinitis (AR), Ketotifen, asthma

1. Introduction

AR is a common disease in the world, which causes various adverse effects on quality of life. There are over 1 billion AR patients globally, with over 300 million cases in China alone. Characterized by its persistent nature, it serves as a precursor to chronic illnesses. To address the correlation between these two diseases, in 2015, the World Health Organization (WHO) put forward the idea of "the same airway, the same disease". AR confers a significant burden on personal health and society. Severe AR significantly disrupts the sleep of 70% of affected individuals and hampers the daily lives and work of 94% of sufferers. Its adverse effects on quality of life surpass even those of major diseases like hypertension and diabetes. Moreover, AR often coexists with some symptoms such as sinusitis, otitis media, nasal polyps, and asthma, amplifying the health risks and imposing a substantial burden on individuals and society.

Being invented in 1970, Ketotifen was an old medicine for asthma treatments and AR, etc. In experiments with rat models and rat peritoneal mast cells, Ketotifen has been demonstrated to effectively inhibit histamine release induced by substances like 48/80. For its safety and cheap merits, Ketotifen is still used in the market till now. We want to introduce what is AR and asthma, and review the information about the properties of pharmacokinetics and clinical application of Ketotifen in treating AR and relevant disease.

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2. Overview of disease

2.1. Allergic rhinitis (AR)

DEFINITION

Allergic rhinitis is an upper respiratory tract inflammatory disease, caused by exposure of sensitive individuals to allergens resulting in immunoglobulin E (IgE) - a mediated inflammation generated in the nasal passages. AR consists of one or more of the following symptoms: itching of the nose, sneezing, nasal discharge, and nasal congestion [1]. It is often accompanied by itching of the palate, throat, ears, and eyes, as well as redness, swelling, and watery discharge from the eyes. The disease can be categorized into different types according to the causative mechanism, with an allergy to certain substances being an important cause and a relationship with relevant occupational exposures. Allergic rhinitis is closely related to asthma; 70.3% of children with allergic rhinitis can develop asthma, and 80-95% of asthmatics have allergic rhinitis. To address the correlation between these two diseases, in 2015, the World Health Organization (WHO) talked about the impact of allergic rhinitis and asthma, then the idea of "the same airway, the same disease" was put forward.

2.2. Prevalence in the World

In the United States, self-reported rates of AR stand at 40% among children and range from 10% to 30% among adults [2-4]. However, data from Canada indicate a higher prevalence, with up to 20% of the population diagnosed with AR by physicians [5]. In 2011, an epidemiological survey encompassing residents from mainland China in 18 major cities, the standardized prevalence of AR was found to have risen from 11.1% to 17.6% over the preceding 6 years [6], leading to an increase of 100 million individuals afflicted by the condition.

Allergic rhinitis, characterized by its persistent nature, serves as a precursor to chronic illnesses such as asthma, chronic obstructive pulmonary disease, cardiovascular and cerebrovascular disorders, diabetes, and other systemic chronic ailments. Given its high incidence and propensity for recurrent episodes, there are now over 1 billion AR patients globally, with more than 300 million cases in China alone. Although it possesses a relatively low mortality rate, its impact on personal health and society is substantial.

Severe AR significantly disrupts the sleep of 70% of affected individuals and hampers the daily lives and work of 94% of sufferers. Its adverse effects on quality of life surpass even those of major diseases like hypertension and diabetes. Moreover, AR often coexists with some symptoms such as sinusitis, otitis media, nasal polyps, and asthma, amplifying the health risks and imposing a substantial burden on individuals and society. Medical expenditures for the treatment of AR nearly doubled from 2000 to 2005, escalating from $6.1 billion to $11.2 billion [7].

2.3. Mechanism of AR

First, proteases from the invasion of the antigen promote penetration of the nasal epithelial barrier and release compounds – cytokines - including IL-25, IL-33, and so on. These cytokines cause the polarization of dendritic cells, then interact with Lymphocytes causing type 2 helper (Th2) cells into a cascade of events. What comes next, dendritic cells would then process allergens, and pass them to naive T-cells and B-cells. Then specific T-follicular helper cells, Th2 lymphocytes, and lymphoid cells produce IL-4, 5, 13 to stimulate B-cells to generate IgE, which could combine receptor FceR1 on nasal mast cells. After initiating the allergic response, mast cells amplify such response by releasing vasoactive substances and cytokines, including TNF-α, GM-CSF, TGF-β, IL-1 to IL-6, and IL-13 [8-10]. It triggers mucus secretion and vasodilation resulting in nasal congestion, enhanced vascular permeability causing edema, and provoking of sensory nerve fibers, induced sneezing.

Important steps in the mechanism of AR include the production of large amounts of IgE, mast cell activation, histamine release, and cellular infiltration.

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3. Ketotifen

3.1. Pharmacokinetic Properties

General Properties

Ketotifen is a compound with a molecular weight of 425.5, and it usually can be seen in the form of a salt with fumaric acid, and the chemical name Ketotifen Fumarate.

Chemical Formula: $C_{19}H_{19}NOS$ [11]

When antigens enter the body, they trigger the release of mediators. These mediators are responsible for inducing symptoms such as asthma in individuals with AR. Ketotifen's mechanism of action involves blocking the release of these mediators from isolated lung tissues and cells. Numerous studies, including experiments with rat models and rat peritoneal mast cells, have demonstrated that Ketotifen effectively inhibits histamine release induced by substances like 48/80[12]. By inhibiting histamine release, Ketotifen can alleviate the symptoms associated with antigen exposure.

Furthermore, experiments conducted on rats and guinea pigs *in vivo,* have shown that Ketotifen acts as an effective suppressor in allergic reaction models, whether administered parenterally or orally. Among asthma patients, even in short-period treatments or using it as a single dose, Ketotifen continually suppresses both sudden and postponed responses triggered by allergens and causes reactions to histamine, without affecting responses to acetylcholine [13].

Ketotifen is well absorbed orally, reaching top plasma concentrations in approximately 2 to 4 hours after Regular dosage forms are administered. However, information about absorption from these kinds of treatments is limited. The drug's bioavailability is around 50% because of the 'first pass' effect. When it comes to multiple oral treatments, using doses of 1mg twice daily, peak plasma concentrations could be measured in adult experiments at a level of 1.92 mg/L and in children experiments at 3.25 mg/L, respectively. Approximately 75% of the drugs have an effect to do with plasma proteins [14].

Ketotifen undergoes extensive metabolism, primarily yielding nor-ketotifen pharmacologically active and inactive ketotifen-N-glucuronide. These metabolites are excreted through urine, accounting for 10% and 50% of the managed dose, while as the parent compound, only 1% is recoverable. The clearance of Ketotifen from plasma has a distribution half-life of 3 hours, an elimination half-life among adults measured approximately 22 hours, and similar within children. Unfortunately, there is limited data available regarding its effects [14].

3.2. Clinical application of ketotifen

Ketotifen is a medicine that was invented in 1970, and then it came into use in 1976[15], till now, it is still one of the anti-histaminic medicines used in treating allergic diseases especially asthma, AR, and many other relevant symptoms [16]. Ketotifen has different dosage forms, such as oral tablets/capsules, eye drops, nasal drops/nasal sprays, etc. Among them, eye drops can be used as a first-line drug choice for the treatment and prevention of allergic conjunctivitis.

According to clinical trials and experiments data, ketotifen has been used in clinics comparably and got good acceptance. Compared with clemastine, Ketotifen has similar protective effects to histamine attack, and during allergen exposure, it is more effective according to the study of Resta et al. (1981). Also, ketotifen has a similar effect as sodium cromoglycate against patients' early reactions for extrinsic asthma and late reactions. Kelly and Taylor [17].

1) Asthma

Ketotifen (Orally) has been prophylactically used to lessen both regularity and intensity of asthma. Maclay and colleagues conducted a study involving 19252 patients (involving 283 children before 12 ys) using ketotifen at a dosage of 2 mg/day (Maclay & Crowder 1985; Maclay et al., 1984), which provided an overview of usage experience. The impression of disease severity during the first 3 months of treatment was used as a relative baseline control, and compared with that in the following 6, 9, and 12 months. 75% of the surveyed patients believe that ketotifen is effective after treatment in the first three months, and up to 85% among children. Approximately 4200 patients withdrew from the study, but among those who proceeded **to** the project, the portion of improved asthma symptoms rose to 89%

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at six months, 93% at nine months, and 94% at twelve months of assessment. At the time of 12 months, 62% of exogenous asthma patients and 57% of endogenous asthma patients (n=3261) can decrease other antiasthma drugs (n=4370) [17].

2) Allergic rhinitis

Ketotifen is effective for AR in both adults and children, especially among children with seasonal physical symptoms.

In placebo-controlled trials of perennial and seasonal allergic rhinitis(AR), ketotifen 1 or 2mg taken orally twice daily for 4 to 12 weeks had a better effect than placebo in relieving symptoms in both nasal and ocular.

In a study of 221 perennial rhinitis patients, compared with oral clemastine 1.34mg bid, ketotifen 0.5 and I mg, bid, were significantly more effective in alleviating several nasal symptoms of AR, in particular sneezing, nasal obstruction, and olfactory disturbance (Okuda 1984). At these dosages, ketotifen demonstrated its effectiveness, with 55% to 73% of patients experiencing significant improvement, compared to only 35% in the clemastine group ($p < 0.01$).

A substantial improvement in symptoms of seasonal rhinitis (Sugi pollinosis) was observed in 81% of patients after four weeks of treatment using ketotifen at a dosage of 1 mg twice daily ($n = 108$), compared to just 38% in the placebo group ($n = 113$) ($p < 0.001$) (Okuda 1986). Additionally, the rhinoscopic evaluation of nasal discharge and eosinophil counts in people with seasonal rhinitis showed a significant enhancement in these parameters following four weeks of ketotifen treatment (Okuda 1986).

In comparative trials, ketotifen proved to have a similar effect as chlorphenamine, clemastine, loratadine, terfenadine or even sodium cromoglycate. However, it was found to be less effective than astemizole in one study.[18]

3.3. How to use ketotifen?

Minimum applicable age: 6 months old and above. Among them, eye drops are suitable for children over 3 years old.

Dosage: oral dose 0.5-1mg each time, twice a day. Eye drops: 1 drop each time (affected eye), twice a day. Nasal drops: 1-2 drops on each nostril each time, 1-3 times a day. The above is only the recommended range of the routine dose for children, and it is recommended to use it in combination with the doctor's assessment of the child's specific condition, and then follow the doctor's advice.

1) Course of treatment

The oral dosage form of ketotifen has a slow onset of action, and it takes at least 4-8 weeks to determine the effect, and the doctor needs to evaluate and follow up according to the child's symptoms and medication control.

Eye drops of Ketotifen can be used for allergic conjunctivitis, the general course of treatment is about 2 weeks, if the symptoms are still not relieved then, a new medical evaluation should be taken. If used for the prevention of seasonal allergic conjunctivitis, it can be used 2 weeks before the pollen season begins.

2) Precautions for the use of ketotifen?

As mentioned earlier, ketotifen has antihistamine effects, so its effect on histamine receptors in the brain (central inhibitory effect) is close to that of the first-generation antihistamines (such as diphenhydramine, chlorpheniramine, etc.), drowsiness are common when used. It should be avoided for workers that requires high concentration like driving cars, trains, airplanes, or before important meetings and social events. In addition, it may also cause dizziness, headache, dry mouth, weight gain, rash and other adverse reactions.

Eye drops include tingling and burning sensation when dropping, cooled eye drops would have a certain relief effect. Other adverse effects include headache and worsening dry eyes.

Weight gain is another problem for ketotifen. Overall, most of the adverse reactions of the drug are relatively mild and can usually recover after stopping the drug.

Even though, pregnant and lactating women should be used with discernment. Those who are allergic to this product are strictly banned, and those who have allergic history should use with caution.

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3) Is it safe for children to take ketotifen for a long time?

As mentioned earlier, the latest medical consensus does not list ketotifen as the first-line medicine for AR or asthma. Therefore, for children with the above diseases, if a long period treatment is needed, first-line drugs should be preferred. In other words, long-term ketotifen should only be considered in children when there are no other alternative drugs with better efficacy and safety.

4. Conclusion

In conclusion, both allergic rhinitis and asthma are chronic diseases, and the treatment process may take years or even longer. With the proceeding of technology of science, kinds of new medicines emerged in the market, however, ketotifen is still commonly for choose for its specific effect, as well as low prices, and matured manufacturing. Ketotifen has performed more prominently effective in a large amount of therapeutic trials concerning children and adults. Even though, a well-designed study, which is essential for evaluating a prophylactic drug, is still lacking. To get better evaluated, well-designed double-blind, randomized controlled, and placebo-controlled multicenter clinical trials for the effectiveness of ketotifen are needed in the future.

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