

KETOTIFEN

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Ketotifen (Fig.) is a non-broncho-dilating anti-asthmatic drug with potential in the long term management of bronchial asthma. It also possesses anti-allergic and anti-anaphylactic properties.

Pharmacodynamics

Ketotifen is a functional antagonist of

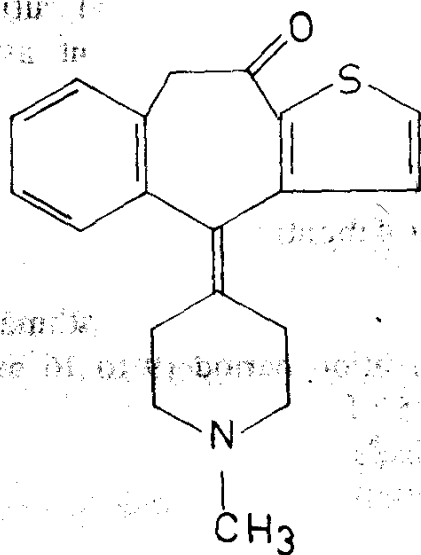


Fig. The structural formula of ketotifen, a benzo cycloheptathiophene compound.

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bronchial hyper-reactivity. Several mechanisms may be responsible for this effect:

1. *Effect on Airway Inflammation:* Inflammation of the tracheobronchial tree as a result of the release of proinflammatory mediators is now recognized as an important cause of airway obstruction via cellular infiltration and edema, mucous production and retention, and which also promote epithelial damage and airway hyperactivity. Inhibition of the release and/or activity of these mediators by ketotifen has been demonstrated *in vitro* or in animals for histamine, platelet-activating factor, arachidonic acid metabolites, neutrophil chemotactic factor and the cytotoxic oxygen intermediate $O_2(1)$. Ketotifen inhibits the bronchial response to inhaled histamine and aspirin but in contrast to sodium cromoglycate, it does not protect against methacholine or exercise induced bronchoconstriction.

2. *Calcium Antagonism:* Besides the requirement of calcium for smooth muscle contraction, it may be integral to the generation and/or release of the inflammatory mediators. Ketotifen appears to have some calcium antagonist properties but differs from classic inhibitors of transmembrane calcium flux by not influencing smooth muscle contraction.

3. *Effect on Adrenoceptors:* Ketotifen reverses β_2 -agonist induced reductions in β -adrenoceptor density and also alters the affinity of these receptors. It, thus appears to be useful in attenuating the tachyphylaxis to β_2 -agonist bronchodilators which results from decreased β_2 -adrenoceptor density.

4. *Effect on Eosinophils:* Some reports

have described peripheral eosinophilia (>6% of the leucocyte differential) in atopic children presenting with asthma or atopic dermatitis and associated airway hyperactivity. There appeared to be correlation between the clinical efficacy of ketotifen in these children and 'normalization' of peripheral eosinophil counts during treatment(2).

Pharmacokinetics

Ketotifen is well absorbed after oral administration, achieving peak plasma concentrations within 2 to 4 hours of administration. However, information regarding absorption from the once-daily slow-release tablet is lacking(3).

Ketotifen is extensively metabolized to the inactive ketotifen-N-glucuronide and the pharmacologically active nor-ketotifen. Clearance of the drug from plasma is biphasic, with a half-life of distribution of 3 hours and a half-life of elimination of 22 hours in adults. Children exhibit a similar pattern of elimination(4).

Therapeutic Use

1. *Bronchial Asthma*: The majority of recent double-blind clinical trials comparing oral ketotifen with matching placebo have reported a beneficial effect for the drug in children with mild to moderate extrinsic asthma(5-11).

Ketotifen was reported to be more effective than placebo in significantly decreasing the respiratory symptoms in all these studies except the ones by White *et al.*(11) and Dawson *et al.*(5). However, in the study by Dawson *et al.*(5), ketotifen treated children had significantly ($p > 0.05$) fewer asthma attacks and school absences than placebo-recipients despite the lack of

a significant improvement in lung function (peak expiratory flow) or asthma symptoms.

Peak expiratory flow (PEF) was improved significantly in children administered ketotifen in two of these studies(6,9), but was unchanged or not tested in the rest. However, this parameter may have limited value in assessing efficacy in children as very young children cannot reliably perform the required manoeuvre, and the majority of children studied had mild asthma and thus, had a near normal PEF at baseline.

Long-term administration of ketotifen ranging from 10-26 weeks in some of these studies also allowed theophylline and β -adrenoceptor agonists to be decreased and even withdrawn in some cases(6-10). Reduction in steroid dosage has been possible in some patients with more severe disease, but the long-term clinical utility of ketotifen in steroid-dependent asthmatic patients has not been established.

A preliminary study in at-risk infants suggests that when ketotifen was administered for 4 months before development of clinical asthma, no infant in the ketotifen-treated group progressed to asthma during the observation period (9 to 16 months), whereas 5 of 10 placebo-treated children were subsequently diagnosed as having asthma ($p < 0.05$)(12).

Well-designed comparisons with sodium cromoglycate, an established non-steroidal prophylactic therapy in patients with bronchial asthma are sparse, but symptom score and lung function improvement in children on ketotifen were closely similar to those on sodium cromoglycate in one study(13). However, in an earlier study involving 10 children with bronchospasm precipitated by catfur dander, ketotifen was indistinguishable from placebo and

significantly less effective than sodium cromoglycate against both early (within 1 hour of exposure) and late reactions(14). Ketotifen may have an advantage over sodium cromoglycate in young children who have difficulty with inhaler technique.

Thus, ketotifen is a useful agent in managing mild to moderate bronchial asthma. In asthmatic patients ketotifen must be given a trial of 6 to 12 weeks before an evaluation of efficacy is made; in those patients who respond, continued reduction in the severity of the disease can be anticipated.

2. *Allergic Rhinitis and Conjunctivitis:* Ketotifen is effective in relieving the nasal and ocular symptoms of perennial and seasonal rhinitis in adults and children, the improvement being most pronounced in children with seasonal symptoms.

3. *Allergic Skin Disorders:* (a) *Urticarial syndromes*—Good and sometimes dramatic improvement was noted in patients with chronic or cold or exercise-induced urticaria treated with ketotifen for 1 to 4 weeks. (b) *Atopic dermatitis*—Despite the variable nature of atopic dermatitis, a good response has been clearly demonstrated for ketotifen, including a decrease in skin lesions and pruritus over the course of 4 to 9 weeks treatment in children.

4. *Food Intolerance and Allergy:* Prophylactic use of ketotifen appears to prevent bronchospasm, urticaria, skin lesions and gastrointestinal upset invoked by food allergens and may allow reintroduction of poorly tolerated foods.

Adverse Effects

Ketotifen is generally well tolerated, especially in young children. Sedation may occur in about 10 to 20% patients but declines after 1 to 2 weeks of continued

use. Dizziness, dry mouth, nausea and headache have been reported in 1 to 2% of patients after initiation of therapy but usually disappear with continued treatment. Weight gain may occur in a small percentage of patients.

With acute overdosage, somnolence, confusion, disorientation, tachycardia, hypotension, convulsions and reversible coma may occur.

Ketotifen may potentiate the effects of sedatives, hypnotics and antihistaminics.

Dosage and Administration

Children aged 6 months to 3 years should be given ketotifen (tablets or syrup) orally in a dosage of 0.5 mg twice daily. Older children should receive the full adult dose, *i.e.*, 1 mg twice daily. Ketotifen is available as tablets containing 1 mg (Airyfen, Asthafen, Ketasma, Tritofen) and as syrup (Asthafen, Tritofen) containing 1 mg/5 ml. The cost of a tablet is Rs. 1.00 to 1.60 and a 60 ml bottle of syrup costs Rs. 20.00.

Place of Ketotifen in Therapy of Bronchial Asthma

The goals of treatment in bronchial asthma are twofold: (i) to improve the prognosis, and (ii) to optimize the quality of life to allow the child with asthma to reach his potential.

It is not known whether drug therapy is capable of improving the prognosis in children with chronic asthma and preventing the irreversible impairment of lung function(15), though suggestions have been made that bronchial hyper-responsiveness may be potentially modifiable in the long term by drug therapy(16).

Therefore, the aim of treatment is to

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