Ketotifen
A Review of its Therapeutic Efficacy in Dermatological Disorders

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Summary

In addition to its antihistaminic properties, ketotifen modulates the immune response to allergen challenge in vitro and attenuates dermatological manifestations of the allergic response in vivo.

In small randomised double-blind trials, ketotifen was significantly more effective than placebo in patients with cold urticaria, paediatric mastocytosis (urticaria pigmentosa) or atopic dermatitis, and in prevention of asthma in infants.
and children with atopic dermatitis. Additional comparative studies showed the drug to be as effective as cetirizine, loratadine, astemizole and emedastine as treatment for chronic urticaria, at least as effective as clemastine as treatment for chronic urticaria and atopic dermatitis but inferior to hydroxyzine as treatment for paediatric mastocytosis.

Ketotifen has shown promise as a treatment for neurofibromatosis, where previously no pharmacological treatment option was available.

The most common adverse event in patients treated with ketotifen is sedation; however, the prevalence of this adverse event appears to subside during continued administration (=14% incidence at 3 months reducing to =2% at endpoint in a 12-month postmarketing study). Other adverse events include dizziness, dry mouth, nausea, headache and weight gain (incidence =1 to 2%).

Thus ketotifen is a potential therapy for cutaneous mastocytosis and neurofibromatosis, and has been shown to be an effective treatment for urticaria and, particularly, atopic dermatitis. The potential for the drug to prevent the development of asthma in infants and children with the latter provides further rationale for its use.

Pharmacodynamic Properties

Ketotifen is a benzocycloheptathiopene with antihistaminic properties. It significantly inhibits skin wheal and flare response to allergen skin prick tests in sensitised individuals. In vitro, ketotifen has been shown to affect the immune response to allergen challenge at several points (although most studies tested the drug at concentrations well in excess of those attainable in serum in vivo). Its actions include inhibition of T lymphocyte proliferation, suppression of interleukin production by T lymphocytes, suppression of IgE receptor expression by lymphocytes and inhibition of IgE-induced release of histamine from mast cells. The drug also interferes with eosinophil degranulation, chemotaxis and longevity, and it reduced serum levels of eosinophil cationic protein in certain patients. Ketotifen inhibited platelet activating factor (PAF)-mediated platelet activation in vitro and attenuated PAF-induced wheal and flare in volunteers.

Pharmacokinetic Properties

The bioavailability of ketotifen is limited to 50% by first pass metabolism. Mean maximal plasma concentration (Cmax) was reached 3.6 hours after administration of a 2mg dose to volunteers. A steady-state Cmax of 1.92 μg/L was achieved during twice daily administration of ketotifen 2mg to volunteers.

Ketotifen is extensively metabolised: the primary metabolites are ketotifen-N-glucuronide (which is inactive) and nor-ketotifen (which appears to have pharmacological activity). Up to 70% of a dose of ketotifen is excreted in the urine in the 48-hour period following administration, with the remainder appearing in the faeces. The elimination half-life of the drug is 22 hours.

Children appear to require a higher dosage of ketotifen, on a milligram per kilogram basis, than adults to achieve a similar pharmacokinetic profile.

Therapeutic Efficacy in Dermatological Disorders

Trials that did not select patients with a specific dermatological condition show ketotifen to be an effective treatment for chronic urticaria and atopic dermatitis. Studies in patients selected according to specific dermatological disorders also report the drug to be useful. Noncomparative studies indicate that the drug is an effective treatment for urticaria, atopic dermatitis and the dermatological symptoms of food intolerance. In randomised double-blind trials it was significantly more effective than placebo as treatment for cold urticaria, paediatric mastocytosis (urticaria pigmentosa) or atopic dermatitis, and in prevention of asthma in infants.