Inhibition of Idiosyncratic Reactions to Aspirin by Ketotifen

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Premedication with ketotifen has been reported to prevent precipitation of asthmatic attacks by aspirin in two aspirin-intolerant patients [1]. With this study we are able to confirm this observation in a larger group of patients and show a good protective effect of this drug in other clinical forms of aspirin idiosyncrasy.

18 adult patients with proven intolerance to drugs that inhibit cyclooxygenase and block the generation of prostaglandins were studied. In 14 of them ingestion of aspirin led to bronchoconstriction, in the other 4 it resulted in urticaria/angioedema. Challenge tests were performed by giving oral aspirin or placebo in increasing doses to determine the threshold dose of aspirin. Clinical symptoms and peak expiratory flow (PEF) were recorded before the tests and then every 30 min over 4–6 h. The test was considered positive on the appearance of dyspnoea and a fall in PEF of at least 25% or of urticaria/angioedema. Ketotifen, 4 mg daily, was then administered for 3 days and on the fourth day the challenge tests were repeated 2 h after the last dose of 2 mg of the drug. Disodium cromoglycate and antihistamines

1 Extended abstract

Full paper to be published elsewhere.

were stopped 2 weeks before the study and bronchodilators were stopped 8 h prior to the test. Adverse symptoms after challenge were relieved by β_2 -stimulants, aminophylline or antihistamines.

The threshold doses of aspirin for the induction of asthma in the 14 patients were 20–70 mg. Symptoms including dyspnoea, lacrimation, conjunctival injection, rhinorrhoea and scarlet flush of head and neck first appeared 90 min after aspirin intake. Premedication with ketotifen resulted in total prevention of bronchoconstriction in 7 and in a marked reduction of dyspnoea and subjective symptoms in 6 patients, the onset of dyspnoea being delayed by 45–120 min. 1 patient showed no changes. Mean peak flow rates recorded 120 and 240 min after challenge were significantly increased after ketotifen treatment.

Ketotifen completely prevented the symptoms in the 4 patients exhibiting skin reactions after aspirin (100–300 mg). 2 patients were further challenged with double amount of the threshold dose. Ketotifen offered complete protection in 1 patient, while in the other the reaction was both delayed and diminished.

It has been suggested [2] that in a large group of patients the idiosyncrasy to aspirin—
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rin-like drugs is not of an immunological type but due to a suppression of cyclooxygenase activity as a common pathogenetic mechanism, the symptoms encountered being dependent upon the tissue affected. The results presented here given additional, though indirect, support to this idea. At least two simultaneous mechanisms are thought to cause adverse reactions when cyclooxygenase is blocked [3], namely tissue deprivation of prostaglandin E with subsequently augmented histamine release from mast cells, and diversion of the arachidonic acid metabolism towards lipoxygenase products which either stimulate mediator release [4, 5] or are bronchoconstrictor agents (SRS-A) themselves [6]. Theoretically ketotifen, affecting mediator release and being a histamine antagonist, could interfere with both of these mechanisms. This dual effect of the drug might explain the excellent clinical results obtained in this study. It remains to be clarified whether prolonged treatment with ketotifen could be of benefit to patients with aspirin-induced asthma.

References

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