

Correspondence

Antagonism of PAF and arachidonic acid by ketotifen

To the Editor:

Kerrebijn (JACI 1990;86:274-5) has suggested that ketotifen does not influence bronchial hyperreactivity and lacks anti-inflammatory effects. Our findings on the pharmacologic actions of ketotifen previously reported¹⁻⁴ are not in agreement with this statement.

It is well-known that platelet-activating factor (PAF) is a potent autocoid mediator implicated in a diverse range of human pathologies, including asthma, shock, platelet aggregation, and chemotaxis.⁵ At the microcirculatory level, the very intensive leakage of plasma appears to result from both a direct PAF effect on the vessel wall and a destabilization of the endothelium by the generation and release of leukotrienes, thromboxane, free radicals, and other toxic products from various blood cells stimulated by the agonist.⁵

In our studies,¹⁻⁴ ketotifen, at concentrations achievable in plasma, inhibited PAF and arachidonic acid-induced human platelet aggregation. Furthermore, administration of a single dose of 2 mg ketotifen, orally, to human volunteers completely inhibited PAF-induced ex vivo platelet aggregation.³ We have also reported the inhibition of platelet lipooxygenase by ketotifen, strongly suggesting that ketotifen, apart from having other actions, also possesses anti-inflammatory effects. These findings point to a new facet of ketotifen action that has not been demonstrated before.

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REFERENCES

1. Saeed SA, Nasreen R, Suria A. Synergistic actions of 5-HT and arachidonic acid in platelet aggregation: effect of 5-HT blockers. *Br J Pharmacol* 1988;94:330.
2. Saeed SA, Nasreen R, Amiral S, Suria A. Inhibition of arachidonate lipooxygenase by ketotifen. *Biochem Soc Trans* 1988;16:814-5.
3. Saeed SA, Mahmood F, Naqvi A, Jafary MH. Inhibitory effect of oral ketotifen on ex vivo platelet-activating factor-induced platelet aggregation [in press]. *Agents Actions*.
4. Saeed SA, Aleem F, Naqvi A, Jafarey MH, Suria A. Synergistic actions of platelet-activating factor and 5-HT in platelet aggregation: effect of 5-HT blockers and anti-asthma drugs. *Br J Pharmacol* 1989;97:544.
5. Braquet P, Touqui L, Shan TY, Vargaftig BB. Perspectives in platelet-activating factor research. *Pharmacol Rev* 1987;39:97-145.

In re: Letter by Kerrebijn in JACI

To the Editor:

Dr. Kerrebijn (JACI 1990;6:274-5) has suggested that therapeutic doses of ketotifen do not influence airway hy-

perreactivity and lack anti-inflammatory effects. We wish to refute such speculation.

Although ketotifen is a potent inhibitor of responses to histamine, it is not a competitive antagonist of histamine (H₁) receptors^{1,2} and hence may have other pharmacologic actions. This prompted us to study whether ketotifen might inhibit airway responses to platelet-activating factor (PAF) and other agents causing airway hyperreactivity or airway eosinophilia. As little as 0.1 µg/kg/min of ketotifen suffices to inhibit PAF-induced airway hyperreactivity in the guinea pig and, in passively sensitized animals, IgE-mediated exacerbation of airway reactivity can be inhibited by sustained infusion of <0.1 µg/kg/min.³ The efficacy of such low doses of ketotifen (<100 µg/kg/day) may depend on the accumulation of ketotifen in lung tissue in which drug concentrations can be orders of magnitude more than in circulating blood.⁴ This clinical finding precludes use of plasma levels as a meaningful index during ketotifen therapy and may account for the slow onset of overt clinical benefit.

Pharmacologic doses (0.1 to 1.0 mg/kg/day) of ketotifen clearly exhibit anti-inflammatory actions by inhibiting influx of eosinophils into the airway lumen of the guinea pig during reactions to allergen⁵ or PAF.^{6,7} Moreover, sustained infusion of ketotifen (0.07 µg/kg/min during 21 days) sufficed to diminish idiopathic airway eosinophilia in the rhesus monkey whose blood levels lay within the clinical range.³

The capacity of ketotifen to inhibit responses to agents, such as PAF,^{6,7} platelet-derived hyperreactivity factor,⁸ isoprenaline,⁹ and granulocyte-monocyte colony-stimulating factor, interleukin-3, and tumor necrosis factor-α¹⁰ as well as allergen,⁵ implies an effect on priming processes, whereby allergen modifies responsivity of target cells, rather than on cell activation after interaction with allergen. A molecular basis for this impressive action of ketotifen has yet to be defined.

To attribute the pharmacologic actions of ketotifen solely to antihistamine activity is unwarranted.

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REFERENCES

1. Martin U, Roemer D. The pharmacological properties of a new, orally active antianaphylactic compound, ketotifen, a benzocycloheptathiophene. *Drug Res* 1978;28:770-82.
2. Thompson CD, Fennessy MR. Antagonism of histamine by ketotifen in the guinea pig-isolated trachea. *Clin Exp Pharmacol Physiol* 1982;9:394-5.
3. Amsler B, Hoshiko K, Chapman ID, Morley J. Effects of therapeutic doses of ketotifen on guinea pig and monkey airways. *Am Rev Respir Dis* 1991;143:A653.
4. Guerret M, Hubert M, Lavene D. Comparative lung distribution of ketotifen after orally administered single and multiple doses. *Eur J Drug Metab Pharmacokin* 1990;15:170.