Effect of Fluticasone Propionate on Acute and Chronic Inflammation

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Key Words

Fluticasone propionate
Mast cell
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Toluene diisocyanate

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Inflammation may be considered in terms of interrelated acute and chronic processes [1]. Acute inflammation develops rapidly and is reversible, involving cell activation, mediator release, vascular permeability changes and inflammatory cell recruitment into tissues. In contrast, chronic inflammation progresses more slowly and is largely irreversible. It involves increased tissue residency of inflammatory cells, a further spectrum of mediator release, and cellular damage and remodelling. The effect of fluticasone propionate (FP), a corticosteroid with increased intrinsic glucocorticoid potency [2] has now been evaluated against experimental models of acute and chronic inflammation.

FP is active in inhibiting cell activation, an initiating event in acute inflammation. For example, interleukin-5-induced blood eosinophilia in the guinea pig, which occurs maximally within 6h, is reduced from 6×10^6 eosinophils/ml to 1.5×10^6 eosinophils/ml by FP, administered systemically at a dose of 25 µg/kg intravenously. Similarly, in rats previously sensitised to toluene diisocyanate (TDI), intra-nasal challenge results in rapid (< 30 min) mast cell degranulation, measured as a decrease in mucosal histamine content. A single intranasal dose of FP (50 µg), given 30 min before TDI, inhibited histamine release by about 50%. FP is also more potent and longer acting than beclomethasone dipropionate (BDP) in inhibiting vascular permeability changes and plasma protein extravasation in the lung, which occur within 30 min following stimulation with directly acting mediators such as histamine and bradykinin. By the inhaled route, FP, at aerosol concentrations of 0.1 and 1 mg/ml, inhibited histamine-induced lung oedema at 1 h and this was sustained for up to 16 h, whereas BDP (1 mg/ml) was ineffective after 4 h.

Alternatively, in rats chronically exposed (8 weeks) to intranasal TDI, mucosal mast cell numbers increased 4.5-fold over baseline levels. Intranasal FP (50 µg), administered twice daily during the TDI sensitisation period, maintained nasal mast cell numbers in a range (1.3-fold) not significantly different from those in the placebo (non-sensitised) animals. This was observed in terms of a reduced mucosal histamine content (TDI: 72 ± 8 ng/g; TDI+FP: 21 ± 9 ng/g; placebo: 17 ± 5 ng/g wet weight tissue). Daily administration of nebulised FP (0.1 mg/ml) completely inhib-

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Table 1. Effect of FP on acute and chronic inflammation

Acute

Inhibition of cell activation

Mast cell degranulation

Inflammatory cell demargination Inhibition of vascular permeability changes (endothelial cells)

Chronic

Inhibition of increased inflammatory cells in tissues

Mast cells

Granulocytes Inhibition of epithelial damage

ited the marked granulocyte accumulation in the airway lumen and the associated epithelial damage (> 90% loss of bronchial epithelium) in guinea pigs repeatedly challenged (daily for 7 days) with lipopolysaccharide.

FP therefore has potent inhibitory activity against both acute and chronic inflammatory processes (table 1) in the upper and lower respiratory tract.

References

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442

Johnson

FP in Acute and Chronic Inflammation