The effects of the selective PAF receptor antagonist CIS-19 on PAF- and antigen-induced bronchoconstriction, microvascular leakage and bronchial hyperreactivity in guinea-pigs.

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Abstract

We investigated the effects of a novel platelet-activating factor (PAF) receptor antagonist, CIS-19 [cis-2-(3, 4-dimethoxyphenyl)-6-isopropoxy-7-methoxy-1-(N-methylformamido)-1, 2, 3, 4-tetrahydronaphthalene], on PAF-, histamine-, substance P- and antigen-induced bronchoconstriction and microvascular leakage, as well as PAF- and antigen-induced bronchial hyperreactivity to methacholine in urethane-anesthetized guinea-pigs. Administration of CIS-19 (0.5–5 mg/kg, i.v.) inhibited the increase in lung resistance induced by PAF (30 ng/kg, i.v.) in a dose-dependent manner, but failed to inhibit the increase induced by histamine (30 μg/kg, i.v.) or substance P (6.5 μg/kg, i.v.). CIS-19 (5 mg/kg, i.v.) did not inhibit the increase in lung resistance induced by ovalbumin (2 mg/kg, i.v.) in actively sensitized guinea-pigs. PAF (30 ng/kg, i.v.)-induced microvascular leakage, measured by the extravasation of Evans blue dye, was dose-dependently inhibited by CIS-19 (0.5–5 mg/kg, i.v.) in the trachea, main bronchi and intrapulmonary airways, but it did not affect histamine (30 μg/kg, i.v.)- or substance P (6.5 μg/kg, i.v.)-induced microvascular leakage at all airway levels. CIS-19 (2.5 and 5 mg/kg) did not affect ovalbumin (2 mg/kg, i.v.)-induced microvascular leakage in all airway levels in actively sensitized guinea-pigs. CIS-19 (2.5 and 5 mg/kg, i.v.) significantly inhibited PAF-induced enhancement of the bronchial response to methacholine, but had no effect on ovalbumin (0.05 mg/kg, i.v.)-induced bronchial hyperreactivity in actively sensitized guinea-pigs. It is concluded that CIS-19 is a potent PAF receptor antagonist which inhibits PAF- but not antigen-induced bronchoconstriction, microvascular leakage and bronchial hyperreactivity. These results suggest that PAF plays little or no role in early airway responses following antigen challenge.