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Differential responses to various classes of drugs in a model of allergic rhinitis in guinea pigs

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Abstract

Different drugs from various pharmacological classes were compared for their ability to protect against the nasal effects of acute allergen challenge in a guinea pig model. In the model, sneezing and nose rubbing were recorded after an initial allergen challenge in guinea pigs previously sensitized to egg albumin. Four days later the same guinea pigs were re-challenged a second time when anesthetised. In these anaesthetized animals, nasal airway pressure, pulmonary inflation pressure and cellular infiltration into nasal lavage fluid were measured. The drug tested were autacoid antagonists (mepyramine—3 mg/kg, cetirizine—3 mg/kg and montelukast—10 mg/kg), L-NAME (10 or 20 mg/kg), heparin (20 mg/kg) and dexamethasone (20 mg/kg) given either intraperitoneally or intravenously; all were given shortly before challenge.

Sneezing induced by allergen challenge was statistically significantly reduced by mepyramine, cetirizine and dexamethasone whereas only cetirizine reduced nose rubbing. Changes in nasal airway pressure due to allergen exposure were reduced by cetirizine, montelukast, L-NAME, and heparin, but not by mepyramine, nor dexamethasone. In the presence of L-NAME, nasal airway pressure actually changed in the opposite direction. Cellular infiltration, as assessed by cytometry in nasal lavage fluid 60 min after acute allergen challenge, was reduced by montelukast and heparin but not by antihistamines, L-NAME nor dexamethasone.

This pattern of effects of the drugs, given by doses and routes previously described in the literature as being effective was not completely consistent with expected responses. The lack of effect of dexamethasone probably reflects the fact that it was given acutely whereas in the clinic chronic administration is used. The two antihistamines were not identical in their actions, presumably reflecting the fact that cetirizine has therapeutic actions not entirely confined to blockade of H1 receptors. Montelukast has not been reported to have major effects on sneezing and itching in the clinic but reduces nasal obstruction (lower nasal airway pressure or nasal patency). Montelukast's effects on cellular infiltration indicate the possible involvement of leukotrienes. Heparin has actions on inflammatory cell infiltration. This could explain its profile of reducing both cellular infiltration, and increased nasal airway pressure.

Keywords: Allergen challenge; Heparin; Montelukast; Dexamethasone; Cetirizine; Mepyramine; Nasal cellular infiltration

1. Introduction

Allergic rhinitis is a common health problem whose treatment with drugs is not ideal. The major signs and symptoms of allergic rhinitis include sneezing, itching, rhinorrhea and nasal congestion, accompanied by infiltration of the nasal mucosa by eosinophils [1]. There are two temporal phases to allergen challenge in sensitized subjects. The earliest response consists mainly of sneezing, itching and rhinorrhea whereas nasal congestion and cellular infiltration occurs later [2].

Histamine is considered to play an important role in allergic inflammation. Nasal challenge with histamine causes sneezing, pain, pruritus, rhinorrhea and nasal blockade [3] and histamine concentrations in nasal lavage fluid increase with allergen challenge [2]. Furthermore, H1-antihistamines administered orally, or topically, reduce some of the signs and symptoms of both seasonal and perennial allergic rhinitis [1]. Other autacoids, e.g. leukotrienes, also play a

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role. Antagonists of cysteinyl leukotriene LTD_4 receptors (montelukast) reduce some of the signs and symptoms of allergic rhinitis [4]. Nitric oxide (NO), the cell-signaling molecule, has been implicated in a wide range of physiological and pathophysiological events in numerous cell types and in patho-physiological processes including the immune system. Interestingly, NO concentrations in exhaled air are elevated in allergic rhinitis patients compared to normal [5].

Anti-inflammatory drugs moderate many of the symptoms of allergy. Topical glucocorticoids are used routinely to treat allergic rhinitis. Steroids are routinely used chronically, but they have not been well investigated when given acutely in models of allergic rhinitis. Heparin, in addition to its anticoagulant properties, has anti-inflammatory actions that reduce the signs and symptoms of allergic rhinitis [6].

We have recently reported a combined conscious/anesthetised guinea pig model for studying allergic rhinitis [7]. The aim of this study was to expand our understanding of the model by testing therapeutic or experimental drugs including antihistamines, montelukast, heparin, L-NAME and dexamethasone.

2. Materials and methods

2.1. Animals

Male Dunkin–Hartley guinea pigs (Charles River Laboratories, Canada), weighing from 300 to 400 g during the sensitization period and 400–600 g at times of challenge, were used. They were housed at $23 \pm 2\,^{\circ}C$ and $55 \pm 5\%$ humidity, on a 12 h light/dark cycle, with food and water *ad libitum*. Animal experiments were approved by the University of British Columbia Animal Care Committee.

2.2. Drugs

The actions of various clinical or experimental drugs in the treatment of allergic rhinitis were assessed in terms of effects on sneezing, nose rubbing, nasal congestion, or patency as reflected by nasal airway pressure, and leukocyte infiltration into nasal lavage fluid. The drugs (see Table 1 for doses and routes) were selected on the basis of their general or particular effectiveness in the allergic rhinitis seen in humans and/or experimental animals. The drugs included first (mepyramine) and second (cetirizine) generation antihistamines, a leukotriene D4 antagonist (montelukast), a nitric oxide synthase inhibitor (L-NAME), and a glucocorticosteroid (dexamethasone), as well as heparin. Doses and routes of administration were chosen from the literature on the basis of their effectiveness in various animal models. Drugs were given intraperitoneally (i.p.) 15 min prior to ovalbumin challenge while intravenous drugs were given 5 min before.

Table 1
Drugs used in this study together with dose and route of administration

Drug	Dose (mg/kg)	Route of administration
Mepyramine	3	Intraperitoneal
Cetirizine	3	Intraperitoneal
Montelukast	10	Intravenous
L-NAME	10	Intravenous
Heparin	20	Intravenous
Dexamethasone	20	Intraperitoneal (for sneezing), intravenously (for nasal airway pressure)

2.3. Sensitization and assessment of sneezing and nose rubbing

The methods used in this study were recently described [7]. Briefly, the same animal was used for measurement of sneezing and nose rubbing (while conscious) and 2 days later (while anesthetized) for measurement of nasal airway pressure, lung inflation pressure and leukocyte infiltration into nasal lavage fluid. The sensitization procedure first described by Yamasaki et al. [8] was used with modifications. Initial exposure was to 1% ovalbumin (Grade V, Sigma, Germany) in saline twice (7 days apart) as an aerosol generated by ultrasonic nebulizer (ULTRA-NEB 99, DeVILBISS Co., Canada) and applied with a ventilation pump at 4 ml/stroke, 70 strokes/min via a nose cone. On days 14, 15 and 16 boosters of 1% ovalbumin in saline (20 μl/nostril/day) was instilled intranasally.

The first challenge, 21 days after beginning sensitization, was given to conscious guinea as 2% ovalbumin in saline to both nostrils 20 μl/nostril (treated groups plus an untreated control groups), or 20 μl saline alone (unsensitized group). Following challenge, guinea pigs were observed individually for sneezing and nose rubbing using standardized observations in a randomized blind fashion for 30 min post challenge. Sneezes were characterized by explosive expiration just after a deep inspiration. A nose rub was characterized by an external peri-nasal scratch with the animal's forelimbs. It was taken to be an index of nasal itching. Thereafter animals were left to recover for 4 days prior to a second challenge in anaesthetized animals for the measurement of nasal and lung pressures, as well as cellular infiltration in the nasal cavities of anaesthetized animals.

2.4. Assessment of specific nasal airway pressure

Guinea pigs were anaesthetized with pentobarbital (35 mg/kg intraperitoneally, plus more as appropriate), and cannulated for blood pressure measurement, intravenous injections, as well as nasal and lung inflation pressures. Nasal airway pressure was measured by a modification of the method of Mizuno et al. [9]. A catheter was passed from the trachea, through the laryngopharynx and the oropharynx, toward the nasopharynx, ending about 1 mm before the posterior nares. A ventilation pump (Harvard Apparatus Limited) was used to deliver air at a rate of 8 ml/stroke, 72 times/min directed toward the nares. In order to prevent air leakage, the buccal (oral) cavity was filled with epoxy-soaked cotton wool and the