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Potential benefits of ibuprofen in the treatment of viral respiratory infections

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1. INTRODUCTION

This review focuses on the pathophysiology of viral infection and diseases of the upper airways in relation to treatment with non-steroidal anti-inflammatory medication. The generation of cold symptoms will be discussed based on current knowledge of inflammatory reactions in the nose.

Recent advances in molecular biological techniques and detection of virus by polymerase chain reaction (PCR) have renewed interest in cold research. The importance of rhinovirus as a pathogen in acute otitis media (Pitkaranta *et al.*, 1998), acute sinusitis (Pitkaranta *et al.*, 1997), exacerbation of asthma (Pattemore *et al.*, 1992; Nicholson *et al.*, 1993; Johnston *et al.*, 1995) and chronic obstructive lung disease (Nicholson *et al.*, 1996; Greenberg *et al.*, 2000) has become evident during the past 10 years (Rotbart and Hayden, 2000). Although severe bacterial super-infection to viral colds occasionally occurs, a considerable proportion of what we previously thought was "bacterial" may in fact be predominantly a direct result of viral infection. Intervention strategies to prevent expansion of the viral infection from the nose to the middle ear, paranasal sinuses, bronchi and lungs are warranted.

We will start this review with a basic description of nasal mechanisms of inflammation since these issues are important for a full understanding of rhinovirus pathogenesis, symptomatology and the rationale for early treatment.

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2. NASAL AIRWAY INFLAMMATION CAUSED BY RHINOVIRUS

Inflammation initiated by viral infection is a dynamic process, a complex series of reactions for the purpose of protecting and restoring natural function. The reactions in the nose will be discussed based on the four classic signs of inflammation: (1) vasodilatation (redness); (2) edema (swelling); (3) cellular infiltration; and (4) pain (sensory nerve stimulation and hyper-responsiveness).

2.1. Nasal vasodilatation

Vasodilatation causes hyperemia and increased blood flow and volume due to distension of submucosal venous sinuses (Mygind, 1986). Increased blood flow in the nasal mucosa by itself does not lead to plasma exudation. The nasal mucosa is normally red, so objective changes during viral infection are difficult to detect. Nasal obstruction is thought to be a marker for vasodilatation. Nasal obstruction is present during the first week of a viral cold (Hendley *et al.*, 1969) and can be evaluated by acoustic rhinometry (Hytoenen *et al.*, 1996) or self-assessment (Groenborg *et al.*, 1983b).

2.2. Nasal and sinus mucosal edema

Increased microvascular permeability leads to plasma exudation which causes both mucosal edema and an increase in nasal secretions. Mucosal swelling is not evident by anterior rhinoscopy or in biopsies from the inferior turbinate in patients with colds (Winther *et al.*, 1984a). Albumin may be used as a marker for exudation since only a minor proportion of albumin is thought to originate from nasal and lacrimal glands (Mygind, 1996). Both albumin and fibrinogen levels increase in nasal secretions in symptomatic patients with rhinovirus infections (Winther *et al.*, 2002a). Inflammatory edema in the nasal mucosa seems to produce vascular leakage and exudation resulting in increased nasal secretions rather than mucosal edema/swelling.

Opacification of the paranasal sinus by computerized tomography (CT scan) is present in the majority of patients with colds (Gwaltney *et al.*, 1994). This is often referred to as "mucosal thickening", but is in fact more likely to be secretion (Winther *et al.*, 2002a). Likewise, Eustachian tube dysfunction, which is present in the majority of patients with colds (Winther *et al.*, 2002b), may be caused by increased secretions in the Eustachian tube rather than by "true mucosal swelling".

2.3. Cellular infiltration

Viral infection in the nasal mucosa results in an early and transient infiltration of neutrophils (Winther *et al.*, 1984a, c). This accumulation of neutrophils occurs in spite of the absence of a concomitant bacterial infection (Winther *et al.*, 1984b). The number of neutrophils in nasal washes seems to correlate with symptoms (Naclerio *et al.*, 1987). No changes in the number of lymphocytes in the lamina propria of

the nasal mucosa have been detected by immunohistochemistry in two studies of rhinovirus infected patients (Winther *et al.*, 1992; Fraenkel *et al.*, 1994).

2.4. Nasal hyper-responsiveness

The nasal mucosa has few pain fibers, but reacts to temperature changes, humidity, irritant gases, chemicals, pH, foreign particles and microorganisms with increased neural irritability, which is mediated primarily in the sensory and autonomic nerves in the trigeminal nerve (Raphael *et al.*, 1988). Nasal hyper-responsiveness involves nerve pathways which utilize both neurotransmitters and neuropeptides (Piedimonte *et al.*, 1993; Petersson *et al.*, 1993). A sneeze is the most commonly recognized nasal reflex, contributing to the symptom complex in the early phase of a viral respiratory infection (Gwaltney *et al.*, 1967). Increased nasal responsiveness is evident during colds, with an increased number of sneezes and secretory response following chemical stimulation with topical histamine and metacholine challenge compared to the normal state (Groenborg *et al.*, 1983a; Doyle *et al.*, 1994).

3. GENERATION OF SYMPTOMS DURING RHINOVIRUS INFECTION

Rhinoviruses are responsible for more than half of the viral respiratory infections in both children and adults (Gwaltney *et al.*, 1997). The majority of rhinoviruses gain entrance to nasal epithelial cells by attachment to ICAM-1 (Greve *et al.*, 1989). A series of cytokines are up-regulated (Naclerio *et al.*, 1987, Proud *et al.*, 1994) and IL-8, which is important as a chemo-attractant of neutrophils, is generated following virus-induced activation of NF-κB in epithelial cells (Zhu *et al.*, 1997). Rhinovirus-infected cells are expelled into the mucus and epithelial regeneration is thought to occur instantaneously, as no destruction can be detected in the nasal cavity (Winther *et al.*, 1984a; Winther *et al.*, 1990). Thus, the symptoms of a cold do not correlate with obvious destruction of the epithelial lining, nor do they strictly correlate with the presence of rhinovirus in nasal secretions. The median duration of cold symptoms is about 11 days (Arruda *et al.*, 1997). Viral titer peaks on day two following rhinovirus inoculation, but rhinovirus continues to be present in nasal secretions for up to three weeks (Winther *et al.*, 1986), until the neutralizing antibodies are produced. The mediators of clinical signs and symptoms of viral respiratory infection remains largely unknown, but an important pathogenic mechanism for generation of symptoms seems to relate to the host response with a neutrophil-dominated inflammation characterized by up-regulation and release of IL-8 and other cytokines and pro-inflammatory mediators (Naclerio *et al.*, 1987). A potential role for prostaglandin levels in nasal mucosa or nasal lining fluid during viral respiratory infection in otherwise healthy individuals has to our knowledge not been reported. Different prostaglandins and intermediates of one pathway in the eicosaniod metabolism may have contrasting actions, resulting in complex events in different cells involved in the inflammation. As a result, it may be difficult

to interpret the impact of nasal prostaglandin level on inflammation. However, intranasal challenge with prostaglandin D_2 and prostaglandin $F_{2\alpha}$ results in sneezing and coughing (Doyle *et al.*, 1990) and the role of prostaglandins in the viral colds may be judged by a clinical effect of non-steroidal anti-inflammatory drugs on those symptoms (Mygind *et al.*, 2003).

4. THE SYMPTOM PATTERN DURING RHINOVIRUS INFECTION

The viral infection triggers a cascade of symptoms. The first symptom of a cold is usually a sensation in the nasopharynx (back of the nose), a throat irritation often referred to as a "sore throat" in layman's terms, but without pain on swallowing. The throat irritation diminishes in a few days when nasal irritation becomes dominant, with sneezing and watery rhinorrhea and generalized symptoms of malaise. Fever may be present in children during the early phase of the viral infection, but is rare in adults. After some days the watery rhinorrhea is replaced by mucoid nasal disharge, a sensation of stuffiness, and nasal blockage and cough. While the nasal symptoms gradually decrease, the cough often persists for another week. Peak severity of symptoms occurs during the early phase of rhinovirus infection in otherwise healthy individuals, whereas patients with mild underlying chronic disease of the ear or sinuses (pre-existing problems with mucus drainage) may experience peak of symptom severity during the phase with mucoid nasal secretion and blockage, and patients with asthma, chronic bronchitis and COPD may experience peak of severity during the phase when viral infection is dominated by cough.

5. EFFECTS OF IBUPROFEN IN VIRAL RESPIRATORY INFECTION AND ILLNESS

Viral respiratory infection therapy has three main purposes: (1) to reduce symptoms; (2) to limit viral involvement of ear, sinus, bronchi and lungs; and (3) to decrease viral replication and spread of infection. At present there are only symptomatic therapies available for rhinovirus colds.

The cascade of inflammatory events caused by viral infection and the relation to specific nasal symptoms is not well understood and more information is needed to design rational therapy. Ibuprofen and other non-steroidal medications are of special interest for the understanding of symptom pathogenesis in rhinovirus infection due to their known anti-inflammatory properties.

By far the most well-described function of ibuprofen is the inhibition of cyclo-oxygenase (COX) and production of prostaglandin, prostacyclin and tromboxane (Vane, 1971), but other not-so-well understood effects may be important for an anti-inflammatory effect of ibuprofen in rhinovirus infections. Ibuprofen decreases the leukocyte migration and function *in vitro* (Maderazo *et al.*, 1983; Venezio *et al.*, 1985; Skubitz and Hammerschmidt, 1986), down-regulates ICAM-1 expression on

endothelial cells (Kapiotis *et al*., 1996) and inhibits central nociception synthesis of neuroactive substances (Satoh *et al*., 1976). In a double-blind randomized study of patients with viral respiratory illness, ibuprofen (400 mg three times daily) significantly decreased the generalized symptoms of malaise, body aches and "pain in the ear", but there was also an effect on nasal hyper-responsiveness, as the number and severity of sneezes were significantly decreased when compared to placebo (Winther and Mygind, 2001). The patients were only treated and evaluated for three days, and were included within 36 h of symptoms. The study was designed to evaluate the effect of ibuprofen when the symptoms of a cold are at their worst. No information can be drawn from this study regarding the effect of ibuprofen on "throat irritation" or cough, since those symptoms are not usually dominant at the time during the cold when ibuprofen was examined. The study did not suggest any effect of ibuprofen on nasal watery rhinorrhea, which is caused by parasymphatic stimulation of submucosal nasal glands (Borum *et al*., 1981).

The symptomatic effect of ibuprofen in patients with natural colds is supported by a similar effect seen with naproxen in patients with induced rhinovirus infection (Sperber *et al*., 1992). Significant improvement was demonstrated for generalized symptoms such as headache (day 1 to 5 after viral inoculation) and malaise (day 4 and 5 after viral inoculation), and an effect on nasal hyper-responsiveness was shown (number of sneezes decreased on day 1 and 4, and cough on day 4). Nasal mucus weight and nasal tissue usage tended to be lower on each study day (day 1 to 5) compared to placebo recipients, but the difference was not significant.

In another study of induced rhinovirus colds, the effect of ibuprofen (1.2 g daily) was compared to acetaminophen (4 g daily), acetylsalicylic acid (4 g daily) and placebo (Graham *et al*., 1990). No significant beneficial symptomatic effect was demonstrated; however, the number of patients in each group was small. Interestingly enough, the study found that both acetaminophen and acetylsalicylic acid but not ibuprofen were associated with suppression of neutralizing antibody response ($P < 0.05$) to the challenge rhinovirus and an increase in nasal symptoms ($P < 0.05$) when compared to placebo recipients, as well as a trend toward prolonged viral shedding. One study of children with colds and "otitis media" found no statistical difference in the tympanic score (objective measure for inflammation) on day 2 with either ibuprofen, acetaminophen or placebo recipients (all treated with antibiotics) (Bertin *et al*., 1996), although the study suggested an anti-inflammatory effect of ibuprofen on tympanic score on day 2. Frequent examination of the tympanic membrane immediately following medication may be necessary to detect possible effect of therapy since improvement usually occurs within 48 h. There was a significant effect on otalgia in children receiving ibuprofen (plus antibiotics) when compared to children only receiving antibiotics, whereas acetaminophen (plus antibiotics) did not significantly relief otalgia.

Ibuprofen has also been studied in combination with other medications in an experimental setting with normal volunteers inoculated with rhinovirus. An added symptomatic benefit was found when ibuprofen (400 mg) was combined with pseu-

doephedrine (60 mg) (Sperber *et al.*, 1989). This combination tended to reduce the cumulative nasal symptoms score (day 1 to 6) when compared to pseudoephedrine alone ($P = 0.09$), but nasal discharge was not reduced in either group when compared to placebo. Ibuprofen (400 mg) combined with chlorpheniramine (12 mg) given every 12 h for 4.5 days showed an overall, non-significant trend towards a reduction of headache and nasal symptoms (mucus weight and severity rhinorrhea score) compared to placebo (Gwaltney *et al.*, 2002). Only sneezing was significantly different (day 2 to 5) following rhinovirus infection.

6. CONCLUSIONS AND FUTURE RESEARCH

The natural cold study of ibuprofen demonstrated an improvement on general symptoms and pain at the time during illness where otherwise healthy patients feel worst.

Further insight into the inflammatory properties of ibuprofen during viral respiratory infections might be gained through examination of the effectiveness of ibuprofen treatment in patients with colds on nasal hyper-responsiveness and the possible effects on neutrophilic inflammation.

Early treatment of colds to prevent the spread of virus to the ear, sinuses, bronchi and lung is warranted. Nose blowing may facilitate spread of virus into the sinus and ear (Gwaltney *et al.*, 2000). Reduction of nasal discharge by a first-generation histamine seems attractive. Further studies of a combination of ibuprofen and an antihistamine are needed to optimize cold treatment to prevent viral otitis media, acute viral sinusitis, exacerbation of chronic bronchitis.

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