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 eicosanoid 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 discharge, 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 cyclooxygenase (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 parasympathetic 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.

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.

REFERENCES

Arruda, E., Pitkaranta, A., Witek, T. J., et al. (1997). Frequency and natural history of rhinovirus infections in adults during autumn, J. Clin. Microbiol. 35, 2864–2868.

Bertin, L., Pons, G., d’Athis, P., et al. (1996). A randomized, double-blind, multicentre controlled trial of ibuprofen versus acetaminophen and placebo for symptoms of acute otitis media in children, Fundam. Clin. Pharmacol. 10, 387–392.

Borum, P., Olsen, L., Winther, B., et al. (1981). Ipratropium nasal spray: A new treatment for rhinorhoea in the common cold, Am. J. Respir. Dis. 123, 418–420.

Doyle, W. J., Boehm, S. and Skoner, D. P. (1990). Physiologic response to intranasal dose-response challenge with histamine, methacholine, bradykinin, and prostaglandin in adults volunteers with and without nasal allergy, J. Allerg. Clin. Immunol. 86, 924–935.

Doyle, W. J, Skoner, D. P, Seroky, J. T., et al. (1994). Effect of experimental rhinovirus 39 infection on the nasal response to histamine and cold air in allergic and nonallergic subjects, J. Allerg. Clin. Immunol. 93, 534–542.

Fraenkel, D. J., Bardin, P. G., Sanderson, G., et al. (1994). Immunohistochemical analysis of nasal biopsies during rhinovirus experimental colds, Am. J. Respir. Crit. Care Med. 150, 1130–1136.

Graham, N. M. H., Burrell, C. J., Douglas, R. M., et al. (1990). Adverse effects of aspirin, acetaminophen and ibuprofen on immune function, viral shedding and clinical status in rhinovirus-infected volunteers, J. Infect. Dis. 162, 1277–1282.
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Greenberg, S. B., Allen, M., Wilson, J., et al. (2000). Respiratory viral infections in adults with and without chronic obstructive pulmonary disease, *Am. J. Respir. Crit. Care. Med.*, **162**, 167–173.

Greve, J. M., Davis, G. and Mayer, A.M. (1989). The major human rhinovirus receptor is ICAM-1, *Cell* **56**, 839.

Groenborg, H., Borum, P., Winther, B., et al. (1983a). Nasal methacholine and antihistamine reactivity during a common cold, *Eur. J. Respir. Dis.* **64** (Suppl. 128 part II), 406–408.

Groenborg, H., Winther, B., Brofjeldt, S., et al. (1983b). Effects of oral norephedrine on common cold symptoms, *Rhino.ology* **21**, 3–12.

Gwaltney, J. M. and Ruckert, R. R. (1997). Rhinovirus. In: *Clinical Virology*, Richman, D. D., Whitley, R. J. and Hayden, F. G. (Eds), pp. 1025–1047. Churchill Livingstone, New York, NY.

Gwaltney, J. M., Hendley, J. O., Phillips, C. D., et al. (2000). Nose blowing propels nasal fluid into the paranasal sinuses, *Clin. Infect. Dis.* **30**, 387–391.

Gwaltney, J. M., Hendley, J. O., Simon, G., et al. (1967). Rhinovirus infection in an industrial population. Characteristics of illness and antibody response, *J. Am. Med. Ass.* **202**, 494–500.

Gwaltney, J. M., Phillips, C. D., Miller, R. D., et al. (1994). Computed tomographic study of the common cold, *New Engl. J. Med.* **330**, 25–30.

Gwaltney J. M., Winther, B., Patrie, J. T., et al. (2002). Combined antiviral-antimediator treatment of the common cold, *J. Infect. Dis.* **186**, 147–154.

Hendley, J. O., Gwaltney J. M. and Jordan, W. S. (1969). Rhinovirus infections in an industrial population IV. Infections within families of employees during two fall peaks of respiratory illness, *Am. J. Epidemiol.* **89**, 184–196.

Hytoenen, M. L., Sala, E. L., Malmberg, H. O., et al. (1996). Acoustic rhinometry in the diagnose of occupational rhinitis, *Rhinology* **10**, 393–397.

Johnston, S. L., Pattemore, P. K., Sanderson, G., et al. (1995). Community study of role of viral infections in exacerbation of asthma in 9–11 year old children, *Br. Med. J.* **310**, 1225–1229.

Kapiotis, S., Sengoelge, G., Sperr, W. R., et al. (1996). Ibuprofen inhibits pyrogen-dependent expression of VCAM-1 and ICAM-1 on human endothelial cells, *LifeSci.* **58**, 2167–2181.

Maderazo, E. G., Breaux, S. P. and Woronick, C. L. (1983). Inhibition of human polymorphonuclear leukocyte cell, *J. Pharm. Sci.* **73**, 1403–1406.

Mygind, N. (1979). *Nasal Allergy*. Blackwell, Oxford.

Mygind, N. (1986). *Essential Allergy*. Blackwell, Oxford.

Mygind, N. (1996), *Essential Allergy*, second edn. Blackwell, Oxford.

Mygind, N., Gwaltney, J. M., Winther, B., et al. (2003). The common cold and its relationship to rhinitis, sinusitis, otitis media and asthma, in: *Respiratory Infection in Allergy and Asthma*, S. L. Johnston and N. G. Papadopoulos (Eds), pp. 529–555. Marcel Dekker, New York, NY.

Naclerio, R. M., Proud, D., Lichtenstein, L. M., et al. (1987). Kinins are generated during experimental rhinovirus colds, *J. Infect. Dis.* **157**, 133–142.

Nicholson, K. G., Kent, J. and Ireland, D. C. (1993). Respiratory viruses and exacerbation of asthma in adults, *Br. Med. J.* **307**, 982–986.

Nicholson, K. G., Kent, J., Hammersley, V., et al. (1996). Risk factors for lower respiratory complications of rhinovirus infection in elderly people living in the community: prospective cohort study, *Br. Med. J.* **313**, 1119–1123.

Pattemore, P. K., Johnston, S. L. and Bardin, P. G. (1992). Viruses as precipitants of asthma symptoms. Epidemiology, *Clin. Exp. Allerg.* **22**, 325–336.

Petersson, G., Bacci, E., McDonald, D. M., et al. (1993). Neurogenic plasma extravasation in the rat nasal mucosa is potentiated by peptidase inhibitors, *J. Pharmacol. Exp. Ther.* **264**, 509–514.

Piedimonte, G., Hoffman, J. I., Huseine, W. K., et al. (1993). Neurogenic vasodilation in rat nasal mucosa involves neurokinin I tachykinin receptors, *J. Pharmacol. Exp. Ther.* **265**, 36–40.

Pitkaranta, A., Arruda, E., Malmberg, H., et al. (1997). Detection of rhinovirus in sinus brushing of patients with acute community-acquired sinusitis by reverse transcriptionPCR, *J. Clin. Microbiol.* **35**, 1791–1793.
Pitkaranta, A., Virolainen, A., Jero, J., et al. (1998). Detection of rhinovirus, respiratory syncytial virus, and coronavirus infection in acute otitis media by reverse transcriptase polymerase chain reaction, *Pediatrics* **102**, 291–295.

Proud, D., Gwaltney, J. M., Hendley, J. O., et al. (1994). Increased levels of interleukin-1 are detected in nasal secretion of volunteers during experimental rhinovirus colds, *J. Infect. Dis.* **169**, 1007–1013.

Raphael, G. D., Meredith, S. D., Baraniuk, J. N., et al. (1988). Nasal reflexes, *Am. J. Rhinol.* **2**, 109–116.

Rotbart, H. A. and Hayden, F. G. (2000). Picornavirus infections, *Arch. Fam. Med.* **9**, 913–920.

Satoh, M., Doi, T., Kawasaki, K., et al. (1976). Effect of indomethacin and the other anti-inflammatory agents on activation of dorsal horn cell in the spinal cord induced by intra-arterial injection of bradykinin, *Jpn. J. Pharmacol.* **26**, 309–314.

Skubitz, K. M. and Hammerschmidt, D. A. (1986). Effects of ibuprofen on chemotactic peptide-receptor binding and granulocyte response, *Biochem. Pharmacol.* **35**, 3349–3354.

Sperber, S. J., Hendley, J. O., Hauden, F. G., et al. (1992). Effects of naproxen on experimental rhinovirus colds, *Ann. Int. Med.* **117**, 37–41.

Sperber, S. J., Sorrentino, J. V., Riker, D. K., et al. (1989). Evaluation of an alpha agonist alone and in combination with a nonsteroidal antiinflammatory agent in the treatment of experimental rhinovirus colds, *Bull. NY Acad. Med.* **65**, 145–159.

Vane, J. R. (1971). Inhibition of prostaglandin synthesis as a mechanism of action for aspirin-like drugs, *Nature* **231**, 232–235.

Venezio, F. R., Divincenzo, C., and Pearlman, F. (1985). Effect of newer nonsteroidal anti-inflammatory agents, ibuprofen, fenoprofen and sulindac on neutrophil adherence, *J. Infect. Dis.* **152**, 690–694.

Winther, B. and Mygind, N. (2001). The therapeutic effectiveness of ibuprofen on the symptoms of naturally acquired common colds, *Am. J. Rhinol.* **15**, 239–242.

Winther, B., Gwaltney, B. and Hendley, J. O. (1990). Respiratory virus infection of monolayer cultures of human nasal epithelial cells, *Am. J. Respir. Dis.* **141**, 839–845.

Winther, B., Brofeldt, S., Christensen, B., et al. (1984a). Light and scanning electronmicroscopy of nasal biopsy material from patients with naturally acquired common colds, *Acta Otolaryngol.* **97**, 309–318.

Winther, B., Brofeldt, S., Groenborg, H., et al. (1984b). Study of bacteria in the nasal cavity and nasopharynx during naturally acquired common colds, *Acta Otolaryngol.* **98**, 315–320.

Winther, B., Farr, B., Turner, R. B., et al. (1984c). Histopathologic examination and enumeration of polymorphonuclear leukocytes in the nasal mucosa during experimental rhinovirus colds, *Acta Otolaryngol.* **413** (Suppl.), 19–24.

Winther, B., Gwaltney, J. M., Mygind, N., et al. (1986). Sites of rhinovirus recovery after point inoculation of the upper airway, *J. Am. Med. Ass.* **256**, 1763–1767.

Winther, B., Gwaltney, J. M., Humphries, J., et al. (2002a). Cross-linked fibrin in the nasal fluid of patient with the common cold, *Clin. Infect. Dis.* **34**, 708–710.

Winther, B., Hayden, F. G., Arruda, E., et al. (2002b). Viral respiratory infection in schoolchildren: Effects on middle ear pressure, *Pediatrics* **109**, 826–832.

Winther, B., Innes, D. F., Bratsch, J., et al. (1992). Lymphocyte subsets in the nasal mucosa and periphery blood during experimental rhinovirus infection, *Am. J. Rhinol.* **6**, 149–156.

Zhu, Z., Tang, W., Gwaltney, J. M., et al. (1997). Rhinovirus stimulation of interleukin-8 in vivo and in vitro: role of NF-kβ, *Am. J. Physiol.* **273**, L814–L824.