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Influenza virus and rhinovirus-related otitis media: potential for antiviral intervention

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Abstract

Adults frequently develop eustachian tube dysfunction and middle ear pressure (MEP) abnormalities during natural and experimental influenza and human rhinovirus (HRV) infections. Oral rimantadine treatment did not reduce the otologic manifestations of experimental influenza in adults or natural influenza in children. However, intranasal zanamivir and oral oseltamivir significantly reduced MEP abnormalities during experimental influenza in adults, and oseltamivir treatment appears to reduce the likelihood of otitis media in children with acute influenza. Investigational anti-HRV agents, including intranasal tremacamra, intranasal AG7088, and oral pleconaril, warrant study in this regard. Depending on the virus, early antiviral therapy has the potential to impact the risk of otitis media following respiratory tract infections.

Keywords: Influenza virus; Rhinovirus; Antivirals; Acute otitis media; Amantadine; Rimantadine; Neuraminidase inhibitors; Zanamivir; Oseltamivir; Interferon; Pleconaril

1. Introduction

Most new episodes of otitis media are temporally associated with acute viral respiratory tract illnesses (VRIs). Following VRI, the risk of developing clinically manifest otitis media is highly age related. Although it is relatively common for respiratory viral infections in children to lead to otitis media with effusion (OME) and acute otitis media (AOM), the frequency of such complications is much lower in adolescents and adults. For example, among 2499 adults and teenagers, mostly previously healthy, with acute influenza virus illness, only 1.6% developed physician diagnosed ear infections leading to antibiotics [1]. Similarly, among adults with proven human rhinovirus (HRV) illness, only two (0.5%) instances of presumed AOM were documented in studies involving 420 persons [2–4]. However, adults frequently develop eustachian tube (ET) dysfunction and middle ear pressure (MEP) abnormalities during naturally occurring and experimentally induced VRIs. Tympanometric measurements in children have also documented an association between upper respiratory tract illnesses and otitis media [5]. Measurement of such changes provide objective means of assessing the effects of therapeutic interventions.

Important differences may exist among the common respiratory viruses in their propensity to cause AOM in infants and children. One longitudinal day care study found that infection with influenza A or B, respiratory syncytial virus (RSV), or adenovirus conferred a greater risk of otitis media than did infection with parainfluenza virus (PIV), enterovirus, or human rhinovirus (HRV) [6]. In a recent pediatric study there was virologic evidence for middle ear invasion by RSV (74%), PIV (52%), and influenza A or B (42%) more often than by enterovirus (11%) and adenovirus (4%) in middle ear fluid (MEF) samples obtained by tympanocentesis [7]. Pathogenic bacteria were recovered from 65% of MEFs containing virus, more often in association with influenza virus. However, among viruses responsible for upper respiratory tract infections, HRV is the most common and accounts for up to 50% of such episodes. In another recent study of children aged 3 months to 7 years with AOM, nasopharyngeal aspirates and MEFs

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were tested by reverse transcription-polymerase chain reaction (RT-PCR) for viral RNA of HRV, RSV, and human coronavirus (HCV) [8]. Three-quarters of the children had detectable viral RNA in either nasopharyngeal aspirates (62% of samples) and/or middle ear effusions (48%) for one or more of these three common respiratory viruses. HRV RNA was detected in both MEF and nasopharyngeal aspirate in 20%, in MEF alone in 4%, in nasopharyngeal aspirate alone in 11%, so that 35% of these AOM episodes were linked to HRV infection. Bacterial pathogens were detected in 62% of MEF samples; one-half of the HRV-positive MEF had no bacterial pathogen identified. HRV infection has also been linked to a higher frequency of antibiotic failure in mixed viral–bacterial AOM than other respiratory viruses [9], as well as to the development of otitis media with effusion (OME) [10].

2. Pathogenesis

The mechanisms by which VRIs cause or predispose to the development of AOM are not fully elucidated. As described above, the presence of virus or its components (antigen or nucleic acid) in MEFs may indicate replication in the eustachian tube (ET) and middle ear mucosa with the potential for direct cytopathic effects, cytokine elaboration, and other inflammatory responses. In addition to direct viral invasion of the middle ear, nasopharyngeal inflammation might cause ET dysfunction due to secretions, mucosal swelling, impaired mucociliary clearance, and/or direct mucosal damage due to virus. This could reduce clearance functions and potentially facilitate bacterial infection in the middle ear. Studies of experimentally induced influenza and HRV infections in adult volunteers have helped document a causal relationship between VRIs and AOM by using objective measures to document ET dysfunction, abnormal middle ear pressures (MEPs), and in some instances otitis media following infection with either of these viruses [11]. The temporal sequence of events appears to be initial ET dysfunction, followed by altered MEP regulation typically leading to middle ear under-pressures. Under-pressures may lead to aspiration of nasopharyngeal secretions into the middle ear and, when prolonged, to the accumulation of fluid and the development of otitis media. However, the relative contributions of virus-induced cytopathology, host inflammation, and other immunomodulating events within the mucosa of the upper respiratory tract are incompletely defined. These are also likely to differ among the different respiratory viruses. For example, HRV infection causes little histologically detectable alteration of the upper respiratory mucosa, whereas influenza is associated with substantial epithelial damage.

2.1. Experimental infections

The measurement of MEP changes during infection by impedance tympanometry has provided a useful tool to assess objectively the severity and duration of pathophysiologic abnormalities affecting the middle ear. For example, a comparison of the otologic outcomes in adults experimentally infected with influenza A(H1N1) or HRV type 39 found that the frequency of abnormal MEPs detected by tympanometry increased in both groups after infection [11]. For HRV infection the frequency reached a maximum on day 3 post infection, at which time 53% of subjects and 37% of ears, were affected. For influenza the frequency of abnormalities reached a maximum on day 5 post infection, at which time 79% of subjects and 64% of ears, had abnormalities. Most of the abnormalities are accounted for by significant under-pressures (≤ -100 mmH_2O), whereas over-pressures (≥ 50 mmH_2O) occurred in approximately 20–25% of subjects. Such physiologic abnormalities tend to resolve spontaneously over several days, so that the frequency of otoscopic evidence of AOM is relatively low. However, experienced otolaryngologists have found otoscopic changes in approximately 6% of HRV-infected and up to 19% of influenza-infected volunteers [11]. Most of these cases are asymptomatic, although some influenza-infected subjects develop otalgia and very uncommonly purulent AOM. Although these two viral infections do not differ in the magnitude of nasal secretions induced by infection, influenza appears to provoke a higher frequency and severity of MEP abnormalities and otitis media. This may reflect an increased epithelial damage of influenza relative to rhinoviruses.

2.2. Natural infections

Changes in MEPs are also found in adults during naturally occurring influenza and HRV illnesses. Such changes are evidence for ET dysfunction and are likely a useful surrogate marker for the risk of AOM development, since sustained underpressures are associated with the development of MEF. Among 17 previously healthy adults with proven febrile influenza A(H3N2) illness, 76% had major MEP abnormalities (≤ -100 or ≥ 100 mmH_2O), primarily under-pressures, during their illnesses [12]. Such abnormalities are observed in $< 5\%$ observed during testing obtained before illness in adults. When they first presented with acute influenza, generally about 1–1.5 days after symptom onset, abnormal MEP values were present in 35%. The frequency increased to approximately 60% 3 days later but then decreased to 35% 2 days later and to 18% at 3 weeks. One patient with sustained under-pressures later developed over-pressures and overt AOM requiring antibiotic therapy. Similarly, in two separate studies of

natural HRV infection involving a total of 91 adults, major MEP abnormalities (≤ -100 or ≥ 100 mmH_2O) were detected in 61 and 47% of subjects during their illness [3]. Underpressures accounted for most of the abnormal measurements. The frequency of abnormal MEP values increased from 24 to 28% on the first day to approximately 35–45% on days 2–3 and remained at approximately 20–45% on day 5 depending on the study, but diminished thereafter. No clear relationships between subjective complaints of ear pain or colds severity were found in these studies. One subject with bilateral underpressures on day 5 later received antibiotics for apparent AOM. Other studies have found that about 10% of adults with proven HRV colds have residual MEP abnormalities, primarily underpressures, at 1 week [2,4]. The rapid spontaneous resolution of such changes probably accounts for the low risk of AOM in adults with natural HRV colds.

3. Antiviral therapies

The available evidence suggests that otitis media developing as a complication of viral upper respiratory illness is due to disruption of normal ET function which in turn causes middle ear underpressures and accumulation of fluid. Although prevention of the viral infection by vaccines can reduce the risk of influenza-associated AOM, it remains to be established whether early inhibition of viral replication can either prevent clinically important middle ear abnormalities from developing or possibly speed the resolution of established ones. Part of this uncertainty stems from lack of information about how important ongoing viral replication is in causing ET dysfunction and how often the middle ear is invaded by virus. Effective prevention of middle ear complications during a VRI may require pre-emptive therapy with both antiviral and adjunctive anti-inflammatory agents. Early treatment of a viral upper respiratory tract illness with an effective antiviral might prevent development of AOM by decreasing virus load and its associated pathophysiologic abnormalities, as well as reducing the likelihood of direct viral invasion of the middle ear. Perhaps it may also affect bacterial colonization and the likelihood of progression to a purulent otitis media. The delay in development of MEP changes in adults with HRV and particularly influenza suggests that there is an opportunity to intervene with antiviral agents to reduce the likelihood of persistent MEP abnormalities and eventual AOM. An important aspect of antiviral therapy is route of administration. Topical administration (e.g. nasal drops or sprays) is unlikely to deliver effective drug concentrations to the ET and middle ear. Orally absorbed agents which distribute to the respiratory mucosa are much more likely to inhibit viral replication at multiple sites in the upper respiratory tract.

3.1. Rhinovirus

The experience with regard to antiviral therapy of HRV infections is limited, and it remains uncertain whether early treatment might prevent middle ear disease. Pirodavir is a capsid-binding anti-picornaviral agent with in vitro activity against most HRV serotypes. A series of studies in experimental HRV infection found that intranasal sprays given $6\times$/day before viral inoculation reduced the frequency of viral infection and clinical colds (efficacy 85%), whereas $3\times$/day administration as prophylaxis or $6\times$/day as early treatment beginning 24 h after viral inoculation provided no clinical benefits [13]. Corresponding reductions in the frequency of abnormal MEPs (< -50 or > 20 mmH_2O) were found in the study employing $6\times$ daily prophylaxis, whereas no significant differences in the frequency of abnormal MEPs were found in the three trials in which no significant clinical effects were observed. Such findings indicate that preventive strategies that reduce the frequency of HRV colds will reduce the frequency of associated MEP abnormalities.

In adults with natural HRV colds of 2-day duration or less, pirodavir given intranasally $6\times$ daily while awake was compared to placebo [4]. Among the persons with laboratory documented HRV colds, pirodavir treatment was associated with reduced frequencies of virus recovery on days 3 and 5 of treatment but no significant differences in the resolution of respiratory symptoms. Similarly, no important effects were observed in the proportions of patients who had middle ear abnormalities during the treatment period. Major abnormalities were detected in 24% of placebo and 27% of pirodavir recipients at enrolment. These proportions did not differ significantly between the groups on day 3 (33% placebo vs. 23% pirodavir), day 5 (18 vs. 19%) or day 7 (13 vs. 10%) of study. One pirodavir recipient was treated with oral antimicrobics for otitis media beginning 2 weeks after study entry. The negative findings were predicted by the negative observations in early treatment of experimental colds with priodavir described above. Such outcomes suggest that beneficial effects on MEP abnormalities require interventions that will impact on the degree of nasopharyngeal inflammation and associated symptoms.

Another small study of experimental HRV infection tested the efficacy of recombinant IFN-β given as early treatment 12 MU $3\times$ daily beginning 36 h after infection [14]. Illness rates and severity did not differ significantly between the interferon and placebo groups but the frequency of virus shedding was reduced on several post-challenge days and abnormal ET function in at least one ear was identified somewhat less often (44% of observations vs. 62% of observations) in infected interferon recipients compared to placebo recipients. Only a fraction of these individuals had detailed otologic test-

ing. MEP abnormalities (< -50 or > 20 mmH_2O) occurred in at least one ear during 18% of observations in interferon recipients compared to 38% of in placebo, and marked ME under-pressures (< -100 mmH_2O) were detected in three (60%) of five placebo compared to only three (22%) of 13 interferon recipients. Marked under-pressures were detected in 25% of observations in a placebo group compared to only 3% in the interferon group. The results suggest that interferon administration was associated with early resolution of abnormalities in ET function and MEP abnormalities, perhaps through its antiviral or immunomodulating effects. The time and course of resolution of ET and MEP abnormalities in the interferon group paralleled that for viral shedding, an observation which suggested a causal relationship. Viral replication in or near the ET may cause dysfunction, and early antiviral treatment is able to impact on this process. If validated in future studies, the findings suggest that, at least in the context of experimental HRV infection, it is possible to intervene with an antiviral agent shortly after infection and moderate middle ear abnormalities.

Studies are needed to determine whether early antiviral therapy can prevent middle ear disease in high risk groups. Recently several investigational agents with differing mechanisms of antiviral action have shown antiviral and clinical activity in experimentally-induced HRV or coxsackievirus A21 of susceptible adults. These include intranasal administration of the receptor decoy soluble intracellular adhesion molecule-1 (sICAM-1, tremacamra) [15], oral administration of the anti-picornavirus capsid-binder pleconaril [16] and intranasal administration of the HRV3C protease inhibitor AG7088 (F. Hayden et al., unpublished observations). Oral pleconaril appears to reduce symptom duration and severity of picornavirus in adults [17] and warrants study in children to determine its possible effects on AOM development.

3.2. Influenza

The effect of antiviral interventions on the course of experimental influenza and its otologic manifestations have yielded somewhat conflicting results. The M2 protein inhibitor rimantadine was tested in a study involving 105 susceptible adults experimentally infected with influenza A(H1N1) virus and randomly assigned to oral rimantadine 100 mg or placebo twice daily for 8 days beginning 48 h after viral inoculation [18]. The initiation of treatment was selected to correspond to the timing of obvious symptom development. Rimantadine treatment was associated with reduced frequencies of virus shedding on days 3–6 after challenge, a lower symptom burden, and a trend toward a reduced illness rate (38% of rimantadine vs. 53% of placebo). However, rimantadine had no effect on objective measures of nasal patency, mucociliary clearance, nasal signs, or specifically otologic manifestations of infection. The frequency of subjects developing otalgia (overall, 38% rimantadine vs. 58% placebo) peaked in both groups at about 30% on day 3 after infection and then decreased. Similarly, the proportion of observations with abnormal ET function showed a progressive increase to a maximum on day 3 after infection and then diminished thereafter. For both groups the frequency of abnormal MEPs increased beginning on the day the treatment was initiated, peaked 2 or 3 days later, and did not differ between the groups. Specifically, the number of days with abnormal MEP (< -100 mmH_2O) during treatment was similar in rimantadine (mean, 2.4 days) and placebo (2.0 days) groups. Three episodes of otitis media developed in the rimantadine group compared to two in the placebo, most commonly between days 3 and 6 after challenge. Two tympanocentesis yielded MEF culture negative for virus or bacteria. In children aged 1–12 years with acute influenza, rimantadine therapy reduced the frequency of virus recovery and illness severity on the first several days of treatment but not thereafter [19]. The frequencies of earache or otitis were higher in rimantadine (19%) than acetaminophen (6%) recipients at study entry, and no important treatment affect on earache frequency was subsequently found on day 5 (27% rimantadine vs. 13% control) or day 7 (23 vs. 8%). These results do not suggest that rimantadine therapy either prevented the development or accelerated the resolution of ear complaints.

The potency and timing of antiviral intervention are important variables in regard to preventing otologic abnormalities. Indeed, studies of the anti-influenza neuraminidase inhibitors, specifically intranasal zanamivir and oral oseltamivir, given at earlier time points in the course of experimental infections have found beneficial effects on otologic endpoints. Not surprisingly prevention of influenza illness also prevents middle ear disease. In a study of experimental influenza A(H1N1) infection of adults, prophylactic administration of intranasal zanamivir starting before virus exposure significantly reduced the frequencies of infection (73 vs. 13%), URI, viral titers, frequency of ear ache or pressure (45 vs. 18%), and MEP abnormalities (≤ -100 or ≥ 100 mmH_2O) (61 vs. 15%). More importantly, early treatment with intranasal zanamivir beginning 26–32 h after virus inoculation found significant reductions in the frequencies of earaches (50 vs. 16%) and abnormal MEPs (73 vs. 32%) among infected subjects, as well as reductions in the number of days with MEP abnormalities. In general, no correlations between the presence of over- or under-pressures and the presence of ear symptoms (ear ache or pressures) have been recognized in experimental influenza studies [12]. However, an association has been recognized between more prolonged underpressures (≥ 2 days) and the presence of URI

symptoms on ≥ 2 days. Furthermore, under-pressures correlate with measures of viral replication, an observation which suggests that antiviral therapy may be beneficial.

When used for prophylaxis for experimental influenza A(H1N1) virus infection, oral oseltamivir once or twice daily was also highly protective against virus recovery from the upper respiratory tract and virus associated in infection-related illness [20]. Early oseltamivir treatment beginning at 28 h after viral inoculation was also associated with significant antiviral effects, reduced symptom scores, and lower nasal proinflammatory cytokine levels (IL-6, TNF-α, IFN-γ). This was associated with halving of nasal mucus weights and symptom scores and 2-day reductions in the duration of viral shedding and time to alleviation of illness. The frequency of upper respiratory tract illness was reduced, and significant MEP abnormalities were seen in 54% of placebo recipients compared to 28% of those receiving oseltamivir. Such results further substantiate a link between virus replication, cytokine elaboration and symptom production during acute influenza. These findings also indicate that early inhibition of viral replication down regulates this series of responses and reduces the likelihood of significant ET dysfunction leading to abnormal MEP. However, the signs and symptoms in such experimental infections are relatively mild compared to naturally occurring influenza in patients presenting for medical care and the timing of antiviral intervention earlier. Despite these caveats, preliminary analysis of results from a study of children aged 1–12 years with acute influenza has found that oseltamivir treatment provided symptom benefit and reduced the likelihood of AOM development [21]. These findings indicate that early antiviral intervention can reduce the risk of middle ear disease during influenza in children.

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