Asthma, rhinitis, other respiratory diseases

Intranasal fluticasone propionate does not prevent acute otitis media during viral upper respiratory infection in children

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Background: Acute otitis media (AOM) is the most common complication of a viral upper respiratory infection (URI) in children. The virus-induced host inflammatory response in the nasopharynx plays a key role in the pathogenesis of AOM. Suppression of this inflammatory process might prevent the development of AOM as a complication.
Objective: We sought to assess the effect of intranasally administered fluticasone propionate on prevention of AOM during a viral respiratory infection.
Methods: A total of 210 children (mean age, 2.1 years; range, 0.7-3.9 years) with normal middle ear status and URI of 48 hours' duration or less were randomly allocated to receive either fluticasone (100 μg twice daily) or placebo for 7 days. The specific viral cause of the infection was determined from nasopharyngeal aspirates obtained at the first visit. The children were re-examined at the end of the 7-day medication period.
Results: In the fluticasone group AOM developed in 40 (38.1%) of 105 children compared with 29 (28.2%) of 103 children receiving placebo (*P* = .13). The viral cause of the respiratory infection was determined in 167 (86.1%) of 194 children from whom a nasopharyngeal aspirate was obtained. In children with rhinovirus infection, AOM developed significantly more often in the fluticasone group (45.7%) than in the placebo group (14.7%, *P* = .005).
Conclusion: Intranasally administered fluticasone does not prevent the development of AOM during URI but may increase the incidence of AOM during rhinovirus infection. (J Allergy Clin Immunol 2000;106:467-71.)

Key words: Acute otitis media, fluticasone propionate, respiratory infection, rhinovirus, virus

> *Abbreviations used*
> AOM: Acute otitis media
> FP: Fluticasone propionate
> URI: Upper respiratory infection

Acute otitis media (AOM) is a frequent complication of viral upper respiratory infection (URI) in children.[1,2] Effective methods to prevent the development of AOM would be of the utmost importance because of the high incidence rates, substantial costs, and potential long-term developmental sequelae of this disease.[3-5] Unfortunately, few preventive methods are currently available.[6] Increasing antimicrobial resistance of bacteria, which may complicate the treatment of AOM,[7] further emphasizes the need to search for new prevention methods on the basis of the knowledge of the pathogenetic mechanisms of AOM.

Respiratory viruses initiate the cascade of events that finally leads to development of AOM.[8] Viruses are known to induce a release of inflammatory mediators (eg, histamine, leukotrienes, kinins, interleukins, and TNF-α) from target cells in the nasopharynx.[8-12] After intranasal challenge, many of these mediators have been shown to provoke dysfunction of the eustachian tube,[13] which is considered the most important factor in the development of AOM.[14] Eustachian tube dysfunction causes negative pressure in the middle ear and may eventually lead to production of middle ear effusion.[15] The median time from the onset of URI to the development of AOM is 3 to 4 days,[16,17] which provides a window of opportunity for intervention to prevent AOM.

Because the host inflammatory response during URI plays a central role in the pathogenesis of AOM, it could be hypothesized that the use of potent anti-inflammatory agents, such as corticosteroids, might suppress the inflammatory process and prevent the development of AOM as a complication. In an experimental study of rhinovirus infection in adults, glucocorticoids were shown to reduce inflammation in the nasopharynx during the first days of the infection.[18] We conducted a randomized, double-blind, placebo-controlled study to assess whether fluticasone propionate (FP) administered intranasally early during the course of URI would prevent the development of AOM in children. Furthermore, to discover

potential differences in the effect of FP between different viral infections, we used extensive methods to determine the specific viral cause of the URIs.

METHODS
Patients

The study participants were recruited by informing families through daycare centers, family daycare, health centers, well-baby clinics, and local media in the Turku area between February 1996 and April 1998. Children qualified for enrollment if they were younger than 4 years and their signs and symptoms of URI had started within the preceding 48 hours. The exclusion criteria were as follows: middle ear effusion in either ear; any infection requiring antimicrobial therapy; any use of antimicrobial agents or steroids during the preceding 2 weeks; previous adenoidectomy or placement of tympanostomy tubes; any known immunodeficiency; Down syndrome; cleft palate; and the use of any investigational drug during the preceding 4 weeks. Of 301 children initially examined at the study clinic, 91 (30%) had to be excluded from participation because of AOM or otitis media with effusion.

Study conduct

This was a randomized, double-blind, placebo-controlled study. The parents of all participants gave written informed consent, and the study protocol was approved by the Ethics Committee of Turku University Hospital. The children were examined at the study clinic within 48 hours of the onset of URI. The middle ear status was carefully examined by pneumatic otoscopy and additionally by tympanometry whenever the child was cooperative. A nasopharyngeal aspirate specimen was obtained by using a disposable mucus extractor (UNO, Maersk Medical). The eligible children were randomly allocated to receive either intranasal aqueous FP (50 μg per nostril twice daily; a total daily dose of 200 μg) or an identical placebo for 7 days (both drugs supplied by GlaxoWellcome, UK). The first doses were given at the study clinic by the parents, who were carefully taught to administer the medication into the nostrils of the child. The parents were provided with a diary card for daily recording of their child's symptoms (rhinitis, cough, fever >37.5°C, and earache), all medications given, and possible adverse events. The children were re-examined at the end of the 7-day medication period or additionally, in the meantime, whenever the parents suspected AOM. The study physician inquired about compliance to medication and the occurrence of adverse events at each visit and at the end of the study period when the diary cards were collected. All visits were free of charge, and the families were not compensated for participation in the study.

Virological analyses

The nasopharyngeal aspirates were processed freshly for antigen detection by time-resolved fluoroimmunoassay, as described earlier.[19-21] The viruses included in the antigen detection panel were respiratory syncytial virus; parainfluenza virus types 1, 2, and 3; influenza A and B viruses; and adenovirus.

Immediately after collection of the nasopharyngeal aspirate, a sterile cotton swab was dipped into the aspirate, inserted into a vial containing viral transport medium (5% tryptose phosphate broth, 0.5% BSA, and antibiotics in PBS), and stored at –70°C for later RT-PCR analysis. Positive controls and several negative controls were included in each PCR analysis. Contamination of the specimens was prevented by strict precautions, including the use of separate rooms during each step of the RT-PCR assay. Nucleic acid sequences for rhinoviruses and enteroviruses were detected by RT-PCR assays with subsequent time-resolved fluorometric microwell hybridization assay[22,23] or gel electrophoresis with ethidium bromide staining.[24] A cutoff value for a hybridization-positive specimen was 5 times the mean value of water template controls. A hybridization-positive specimen was identified as rhinovirus or enterovirus if there was at least a 10-fold difference between the fluorescence values from rhinovirus- and enterovirus-specific probes. A second RT-PCR analysis was done for aliquots of RNA from specimens that yielded a visible band corresponding with the expected amplicon size on the agarose gel but which gave a negative or dual-positive hybridization result. Using another PCR primer pair, rhinoviruses and enteroviruses could be discriminated by amplicon size.[24] If the picornavirus-positive amplicons from the first PCR could not be resolved into rhinoviruses or enteroviruses by the hybridization assay or by the second RT-PCR analysis, they were regarded as unclassified picornaviruses. In addition, 29 specimens that were negative according to all the other methods described were tested by an in-house RT-PCR assay for human coronavirus strains 229E and OC-43 (M. Waris, unpublished data). The primers and probes were modified from primers and nucleotide sequences either described earlier[25-27] or available from GeneBank and synthesized by Eurogentec (Seraing, Belgium). PCR products were detected by using agarose gel electrophoresis and ethidium bromide staining. Bands corresponding to 229E and OC-43 amplicon sizes were identified on the gel, and the results were confirmed by Southern hybridization.

Definitions

AOM was defined as the presence of middle ear effusion (on the basis of the appearance and mobility of the tympanic membrane), together with one or more signs or symptoms of acute infection (rhinitis, cough, fever, earache, and irritability).[28] The same experienced otoscopist (A.R.) performed 93% of all otoscopic examinations during this study. The diagnosis of URI was based on new-onset rhinitis alone; rhinitis together with cough, fever, or both; or cough and fever without signs of a lower respiratory infection. The duration of URI symptoms (rhinitis, cough, and fever >37.5°C) was recorded as whole days; a part of a 24-hour-period was defined as 1 day.

Sample size and statistics

The prespecified primary outcome measure was the number of attacks of AOM. It was estimated that AOM would develop in 25% of the children receiving placebo.[29] To detect a 60% reduction in the number of attacks of AOM at the significance level of 5% and with a power of 80%, the minimum required number of children in each group was 97. The Pearson χ^2 test was used to analyze the occurrence of AOM between the treatment groups. Among rhinovirus-positive children, the associations between the primary outcome variable (AOM) and the predictive variables (risk factors for AOM and the use of FP) were studied by using multivariate logistic regression analysis. Probability (*P*) values of less than .05 were considered statistically significant, and all P values were two-sided.

RESULTS

A total of 210 children were randomized; one child discontinued the study medication, and another used it improperly. Of 208 children who acceptably completed the study, 105 received FP, and 103 received placebo. The demographic characteristics of the groups were comparable, except that parental smoking was more frequent in the FP group (Table I). Compliance to medication was good; a single dose was missed by 10 children in the FP group and 14 children in the placebo group. There were 8 adverse events recorded: blood-tinged nasal mucus (2 in

the FP and 4 in the placebo group); herpes simplex vesicle (one in the placebo group); and hospitalization caused by pneumonia (one in the FP group).

Of the 105 children in the FP group, AOM developed during the treatment in 40 (38.1%) children. In the placebo group AOM was diagnosed in 29 (28.2%) of the 103 children, and the difference was not statistically significant ($P = .13$). The median day for diagnosing AOM was day 7 of the study (ie, the day of the preplanned control visit). Sixteen (23%) of 69 cases of AOM were diagnosed before day 6 and 3 (4%) of 69 cases before day 3 of the study. The median durations of rhinitis, cough, and fever after commencement of the study medication were 6.0, 3.0, and 0.0 days, respectively, in both groups.

The specific viral cause of URI was determined in 167 (86.1%) of 194 children from whom a nasopharyngeal aspirate specimen was obtained (Table II). Rhinovirus was the most frequently found causative agent, occurring in a total of 74 (38.1%) children. Enteroviruses were detected in 48 (24.7%) children. Among both rhinovirus- and enterovirus-positive children, the demographic characteristics were comparable between the treatment groups, as well as between these and other children (data not shown).

In the 69 children with rhinovirus as a single causative agent, AOM developed in 16 (45.7%) of 35 FP recipients compared with 5 (14.7%) of 34 children receiving placebo ($P = .005$, Table III). Even after adjustment with known risk factors for AOM (age, sex, breast-feeding, parental smoking, use of pacifier, and daycare outside home), the use of FP was significantly associated with the increased incidence of AOM (odds ratio, 4.1; 95% confidence interval, 1.2-14.5; $P = .027$). No significant differences were observed in the occurrences of AOM between the FP and placebo groups in children with any other cause of URI (Table III).

DISCUSSION

The results of this study demonstrate that intranasally administered FP started early during the course of viral URI does not prevent the development of AOM in young children. This finding is in good accordance with previous studies of the efficacy of steroids in the treatment or prevention of URI in adults. In an experimental study of rhinovirus infection, Gustafson et al[30] showed that although oral prednisone therapy decreased local kinin concentrations in the nasopharynx, it did not alleviate the clinical symptoms of the volunteers. In another experimental study[18] combination of intranasal beclomethasone and oral prednisone had only a modest and short-lived effect on the clinical symptoms of the patients infected with rhinoviruses. Recently, Puhakka et al[31,32] studied the efficacy of intranasally administered FP in the treatment of natural common cold in otherwise healthy young adults and reported that this treatment neither decreased the incidence of sinusitis nor diminished the clinical symptoms of the patients. The results of all these studies, including the present one, clearly indicate that steroid treatment alone may not be effective in

TABLE I. Demographic characteristics of the treatment groups[*]

Variable	FP (n = 105)	Placebo (n = 103)
Male	48 (45.7%)	48 (46.6%)
Age (y)	2.0 ± 0.8	2.2 ± 0.8
Duration of preceding symptoms		
<24 h	82 (78%)	87 (84%)
24-48 h	23 (22%)	16 (16%)
Attacks of otitis media before study entry	4.0 ± 2.4	4.2 ± 2.9
Exclusive breast-feeding (mo)	2.8 ± 1.8	3.0 ± 1.7
Parental smoking	49 (47%)	31 (30%)
Current use of pacifier	50 (48%)	47 (46%)
Daycare outside home	83 (79%)	84 (81%)
History of any allergy	12 (11%)	16 (16%)
History of allergic rhinitis	2 (2%)	4 (4%)

[*]Data are shown as means ± SD for continuous variables and number (percent) for categoric variables.

TABLE II. Viral cause of URI in 194 children[*]

Virus	No.	%
Rhinovirus	74	38.1
Enterovirus	48	24.7
Unclassified picornavirus	30	15.5
Respiratory syncytial virus	8	4.1
Parainfluenza virus type 3	6	3.1
Influenza A virus	4	2.1
Adenovirus	3	1.5
Coronavirus	2	1.0
Influenza B virus	1	0.5
Parainfluenza virus type 1	1	0.5
Negative	27	13.9

[*]Ten children had a dual viral infection: rhinovirus and parainfluenza virus type 3 (n = 2), rhinovirus and parainfluenza virus type 1 (n = 1), rhinovirus and influenza A virus (n = 1), rhinovirus and adenovirus (n = 1), enterovirus and influenza A virus (n = 1), enterovirus and adenovirus (n = 2), unclassified picornavirus and respiratory syncytial virus (n = 2).

reducing the severity or duration of the symptoms of URI or in preventing the development of common complications, such as AOM or sinusitis.

Our finding that treatment with FP significantly increased the incidence of AOM during rhinovirus infections was entirely unexpected. This observation may have substantial clinical implications because rhinoviruses are the most common causative agents of URI[33] and steroids are widely used in the treatment of various conditions in both children and adults. No explanations are readily available for the increased risk of AOM caused by FP treatment during rhinovirus infections. Systemic effects of FP are very unlikely because the systemic bioavailability of this drug after intranasal administration is very low (<2%).[34] In adults the use of steroids during rhinovirus infections has been shown to increase the viral titers in the nasopharynx[30] and result in prolonged shedding of rhinoviruses.[32] In this way steroids might inten-

TABLE III. Incidence of AOM in the FP and placebo groups according to the viral cause of URI

Viral cause	FP		Placebo		P value*
	No.	AOM	No.	AOM	
All children	105	40 (38.1%)	103	29 (28.2%)	.13
Rhinovirus†	35	16 (45.7%)	34	5 (14.7%)	.005
Enterovirus†	21	8 (38.1%)	24	8 (33.3%)	.74
Other than picornavirus or no virus detected	24	8 (33.3%)	18	10 (55.6%)	.15

*Pearson χ^2 test.
†The virus as a single finding.

sify, rather than suppress, the inflammatory reaction in the nasopharynx, which could lead to more severe dysfunction of the eustachian tube. This theory may not, however, sufficiently explain our present observation because steroids have been reported to increase viral shedding also in infections with causes other than rhinovirus.[35-37] Furthermore, a recent in vitro study suggested that steroids have no direct effect on rhinovirus replication in cultured respiratory epithelial cells.[38] We found no effect of FP on the incidence of AOM in children with URI caused by enteroviruses or any other viruses. However, we cannot exclude the possibility that intranasal FP might even prevent AOM during some viral infections because the incidence of many viral infections was too low for any meaningful analysis. Taken together, our findings suggest that the effect of FP, and perhaps that of steroids in general, may vary significantly during different viral infections.

The use of extensive methods for detection of viruses in nasopharyngeal aspirates enabled us to determine the specific viral cause of URI in more than 80% of the children. Despite the high recovery rate of viruses, the relative distribution of different types of viruses in this study is not generalizable to unselected groups of children because we had to exclude almost one third of all children brought to the study clinic because they already had AOM. Also, it is probable that the parents of the sickest children did not want to participate in any clinical trial. These reasons might at least partly explain the low rates of respiratory syncytial virus and influenza viruses in the study children. In spite of these limitations, our results suggest that enteroviruses have a prominent role in the cause of URI in children. Although enteroviruses have been identified as a cause of URI in children previously,[39] descriptions of enterovirus infections have mostly concentrated on large outbreaks with severely ill patients,[40] and URI is infrequently included in the list of manifestations of enterovirus infections.[41]

We conclude that intranasally administered FP does not prevent the development of AOM during URI in children and may even increase the risk of AOM during rhinovirus infections. These findings suggest that the effect of steroids may vary significantly during different respiratory viral infections. Because of the widespread use of steroids and the high prevalence of rhinovirus infections in the community, further studies in this area are needed.

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