The Journal of Laryngology & Otology (2014), ***128***, *580–585*.

doi:10.1017/S0022215114001340

REVIEW ARTICLE

Xylitol and its usage in ENT practice

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Abstract

Background: Xylitol is a five-carbon sugar alcohol. Natural sources of xylitol include plums, strawberries and raspberries. Xylitol is commercially available in chewing gums, lozenges, syrups, nasal sprays, toothpastes, mouthwashes and other products in some countries. It has gained relative prominence in the past decade as a naturally occurring antibacterial agent.

Objective: A review of contemporary literature was conducted to evaluate the efficacy of xylitol usage in ENT practice.

Method: The English-language literature was searched using the following terms: xylitol, otitis media, nasal, sinusitis, dental caries and preventive therapy. The articles identified were included in this review.

Results: Xylitol has no antibacterial properties of its own; rather, it appears to enhance the body's own innate immunity. Xylitol has anti-adhesive effects on micro-organisms like *Streptococcus pneumoniae* and *Streptococcus mutans*, inhibiting their growth. Xylitol has already been used for preventing otitis media, rhinosinusitis and dental caries. The worldwide spread of drug-resistant strains of pneumococci substantiates the need for new approaches to prevent ENT-related infectious diseases.

Conclusion: Xylitol may be a promising agent for this purpose in ENT practice, but further experimental and clinical studies are required.

Key words: Xylitol; Otitis Media; Rhinitis; Sinusitis; Dental Caries; Preventive Therapy

Introduction

Xylitol is a five-carbon sugar alcohol that is widely distributed in plants; it is found in significant concentrations in plums, strawberries and raspberries.[1] It is used as a bulking agent in foods, and as a low-caloric sweetener in medications, dental care products, chewing gums and candies.[2] Xylitol may also be consumed by diabetics, as an insulin-independent dietary sweetener, having about one-third less calories than sugar.[3] In humans, xylitol is metabolised in the liver to glucose, glycogen and lactic acid. It affects blood glucose levels less than glucose does.[4] It has also been used as a component in parenteral nutrition.[5]

Xylitol is an unsuitable source of energy for many micro-organisms, and it inhibits the growth of *Streptococcus pneumoniae* in the presence of glucose.[6] It has anti-adhesive effects on both *S pneumoniae* and *Haemophilus influenzae*.[7] In addition, xylitol decreases the salt concentration of human airway surface liquid that contains many antimicrobial substances, including lysozyme, lactoferrin, human β defensins and cathelicidin LL-37.[8] Lowering the human airway surface liquid salt concentration can increase the efficacy of the innate immune system, and thereby decrease or prevent airway infections.[9] Xylitol also reduces the adhesiveness of mutans streptococci to tooth biofilms and inhibits the growth of *Streptococcus mutans*, which is the most important bacterium in the development of dental caries.[10] Xylitol exerts selective antibacterial-like actions against mutans streptococci by disrupting glucose cell-wall transport and intracellular glycolysis, thus inhibiting growth.[11]

This review of contemporary literature aimed to evaluate the efficacy of xylitol usage in ENT practice. For this purpose, the English literature was searched using the following terms: xylitol, otitis media, nasal, sinusitis, dental caries and preventive therapy. The articles identified were included in this review.

Xylitol for acute otitis media

Acute otitis media is a common disease and is the main reason for antimicrobial treatment in children. *Streptococcus pneumoniae* is the most common bacterium causing middle-ear infections or sinusitis, and nasopharyngeal carriage of this bacterium has been shown to be a predisposing factor.[12] In their *in vitro*

Accepted for publication 29 October 2013 First published online 7 July 2014

study, Kontiokari *et al*. showed that xylitol reduced the growth of *S pneumoniae* in the nasopharynx, and thus could reduce the carriage of bacteria.[6] This has clinical significance for preventing attacks of acute otitis media caused by pneumococci.

In 1996, a group from Finland (Uhari and colleagues) reported their first trial on xylitol chewing gum for the prevention of acute otitis media. In this randomised trial, a total dose of 8.4 g of xylitol was administered regularly in the form of chewing gum, five times a day for two months. This was shown to reduce the occurrence of acute otitis media by about 40 per cent when compared with a sucrose (control) gum group. However, unexpectedly, there was no decrease in the carriage rate over time in the xylitol group.[13] Two years later, the researchers published the findings of a second trial. In that trial, xylitol was given in syrup form to those children who were not able to chew gum, and in gum or lozenges to those who were old enough to consume them, for three months. The authors reported a significant reduction in the occurrence of acute otitis media when xylitol chewing gum or xylitol syrup was administered five times daily. There was also a decrease in the occurrence of acute otitis media with xylitol lozenges, but the difference was not significant. The use of antimicrobials was significantly lower among those receiving xylitol syrup and xylitol chewing gum compared with their controls, but not in the lozenge group as compared with the control chewing gum group.[14] The results of the clinical trials reviewed in this paper are summarised in Table I.[13–20]

The practicability of giving xylitol five times per day for preventing acute otitis media was questioned, but the group's search for more convenient ways of administering xylitol was not successful. In Uhari and colleagues' subsequent study (Tapiainen *et al*.), they reported that xylitol administered only during an acute respiratory infection was ineffective in preventing acute otitis media (Table I).[15] In addition, xylitol seemed to be ineffective when given immediately after the placement of tympanostomy tubes.[21] Later, Hautalahti *et al*. reported that xylitol given regularly three times a day during acute respiratory infection episodes for three months also failed to prevent the occurrence of acute otitis media (Table I).[16] The authors pointed out once more that continuous xylitol prophylaxis administered five times a day was able to effectively prevent acute otitis media attacks. In 2007, Vernacchio *et al*. demonstrated that oral xylitol solution, at dosages of 5 g three times a day and 7.5 g once daily, is reasonably well tolerated by and acceptable for children at the highest risk of recurrent acute otitis media.[2] They suggested that clinical trials using these dosages of xylitol could be conducted, given the potential for xylitol as a safe, inexpensive option for acute otitis media prophylaxis. Hence, the search for the most suitable dosage of xylitol for acute otitis media prophylaxis continues.

In a systematic review published in 2010 on acute otitis media preventative treatment, Danhauer *et al*. stated that the prophylactic effects of xylitol have been shown in children with acute otitis media.[22] Xylitol is well tolerated in children, with minimal side effects. The best vehicle for administration in children is chewing gum. The act of chewing and swallowing assists with the disposal of earwax and clearing of the middle ear, whilst the presence of xylitol prevents the growth of bacteria in the eustachian tubes.[23] As mentioned above, the Finnish group of researchers observed that 10 g of xylitol daily, given as 2 g orally five times a day, is well tolerated in children as young as nine months of age for acute otitis media prevention. Xylitol lozenges, however, seem to be poorly tolerated; abdominal discomfort and a dislike of the product are more common.[13–15]

Sezen *et al*. investigated the effect of chewing gum containing xylitol on middle-ear pressure in children with chronic otitis media with effusion (Table I).[17] The patients who received the xylitol chewing gum had more improvement in pressure levels for the right and left ears than those in the sorbitol group. However, there were no statistically significant differences between the groups in terms of the presence of glue in the middle ear or the pure tone audiometric results for right and left ears after the treatment.

Danhauer *et al*. mailed a 48-item questionnaire to a random sample of 506 paediatricians within the USA to assess their opinions on the prophylactic use of xylitol in children with acute otitis media.[22] The authors found that most of the paediatricians knew about the medical uses of xylitol and most were aware of its use in chewing gum to prevent acute otitis media. However, the majority had not used xylitol in their practice, and were not sure of the effectiveness or appropriate dosage.

In a case report, it was stated that nasally administered xylitol dramatically reduced acute otitis media episodes in children who previously suffered chronic ear complaints (Table I).[18] In the same paper, two other patients with asthma were reported to benefit from nasal saline sprays containing xylitol.

Xylitol for rhinosinusitis

Bacteria are thought to play a central role in sinusitis. In establishing rhinosinusitis, bacteria first need to overcome the body's natural defences. In the treatment of rhinosinusitis, especially in refractory cases, attention on innate immunity has been limited.

Respiratory tract secretions contain a variety of antimicrobial factors, including lysozymes, lactoferrin, β-defensins, secretory phospholipase A2 and cathelicidins.[24] These antimicrobial factors reside in the thin layer of airway surface liquid. Experimentally lowering the airway surface liquid salt concentration increases the activity of endogenous antimicrobials. A promising osmolyte for lowering airway surface liquid ionic strength is sugar xylitol. Zabner *et al*. showed that

https://doi.org/10.1017/S0022215114001340 Published online by Cambridge University Press

TABLE I
CLINICAL TRIALS ON XYLITOL USAGE IN ENT PRACTICE

Author (year)	Methods	Outcome measures	Results
Uhari *et al*. (1996)[13]	Design: DBPCRT Subjects: 336 healthy children Age range: 1–5 years Dropout: $n = 30$ Vehicles: xylitol gum, 2 pieces 5 times daily (xylitol, 8.4 g/day) for 2 months *vs* sucrose gum (placebo)	Occurrence of AOM (examination with pneumatic otoscope), prescriptions for antibacterials & nasopharyngeal carriage of *S pneumoniae*	Xylitol: 19/157 (12.1%) had ≥1 AOM attack Placebo: 31/149 (20.8%) had ≥1 AOM attack Difference: significant ($p = 0.04$) Overall 40% implied reduction in incidence of AOM in control group A clear decrease in AOM occurrence in children who chewed xylitol gum 5 times daily Side effects (e.g. gastrointestinal discomfort) were minimal, & similar for experimental & control groups
Uhari *et al*. (1998)[14]	Design: PCRT – double-blind for syrup & gum groups, but not gum & lozenge groups Subjects: 857 healthy children Age range: 6 months–6 years Dropout: $n = 93$ Vehicles: xylitol gum (8.4 g/day), xylitol lozenge (10 g/day) or xylitol syrup (10 g/day), *vs* placebo gum or placebo syrup	Occurrence of ARI & AOM, & prescriptions for antibacterials	*For younger children*: Xylitol syrup: 46/159 (29%) had ≥1 AOM attack Control syrup: 68/165 (41%) had ≥1 AOM attack Significant difference, $p = 0.04$ Overall 30% implied reduction in incidence of AOM in control group *For older children*: Xylitol gum: 29/179 (16%) had ≥1 AOM attack Control gum: 49/178 (28%) had ≥1 AOM attack Significant difference, $p < 0.05$ Overall 40% implied reduction in incidence of AOM in control group Xylitol lozenge not as effective
Tapiainen *et al*. (2002)[15]	Design: PCRT – double-blind for syrup & gum groups, but not gum & lozenge groups Subjects: 1277 healthy children Age range:10 months–7 years Dropouts: $n = 24$ Vehicles: xylitol syrup & lozenge (10 g/day) & xylitol gum (8.4 g/day), *vs* placebo syrup or gum (0.5 g/day) 5 times daily	Occurrence of AOM when xylitol administered during ARI	*For younger children*: Xylitol syrup: 34/166 (20.5%) had ≥1 AOM attack Placebo: 32/157 (20.4%) had ≥1 AOM attack *For older children*: Xylitol gum: 24/218 (11.0%) had ≥1 AOM attack Xylitol lozenge: 31/220 (14.1%) had ≥1 AOM attack Placebo: 34/219 (15.5%) had ≥1 AOM attack Xylitol not effective when administered intermittently during episodes of ARI
Hautalahti *et al*. (2007)[16]	Design: DBPCRT Subjects: 663 healthy children Age range: 7 months–7 years Dropouts: $n = 27$ Vehicles: xylitol solution or xylitol gum (9.6 g/day), *vs* placebo solution or gum (0.5 g/day) TID	Occurrence of first AOM attack	Xylitol: 98/331 (30%) had ≥1 AOM attack Placebo:94/332 (28%) had ≥1 AOM attack Xylitol administered TID not effective for preventing AOM because of bacterial regeneration & impaired anti-adhesive effect of xylitol with lengthened intervals between doses
Sezen *et al*. (2008)[17]	Design: single-blind PCRT Subjects: 29 COME patients Age range: 4–10 years Dropout: $n = 0$ Vehicles: xylitol gum (8.4 g/day) *vs* sorbitol gum (placebo)	Tympanometry (middle-ear pressure), frequency of glue ear & audiometric evaluation	Xylitol: difference in R middle-ear pressure (117.71 daPa) was highly significant ($p < 0.01$); difference in L middle-ear pressure (167.00 daPa) was highly significant ($p < 0.05$) Sorbitol: difference in R middle-ear pressure (39.21 daPa) was significant ($p < 0.05$); difference in L middle-ear pressure (11.85 daPa) was not significant No differences in frequency of glue ear & PTA between groups

Continued

Table I *Continued*

Author (year)	Methods	Outcome measures	Results
Jones (2001)[18]	Design: case report Vehicle: xylitol + saline nasal spray	Occurrence of ear infection	Over an average of 11 months FU, AOM incidence decreased from 0.86 to 0.06 per month
Zabner *et al.* (2000)[19]	Design: DBPCRT cross-over Subjects: 21 healthy subjects Age range: 20–52 years Vehicle: xylitol nasal spray (xylitol/water 5% w/v spray for 4 days) *vs* saline (placebo)	Coagulase-negative staphylococcus in culture of nasal swabs	Xylitol significantly reduced coagulase-negative staphylococcus on nasal surface compared with saline Xylitol may be of value in decreasing ASL salt concentration & enhancing innate antimicrobial defence at airway surface
Weissmann *et al.* (2011)[20]	Design: DBPCRT cross-over pilot study Subjects: 20 subjects with CRS Average age: 44 years Dropout: $n = 5$ Vehicle: xylitol nasal irrigation (10-day course, 12 g dissolved in 240 ml water – 5% w/v) *vs* saline irrigation (placebo)	SNOT-20 & VAS scores	Significant reduction in SNOT-20 score during xylitol phase of irrigation (mean reduction of 2.43) compared with saline phase (mean increase of 3.93), indicating improved sinonasal symptoms ($p = 0.0437$) No difference in VAS scores Short-term, xylitol irrigations resulted in greater improvement of CRS symptoms compared with saline irrigation

DBPCRT = double-blind, placebo-controlled, randomised trial; AOM = acute otitis media; PCRT = placebo-controlled, randomised trial; ARI = acute respiratory infection; TID = three times a day; COME = chronic otitis media with effusion; R = right; L = left; PTA = pure tone audiometry; FU = follow up; ASL = airway surface liquid; w/v = weight/volume; SNOT-20 = Sino-Nasal Outcome Test 20; VAS = visual analogue scale; CRS = chronic rhinosinusitis

xylitol can lower the airway surface liquid salt concentration in both cystic fibrosis and non-cystic fibrosis airway epithelia *in vitro*, and can thus enhance the innate immunity. In the nasal mucosa, xylitol spray was observed to reduce nasal staphylococcal carriage rates in normal volunteers (Table I).[19]

In an experimental study, Brown *et al.* administered xylitol, saline and *Pseudomonas aeruginosa* to the rabbit maxillary sinus.[25] They observed that the simultaneous administration of xylitol and *P aeruginosa* produced a statistically significant increase in bacterial killing after 20 minutes compared with normal saline. They reported that xylitol reduced experimentally induced sinusitis when administered simultaneously with bacteria, but its effect in established sinusitis was not clear.

Recently, Weissman *et al.* evaluated the effect of nasal irrigation with xylitol in subjects with chronic rhinosinusitis (Table I).[20] Twenty subjects with chronic sinusitis were instructed to complete two sequential 10-day courses of daily xylitol and saline irrigations, in a randomised fashion. The authors observed a significant reduction in Sino-Nasal Outcome Test 20 scores associated with xylitol irrigation as compared with saline irrigation, indicating improved sinonasal symptoms for xylitol irrigation.

Miscellaneous studies on xylitol in ENT disorders

An *in vitro* study by Kontiokari *et al.* showed that xylitol markedly reduced the growth of α-haemolytic streptococci, including *S pneumoniae*.[6] In addition, it slightly reduced the growth of β-haemolytic streptococci, but not that of *H influenzae* or *Moraxella catarrhalis*. A later study by the same research group indicated the anti-adhesive effects of xylitol against both *S pneumoniae* and *H influenzae* in a mixture of oropharyngeal epithelial cells and bacteria.[7]

In an experimental study, Renko *et al.* reported the beneficial effects of xylitol-supplemented nutrition on both the oxidative killing of bacteria in neutrophilic leucocytes and on the survival of rats with experimentally induced sepsis with *S pneumoniae*.[26] Xylitol was also shown to be cytoprotective during oxidative stress.[27]

In clinical trials, xylitol supplementation has been shown to decrease the occurrence of acute otitis media in day-care children; however, the nasopharyngeal carriage of the pneumococci was not reduced.[13]

The capsular cpsB gene is essential for encapsulation and for regulation of the production of capsular polysaccharide for streptococci.[28] Kurola *et al.* showed that exposure to xylitol significantly lowered cpsB gene expression levels in *S pneumoniae* isolates.[29] They reported that xylitol changed the ultrastructure of the pneumococcal capsule, which could explain the high clinical efficacy of xylitol in preventing otitis media without reducing nasopharyngeal carriage.

https://doi.org/10.1017/S0022215114001340 Published online by Cambridge University Press

Xylitol safety and side effects

Xylitol is absorbed slowly by the gut wall and may cause loose stools when ingested in large amounts. Oral xylitol is well tolerated in adults and children. Whilst adults can tolerate daily doses of up to 200 g of xylitol without gastrointestinal symptoms, children can only tolerate daily xylitol doses of up to 45 g without gastrointestinal symptoms.[30,31] In addition to loose stools, large amounts of xylitol may cause abdominal discomfort and osmotic diarrhoea.[15] These side effects do not appear particularly dependent on age or weight. It has been shown that adaptation to xylitol occurs rapidly, such that the laxative effect diminishes within several days of regular use.[32] Parenteral xylitol can cause minimal hyperuricaemia without any pathophysiological consequences.[5] Though tolerated well in modest doses, large amounts of xylitol administered intravenously have been reported to cause reno-cerebral oxalosis with renal failure.[33]

Conclusion

Acute otitis media is one of the most prevalent and costly illnesses in children throughout the world. The prophylactic use of antibiotics has the desired effect, but is liable to lead to the development of antimicrobial-resistant bacteria. Thus, new approaches are required to prevent acute otitis media. The efficacy of xylitol is comparable to that of the best-known prophylactic methods, such as continuous antimicrobial prophylaxis and surgical procedures. Xylitol delivered to the nasal or sinus mucosa may enhance innate bacterial defences by modifying the airway surface liquid salt concentration. Xylitol can be used to prevent the onset or delay the progress of rhinosinusitis. Furthermore, in populations with high rates of tooth decay, xylitol interventions are likely to be cost-effective. The worldwide spread of drug-resistant strains of pneumococci substantiates the need for new approaches to prevent ENT-related infectious diseases. Xylitol may be a promising agent for this purpose in ENT practice, but further experimental and clinical studies are required.

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Dr I Adadan Guvenc takes responsibility for the integrity of the content of the paper
Competing interests: None declared