

The negative effects of mucolytics in otitis media with effusion

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Summary

Much controversy still exists in the treatment of otitis media with effusion. A double-blind randomised prospective trial during which bromhexine hydrochloride was compared with a placebo is reported. Information from 60 patients was analysed and the results reveal interesting findings on the effects of bromhexine on middle-ear clearance. The data clearly reveal that bromhexine retards resolution of the effusion.

Further discussion of the literature gives insight into the controversy surrounding the treatment of middle-ear effusion. Steroids are proposed for further research and clinical trials.

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Many drugs have been used for the treatment of otitis media with effusion (OME). The great majority, however, do not have their reputations enhanced by repeated scientific investigation. In fact, Bluestone¹ has gone so far as to say: 'We have arrived at the point of using the wait-and-see approach and do nothing.' This form of treatment has become more acceptable since the review of Paradise² which allays many of the concerns regarding the adverse affects of untreated periodic hearing loss on the development of language and learning skills. Further insight is gained from the spontaneous improvement of secretory otitis media as documented by Thomsen and Tos,³ who found that 88% of a type B tympanogram (middle ear with an effusion) improved in the course of 1 year. Less than 1% of cases presented with tympanic membrane changes.

We tested the efficacy of a mucolytic in OME to ascertain its place, if any, in the treatment. The active agent chosen to test in this study was bromhexine hydrochloride, an oral mucolytic agent derived synthetically from the alkaloid vasicine. It reduces the viscosity of the mucus secretions in chronic chest disease, but its role in OME has not been proven.

Patients and methods

Sixty consecutive patients with OME seen in the routine outpatient clinics of Tygerberg Hospital were entered at random into the trial. Patients with previous ear surgery were excluded. Ninety-one per cent of the patients were under the age of 12 years, and 20 were female and 40 male.

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On the initial visit a history was taken, with special attention being paid to previous illnesses such as allergy, upper respiratory tract infection, infectious diseases and previous medication used. Relevant symptoms such as snoring, mouth breathing, deafness, pain in the ears and behavioural problems were also recorded in addition to other more general aspects including questions on swimming and failure to thrive.

The clinical examination included a general and full ear, nose and throat (ENT) examination, with special attention being paid to the appearance and movement of the tympanic membrane. A clinical hearing evaluation, including the tuning fork tests, was performed if possible. A formal hearing evaluation was then conducted, comprising a pure-tone audiogram or free-field responses, according to the patient's age, and tympanometry in all cases.

The treatment programme was then commenced. Patients received their medication on a strict double-blind basis with bromhexine as the active ingredient being tested against inactive placebo. The active substance and the placebo were supplied by a pharmaceutical company, who also kept the key until the trial was complete. The dosage of active ingredient used was as follows; < 1 year — 1,25 ml (2,5 mg) 3 times per day; 1 - 5 years — 2,5 ml (5 mg) 3 times per day; 6 - 10 years — 4 ml (8 mg) 3 times per day; and > 10 years — 8 ml (16 mg) 3 times per day. The medication was taken for 1 month.

The second visit after 2 weeks consisted of an ENT examination, again with emphasis on tympanic membrane appearance and movement, audiometry and tympanometry. The third and fourth visits were after 4 and 12 weeks respectively. Follow-up dropped off as the trial progressed; some patients failed to return and were lost to follow-up, and others were removed from the trial due to longstanding severe (> 40-50 dB) bilateral conductive hearing loss. In the bromhexine group 89,7% returned after 2 weeks, 72,4% after 4 weeks and 55,2% after 12 weeks. A higher percentage returned in the placebo group, viz. 89,7% after 2 weeks, 89,7% after 4 weeks and 58,6% after 12 weeks.

A percentage of the remaining ears was calculated, and results from those patients who did not return were excluded. A speculation that the bromhexine group follow-up was worse because of treatment success is invalid, since the return of most of this age group depended on the parents and was not the result of subtle changes not even noticeable by the patients. Patients with severe hearing loss were treated by tympanostomy.

Results

The clinical evaluation — a 'yes' or 'no' impression for effusion in the middle ear — was recorded. At both the 2-week and 4-week follow-up, statistically significant differences in resolution favouring placebo were found ($P < 0,05$ and $P < 0,001$ respectively) (Fig. 1). After 12 weeks the two groups were once again even, with resolution in the active treatment group catching up to the placebo group following cessation of treatment. Tympanometric studies followed exactly the same pattern, with type B tympanograms being resolved in statistically significantly more patients in the placebo than the bromhexine group at both 2 ($P < 0,05$) and 4 weeks ($P < 0,01$) (Fig. 2).

The conductive hearing loss at audiometry was divided into three grades; 0-15 dB, 15-30 dB and > 30 dB. Free-field responses were corrected by subtracting 10-15 dB to compare with pure-tone audiometry. Audiometry confirms the statistical difference between hearing loss grades in the two groups with the placebo group hearing being better at 4 weeks ($P < 0,01$) (Fig. 3).

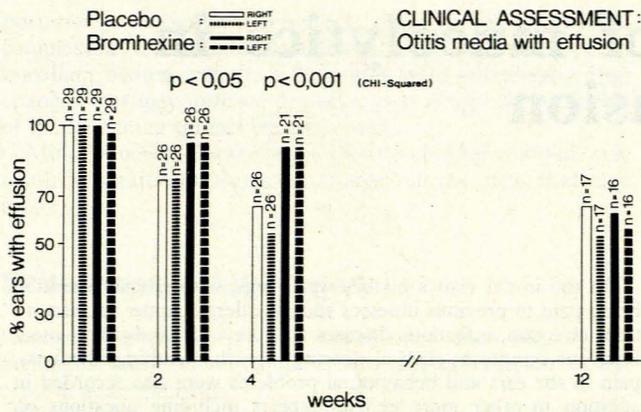


Fig. 1. Histogram showing the percentage ears with an effusion. Clearance is demonstrated over 12 weeks.

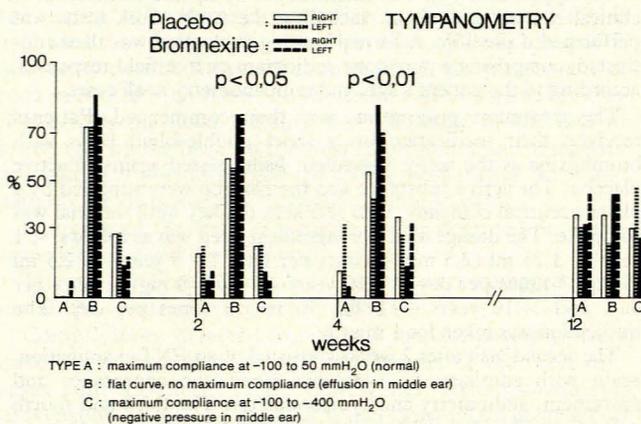


Fig. 2. Histogram indicating the resolution from a type B tympanogram to either a type C or type A.

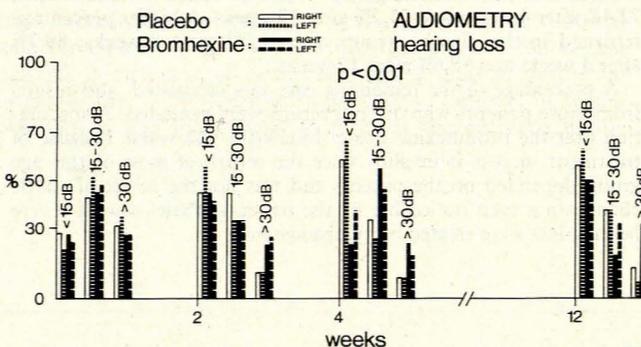


Fig. 3. The percentage ears in the groups 15 - 30 dB and > 30 dB change over 12 weeks. With resolution the < 15 dB group increases over 12 weeks.

Discussion

A review of the literature reveals that the problem of OME remains unresolved. Elcock and Lord⁴ in 1972 performed a double-blind trial showing no statistical difference between bromhexine and placebo. Edström *et al.*⁵ in 1977 showed that

oral mucolytics and a decongestant had no effect on the course of a healing serous otitis media. Wing's⁶ series in 1978 suggested that bromhexine and Actifed (Wellcome) in combination in the treatment of glue ear gave a 90% chance of successful resolution in the first month. Roydhouse⁷ showed in 1981 that bromhexine is a valuable adjunct in the treatment of OME.

Such confusion in an area of controversy often implies that the treatment has, in fact, very little significant effect on the natural course of the disease. Our results support this contention and suggest that the treatment might in fact worsen the disease.

There is a theoretical explanation for these rather disconcerting findings. Acid mucopolysaccharide fibres are present in secretions found in chronic serous otitis media.⁸ Fragmentation of the fibres reduces the viscosity of the effusion. Viscoelasticity is a property of mucus which is necessary for its propulsion by the cilia, and mucus transport is particularly well correlated with the elasticity of the sample. Studies of the rheologic properties of middle-ear mucus show the maximum mucociliary transport rate taking place at a mucin concentration of 0,4%.⁹ Any treatment which changes this concentration to something further from the ideal, even by making the mucus far thinner, will theoretically result in less effective clearance by the ciliary transport mechanism.

Interesting new information is appearing in the world literature on certain aspects of OME, particularly as regards microbiology and immunology. From these findings it would appear that of the various forms of treatment available to us for managing OME by altering the nature of the mucus and reversing the changes in the mucous membrane, the most profitable area of research could well be in the role to be played by steroids.¹⁰

Conclusion

This study clearly shows that bromhexine retards the normal resolution of OME when compared with inactive placebo.

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