Double-blind, Placebo Controlled Randomised Trial of Medical Therapy in Otitis Media with Effusion

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Abstract:
Objective: To explore rhinitis treatment, with and without autoinflation of the middle ear, as therapy for otitis media with effusion

Design: Prospective, randomised, double blind, placebo-controlled trial of long-term treatment with nasal corticosteroids in OME. Otovent auto-inflation device used when needed over 2 years, with either nasal corticosteroid or placebo, using a 2 × 2 factorial design


Participants: 200 children with documented OME persisting over 3 months were randomised to receive in double blind fashion either fluticasone propionate aqueous nasal spray (FP) 100mcg daily or matching placebo administered over 2 years. Children with odd trial numbers also received the Otovent auto-inflation device with instructions to use this 3 times daily until hearing improved and to restart use 2 weeks after any upper respiratory tract infection

Main outcome measures: The primary outcome measure was treatment failure defined as hearing loss of over 30dB in at least one ear or grommet insertion.

Results: An unexpected interaction was apparent between FP and Otovent on time to hearing loss/grommet insertion. Therefore the only comparisons made are between FP and placebo and Otovent and placebo. The FP group had significantly improved disease-free survival compared with placebo (p=0.021). The Otovent group showed improved survival, but this did not reach statistical significance (p=0.140).

Conclusion: FP alone decreases the need for grommet insertion or hearing loss. When Otovent is used in addition to FP the effect is less than either treatment modality given alone.

Keywords: Otitis Media with Effusion; Intranasal Corticosteroid; Autoinflation; Grommets
1. INTRODUCTION

Otitis media with effusion (OME) or “glue ear” is an inflammation of the middle ear with a collection of fluid behind an intact tympanic membrane [1]. Most children are affected at some point in their lives with a bimodal peak incidence at two years and five years [2]. Most effusions are self-limiting, but in some children persist over three months and are then labelled as chronic. Chronic OME is the commonest reason for surgery in childhood [3], the most frequent intervention being insertion of ventilation tubes (grommets) into the tympanic membrane, sometimes accompanied by adenoidectomy. Recent studies have identified the benefit from grommet insertion and from adenoidectomy [4–6]. Black [4] noted that when inserted unilaterally to children with bilateral OME after six months the hearing in the grommeted ear was not significantly different to that in the untreated ear. For many children OME is a recurrent condition until around the age of nine years.

The aetiopathogenesis of OME is probably multi-factorial [7] involving infection, both viral [8, 9] and bacterial [10] in 16% to 43% of children. The role of allergy in OME has been disputed for years, but recent papers [11, 12] suggest that older children with OME have concomitant atopic disease. Our own observations (Umapathy D, MSc thesis) suggest that there is a strong association between the presence of rhinitis and OME, and that in many children this is allergic in origin. An open interventional long-term (18 month) study [13] with beclomethasone dipropionate nasal spray suggested that this form of treatment reduced the need for grommet insertion by 50% irrespective of any allergen avoidance measures undertaken.

Previous studies of nasal steroids in OME suffer from being either short-term, open or employing other treatment modalities in addition [14–17]. We therefore designed a double-blind placebo controlled study using intranasal fluticasone propionate (because of its low systemic bioavailability from the nose and gut and consequent safety), compared to placebo over two years in children aged 4 to 8 years with chronic OME. As auto-inflation of the middle ear had also been shown to be effective in treating glue ear [18], we allocated 50% of the children (those with odd numbers in the study) to receive the Otovent device in addition to a nasal spray which could be FP or placebo. Our hypothesis was that combined treatment with FP and Otovent would be superior to either alone, both of which would be superior to placebo nasal spray. Since FP is licensed for children over 4 and since children under 4 years cannot easily use the Otovent device, this study was restricted to children of 4 to 8 years old with glue ear.

2. SUBJECTS AND METHODS

Subjects: Children aged between 4 and 8 years with a documented history of 3 months of glue ear or more than 2 episodes in the past 6 months plus type B (flat) or type C (negative middle ear pressure less than -100 decaPascals), tympanograms were offered a place in the study regardless of atopic status. All had nasal symptoms in addition to their hearing problem. Children with known predisposing conditions such as cleft palate, Down’s syndrome and cystic fibrosis were excluded; those with acute otitis media or upper respiratory infection together with otalgia at the time of the visit were treated and reviewed over a month later to see whether they were eligible.

Study design: Children eligible for the trial and their parents were given a detailed explanation and information sheet and signed the appropriate consent forms. Ethical approval was given by The Royal National Throat, Nose and Ear Hospital Ethics Committee. Subjects were randomised to receive FP or
matching placebo in a 1:1 ratio according to a computer-generated randomisation schedule using a block size of 8. This was held in the pharmacy, and both subjects and observers were blind as to the nature of this treatment. In addition those children entering the trial with an odd number were also given the Otovent device; this part of the study was open. During the study the children were reviewed at 3 monthly intervals and at each visit underwent symptom scores, examination including ENT and chest, peakflow, tympanometry and audiometry.

**Questionnaire:** At the initial visit the patient’s parent or guardian completed a questionnaire including presenting symptoms, secondary complaints, allergic symptoms, environmental risk factors, previous medical and surgical history, medication for the presenting complaint and family history of atopy.

**Symptom Scores:** At each visit parent/guardian and patient were asked to complete together a validated symptom score chart detailing the symptoms present over the last week on a 0 (not present) to 9 (present severely all the time) basis. The symptoms charted were as follows: nasal: blocking, running, itching and sneezing, ears: hearing, ear pain/discomfort, chest: day cough, night cough, shortness of breath on exercise, wheezing or chest tightness, behaviour: irritability. The worst score possible was 99.

**Examination:** This included routine ear, nose and throat examination, using an otoscope, plus inspection and auscultation of the chest and examination of the skin by the doctors in the clinic. Height and weight measurements were recorded at each visit by the clinic nursing staff using Salter scales and a stadiometer.

**Peak expiratory flow rate (PEFR):** A mini Wright paediatric peakflow meter was used and the best of three attempts following detailed instruction and encouragement was taken as a definitive measure. Our guide was a nomogram [19], which compared peakflow with respect to height. These data, together with questionnaire responses, will be the subject of a second publication.

**Pure Tone Audiometry (PTA)/ Impedance Audiometry:** Hearing thresholds were determined using a Peters AC audiometer and averaged over 500Hz, 1kHz and 2kHz. Middle ear compliance and pressures were measured by using a GS1 screening tympanometer.

**Treatment:** Children were randomised to receive an aqueous spray, which could be FP (50mcg per actuation), or its matching placebo. This was administered twice daily for the first 2 weeks in order to decrease upper airways obstruction, one puff per nostril (two puffs per nostril bd for children over 35kgs) then a maintenance dose of one puff per nostril (100mcg) once daily was used. The children were asked to use this on a regular basis.

**Otovent:** The use of the device was demonstrated by our allergy nurse to both child and parent. The child was asked to use the Otovent 3 times daily for the first box of balloons i.e. 4 to 5 weeks, and then cease use if hearing was not troublesome. However, use should be re-established if the glue ear re-presented, especially after a cold. Instructions were given that Otovent should not be used during colds, and should not be re-started until 2 weeks after the cold finished.

**Outcome:** The primary outcome measure was treatment failure which defined as persistent hearing loss of over 30dBs or grommet insertion.

**Statistical analysis:** This 2 by 2 factorial study was designed under the assumption that there would be no interaction between the effects of FP and the Otovent device. Such designs are efficient in that they address two therapeutic questions within one study. Sample size calculations suggested a total of 400 children should be included. However, practical considerations led to a decision to cease entering children after 200 were enrolled over the years 1994-2000. Approximately 50 children were randomized into each of the four therapy groups:
1. Placebo nasal spray, no Otovent
2. Placebo nasal spray plus Otovent
3. FP, no Otovent
4. FP plus Otovent

50 patients per group give at least a power of 85% to detect as statistically significant the difference in survival of 50% and one group versus 80% in another, using a two-sided 5% log rank test.

The primary efficacy measure was treatment failure defined as the need for grommet insertion or hearing loss ≥ 30dB. The time to treatment failure has been examined using Kaplan-Meier plots and tested using the log rank test. The interaction between the treatments was tested using Cox proportional hazards modelling. Summary statistics are presented for secondary endpoint of symptom scores.

Because an unexpected interaction between the treatment modalities was apparent, results for each treatment group have been presented but comparisons between each of the two treatments alone and the placebo treatment only are made.

Sensitivity analyses have been undertaken because some children discontinued study treatment because of recurrent upper respiratory tract infections (although they had not reached the endpoint of hearing loss/grommet insertion). A further efficacy analysis considering these children as having reached the endpoint was carried out as a sensitivity analysis.

The analysis was carried out using SAS version 9.2.

3. SAFETY MEASURES

To investigate any possible effect of FP on growth, rate of growth (as cm/year) has been examined. Plots of growth for each child whilst on treatment have been examined. Increase in height over time has been analysed using a mixed modelling approach with subject included as a random effect and additionally with age, gender, baseline height, baseline weight, history of asthma and previous grommet insertion as covariates. The effect of FP was examined by comparing the growth velocity in those taking FP with those not taking FP. Further modelling with random effects for both subject and growth rate were unsuccessful, probably due to the lack of variation in growth rate. Adverse events were recorded at each visit by questioning both child and parents.

Compliance: This was assessed by questioning the child and the parent/guardian and by the number of bottles used. Those who reported spray use on at least 3 days a week remained in the study.

4. RESULTS

An Intention to Treat analysis has been carried out including all patients according to their randomised treatment group. Two hundred children were randomised into the study. Their details are shown in Table 1. Patient characteristics were fairly similar for all 4 groups at baseline, the FP group are slightly younger and shorter. Table 2 shows the baseline symptom scores, nasal symptoms having the highest score, and behavioural ones the lowest.
Table 1. Demography and Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Otovent</th>
<th>FP</th>
<th>FP + Otovent</th>
<th>All</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>n</strong></td>
<td>48</td>
<td>52</td>
<td>52</td>
<td>48</td>
<td>200</td>
</tr>
<tr>
<td><strong>Age (yrs)</strong></td>
<td>5.7 (1.3)</td>
<td>5.7 (1.3)</td>
<td>5.4 (1.2)</td>
<td>5.9 (1.1)</td>
<td>5.7 (1.2)</td>
</tr>
<tr>
<td><strong>Gender F</strong></td>
<td>16 (33%)</td>
<td>27 (52%)</td>
<td>21 (40%)</td>
<td>19 (40%)</td>
<td>83 (42%)</td>
</tr>
<tr>
<td><strong>Height (cm)</strong></td>
<td>112.7 (8.9)</td>
<td>113.7 (12.5)</td>
<td>110.0 (8.9)</td>
<td>114.1 (7.7)</td>
<td>112.6 (9.8)</td>
</tr>
<tr>
<td><strong>Weight (kg)</strong></td>
<td>21.0 (4.8)</td>
<td>20.9 (5.9)</td>
<td>20.0 (5.3)</td>
<td>21.3 (4.0)</td>
<td>20.8 (5.0)</td>
</tr>
<tr>
<td><strong>Previous grommets</strong></td>
<td>10 (21%)</td>
<td>12 (24%)</td>
<td>6 (12%)</td>
<td>5 (10%)</td>
<td>33 (17%)</td>
</tr>
<tr>
<td><strong>Asthma treatment</strong></td>
<td>15 (31%)</td>
<td>15 (29%)</td>
<td>11 (22%)</td>
<td>16 (33%)</td>
<td>57 (29%)</td>
</tr>
<tr>
<td><strong>Tymp R</strong></td>
<td>-271 (78)</td>
<td>-199 (202)</td>
<td>-234 (94)</td>
<td>-288 (90)</td>
<td>-246 (131)</td>
</tr>
<tr>
<td><strong>L</strong></td>
<td>-176 (143)</td>
<td>-231 (132)</td>
<td>-236 (111)</td>
<td>-239 (88)</td>
<td>-223 (119)</td>
</tr>
<tr>
<td><strong>Audio R</strong></td>
<td>24.8 (12.5)</td>
<td>25.9 (10.4)</td>
<td>23.3 (8.5)</td>
<td>25.2 (12.3)</td>
<td>24.8 (11.0)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>25.8 (11.8)</td>
<td>24.3 (10.1)</td>
<td>24.1 (9.7)</td>
<td>22.8 (9.9)</td>
<td>24.3 (10.3)</td>
</tr>
</tbody>
</table>

Summary of Demography and Baseline Characteristics Mean (standard deviation)

Table 2. Baseline Symptoms

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Otovent</th>
<th>FP</th>
<th>FP + Otovent</th>
<th>All</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nasal</td>
<td>8.36 (6.67)</td>
<td>11.13 (8.07)</td>
<td>10.84 (7.59)</td>
<td>10.44 (7.14)</td>
<td>10.23 (7.43)</td>
</tr>
<tr>
<td>Ears</td>
<td>6.83 (4.79)</td>
<td>7.46 (4.82)</td>
<td>6.74 (4.73)</td>
<td>6.56 (4.62)</td>
<td>6.91 (4.72)</td>
</tr>
<tr>
<td>Chest</td>
<td>4.89 (5.51)</td>
<td>8.44 (7.58)</td>
<td>7.71 (7.63)</td>
<td>6.92 (7.14)</td>
<td>7.04 (7.12)</td>
</tr>
<tr>
<td>Behaviour</td>
<td>2.94 (2.65)</td>
<td>2.16 (2.50)</td>
<td>3.02 (2.85)</td>
<td>2.60 (2.59)</td>
<td>2.67 (2.65)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>23.02 (14.18)</td>
<td>28.78 (16.19)</td>
<td>28.58 (18.31)</td>
<td>25.70 (16.02)</td>
<td>26.58 (16.30)</td>
</tr>
</tbody>
</table>

Summary Statistics for Baseline Symptom Levels Mean (standard deviation)

The subject disposition is presented in Table 3: the placebo group had the highest percentage of patients with hearing loss or grommet insertion and the FP group had the lowest. Figure 1A shows the Kaplan-Meier disease-free survival plots for the four treatment groups, which reflects the proportions experiencing the endpoint of grommet insertion/hearing loss shown in Table 3. An interaction between the effects of the two individual treatments is apparent, whereby the combined treatment has a worse survival curve than either of the two treatments given alone. A formal test of this interaction, using the Cox proportional hazards model, gave $\chi^2$ of 3.23 (p=0.073). Because of this interaction pair wise comparisons between each of the treatments alone and the placebo group have been undertaken.

Table 3. Patient Disposition

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Otovent</th>
<th>FP</th>
<th>FP + Otovent</th>
<th>All</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hearing loss/grommets</td>
<td>18 (38%)</td>
<td>16 (31%)</td>
<td>11 (21%)</td>
<td>16 (33%)</td>
<td>61 (30%)</td>
</tr>
<tr>
<td>2 years completed</td>
<td>6 (12%)</td>
<td>12 (23%)</td>
<td>15 (29%)</td>
<td>10 (21%)</td>
<td>43 (22%)</td>
</tr>
<tr>
<td>Lost to follow-up</td>
<td>18 (38%)</td>
<td>22 (42%)</td>
<td>20 (38%)</td>
<td>17 (35%)</td>
<td>77 (38%)</td>
</tr>
<tr>
<td>Recurrent URTIs</td>
<td>6 (12%)</td>
<td>2 (4%)</td>
<td>6 (12%)</td>
<td>5 (10%)</td>
<td>19 (10%)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>48</td>
<td>52</td>
<td>52</td>
<td>48</td>
<td>200</td>
</tr>
</tbody>
</table>

The log rank test comparing the effect of FP with placebo gave a chi-squared value of 5.35 (p=0.021) and otovent versus placebo gave a chi-squared value of 2.18 (p=0.140). Because children experiencing recurrent infections were removed from the study, a sensitivity analysis regarding these cases as having
Double-blind, Placebo Controlled Randomised Trial of Medical Therapy in Otitis Media with Effusion

Figure 1. Kaplan Meier Plots of event-free survival primary analysis (1A) and sensitivity (1B) analysis.

experienced the endpoint has been undertaken. These subjects are shown in Table 3 under ‘Recurrent URTIs’. Figure 1B shows the Kaplan Meier plots for this sensitivity analysis and the results confer with the primary analysis, with the exception that the effect for otovent alone compared with placebo achieved formal statistical significance (chi-square 4.83, p=0.028).

Symptom scores: Symptom scores were reduced by both active treatments (Table 4). Treatment with both FP alone and Otovent alone resulted in significant reductions in nasal and chest symptoms compared with the placebo group. These were sustained over the two year study period. The interaction effect on symptoms of both treatments together is apparent.

Table 4. Change in Symptoms

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Otovent</th>
<th>FP</th>
<th>FP + Otovent</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1 yr</td>
<td>2 yr</td>
<td>1 yr</td>
<td>2 yr</td>
</tr>
<tr>
<td>Nasal</td>
<td>0.62 (6.43)</td>
<td>0.54 (6.29)</td>
<td>-2.32 (8.05)*</td>
<td>-2.38 (7.66)*</td>
</tr>
<tr>
<td>Ears</td>
<td>-1.31 (3.97)</td>
<td>-1.35 (4.01)</td>
<td>-2.37 (5.34)</td>
<td>-2.33 (5.62)</td>
</tr>
<tr>
<td>Chest</td>
<td>2.77 (7.26)</td>
<td>2.68 (7.18)</td>
<td>-1.40 (6.54)*</td>
<td>-1.55 (6.41)*</td>
</tr>
<tr>
<td>Behaviour</td>
<td>0.26 (0.41)</td>
<td>0.27 (0.40)</td>
<td>0.28 (0.41)</td>
<td>0.28 (0.39)</td>
</tr>
<tr>
<td>Total</td>
<td>1.51 (12.81)</td>
<td>1.35 (112.74)</td>
<td>-5.10 (14.53)*</td>
<td>-5.35 (14.56)*</td>
</tr>
</tbody>
</table>

Symptom changes (a negative value indicates improvement) at 1 and 2 years. Mean (standard deviation) * p<0.05. Both FP and Otovent significantly reduced nasal and chest symptoms compared to Placebo.

Adverse effects: There were no serious adverse events in this study. Minor adverse events were recorded, but none was of sufficient severity to cause cessation of the treatment or withdrawal from the trial. The commonest was minor epistaxis which occurred in fewer than 10% of subjects.

Growth: The plots of growth rate (not presented) indicated a uniform increase in height over the time period, independent of treatment. The mixed model fitted indicated no significant difference in growth rates between those children receiving FP and those given placebo on either method of analysis. (Table 5)
The growth curves did not show any significant difference from the normative data charts in use in the UK.

Table 5. Growth

<table>
<thead>
<tr>
<th>Type of Analysis</th>
<th>Growth rate FP cm/year</th>
<th>Growth rate no FP cm/year</th>
<th>Difference cm/year</th>
<th>95% CI for difference cm/year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unadjusted</td>
<td>6.27</td>
<td>6.08</td>
<td>0.18 (0.26)</td>
<td>-0.34 to 0.70</td>
</tr>
<tr>
<td>Adjusted</td>
<td>6.31</td>
<td>6.11</td>
<td>0.20 (0.25)</td>
<td>-0.29 to 0.70</td>
</tr>
</tbody>
</table>

Summary of analysis of growth velocity over entire treatment period in those treated with and without FP. A mixed model was fitted without and with covariates. Mean (standard error)

5. DISCUSSION

This is the first large randomised double-blind, placebo controlled study of the long-term use of topical corticosteroids in persistent OME. As recommended by a recent Cochrane review [20] our study was designed to have a clinically relevant outcome measure, –30dB hearing loss or grommet insertion. In addition to hearing loss, grommets may be indicated for failure at school, marked drum retraction, pain or recurrent infections.

Previous studies have been compromised by being short–term, using other treatment modalities in addition or lacking blinding. Using evidence based on three brief studies [15, 16, 21] Chaffee et al. [22] state that treatment of OME with nasal corticosteroids is not recommended since although there is limited evidence suggesting increased rate of resolution in the short term, within 3-12 weeks resolution was no better than with placebo. Since OME is a relapsing and remitting disorder short-term studies are inappropriate and can be misleading. A more recent 3 month study in primary care [23] showed no difference between therapy with mometasone furoate or placebo, but the fact that 45% of subjects on placebo improved at 1 month and 52% at 3 months suggests that mild transient disease was being included. Our patients had 3 months of documented OME before entry but the two year treatment period meant that we had a high proportion of subjects lost to follow-up, as the clinic serves a mobile inner city population.

Our findings confirm our previous observation that topical nasal corticosteroids used regularly over two years reduce hearing loss or the need for grommet insertion in chronic OME [13]. At two years there was an approximate 35% difference between FP and placebo in the disease free survival (FP 74% disease-free and placebo 38% disease-free), statistically significant at the 5% level. The corresponding difference for otovent is 22% (otovent 60% disease-free survival and placebo 38%). The difference in survival experience for otovent did not reach statistical significance in the main analysis, but did in the sensitivity analysis.

The unexpected outcome of the study was the negative interaction apparent between the effects of FP nasal spray used together with the Otovent device. This interaction influenced the analysis we carried out and the power of the study to detect treatment effects. This finding may illuminate the pathogenesis of OME. We suspect that the FP nasal spray is effective because it reduces rhinitis, which we hypothesize promotes OME via nasal obstruction, eustachian tube dysfunction and impairment in mucociliary clearance. FP has beneficial effects upon all of these [24]. Intranasal corticosteroids could also be effective in reducing OME via reduction of ostiomeatal complex obstruction and increased perfusion of the postnasal space by bactericidal nitric oxide gas generated in the paranasal sinuses [25, 26].
Intranasal corticosteroids are also known to act upon the adenoid [27]. In a study on children on the waiting list for adenoidectomy and tonsillectomy FP reduced obstructive symptoms and activation of T lymphocytes in adenoid tissue (Wheeler personal communication). In that study those children listed for adenotonsillectomy because of recurrent tonsillar infection were slightly worse on FP. Thus we speculate that FP spray is likely to be beneficial where obstruction is a major factor; however topical corticosteroids may slightly reduce local immunity in the nasal mucosa and nasopharynx. Evidence for this also comes from studies on the common cold where FP treatment increased the culture of rhinoviruses from the nasopharynx [28] and the development of OME [29]. This is not a problem in uncomplicated allergic rhinitis, nor, it would appear from our present and previous topical corticosteroid studies, in OME in 4-8 year olds when FP is used alone. However where there is chronic FP-treated nasal inflammation and a tendency to OME the addition of auto-inflation reverses any benefit seen with FP alone. The likely explanation lies in nasopharyngeal secretions being transferred to the middle ear cavity when Otovent is used. If these contain bacteria (and post nasal carriage is common in children) then transfer to the middle ear cavity may give rise to low grade infection and inflammation with a further bout of otitis media, as suggested previously [7]. Thus the likely source of organisms involved in middle ear infections is the nasopharynx. It is conceivable that the post nasal space supports a bacterial biofilm the contents of which, when disturbed by virus infection or swimming, can be intermittently transferred to the middle ear cavity, giving rise to a biofilm there as the underlying cause of OME [30]. This could explain the more prolonged benefits seen when adenoidectomy is added to grommet insertion [5, 6] and the reduction in frequency of otitis media by oral xylitol [31].

Since we have shown that children aged 4 and above with OME also suffer from rhinitis and asthma [11], we recorded symptoms referable to the upper and lower respiratory tracts, in addition to those relevant to the ears and attempted to quantify the effects on behaviour, using our previously validated visual analogue scale. In this trial FP spray not only improved the hearing problem reducing the need for surgery, but also reduced nasal and chest symptoms, both of which increased over the two year course of the study in the placebo-treated control group. This is an example of nasal treatment benefiting lower respiratory tract disease. Insertion of ventilation tubes has not been shown to confer such benefits.

The long term use of topical nasal corticosteroids in children necessitates the use of molecules without significant systemic absorption - at present fluticasone propionate (FP) and mometasone furoate (MF) are the least bioavailable from the nose [32]. Both have good safety profiles when used over a year [33, 34], in contrast to the growth suppression seen when beclomethasone dipropionate is used nasally twice daily [35]. We did not find any major adverse events in this study and the children grew normally.

OME is part of a spectrum of inflammatory conditions affecting the respiratory tract, with close links to rhinitis. As such it appears to be amenable to local anti-inflammatory therapy. A study in primary care, this time involving children with chronic OME, would seem sensible.

ACKNOWLEDGMENTS

We are grateful to the nursing staff of the glue ear clinic for their help with this study and to the staff of the Audiology department who undertook hearing tests on these children.

We are grateful to Glaxo Smith Kline, Inphormed and Merck for funding for this project.
CONFLICTS OF INTEREST

This study was conceived by Glenis Scadding and funded by Glaxo Smith Kline (including the salary of Abhijeet Parikh as a PhD student) together with Inphormed who provided Otovent devices free of charge. Merck Sharp and Dohme provided funding for further independent statistical analysis since this was advised by a referee when the paper was originally submitted. Glenis Scadding has received funding from GSK and MSD for other trials, serves on an advisory panel and has lectured for them at meetings.

Helen Tate has worked as an independent statistical consultant for Merck, Sharp and Dohme. At the time of the study, DR was a full-time employee of GlaxoSmithKline R&D.

None of the other authors has any interests to declare.

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Intranasal beclomethasone as an adjunct to treatment of chronic middle ear effusion,


Conservative treatment of otitis media with effusion by autoinflation of the middle ear,


Spirometry, lung volumes and airway resistance in normal children aged 5 to 18 years,


Oral or topical nasal steroids for hearing loss associated with otitis media with effusion in children,


Beclomethasone nasal spray in the treatment of middle-ear effusiona double-blind study,


Are nasal steroid sprays effective for otitis media with effusion?,


Topical intranasal corticosteroids in 4-11 year old children with persistent bilateral otitis media with effusion in primary care: double blind randomised placebo controlled trial,


Clinical and physiological effects of fluticasone propionate aqueous nasal spray in the treatment of perennial rhinitis,


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Paradoxical low nasal nitric oxide in nasal polyposis,


Clinical and experimental inflammation,

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


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