Amoxicillin/clavulanic acid is ineffective at preventing otitis media in children with presumed viral upper respiratory infection: a randomized, double-blind equivalence, placebo-controlled trial

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Aims To assess the equivalence of amoxicillin/clavulanic acid and placebo in the prevention of acute otitis media in children at high risk of acute otitis media who develop upper respiratory tract infection.

Methods This was a multicentre, equivalence, randomized, double-blind trial of two parallel groups comparing 5 days of amoxicillin/clavulanic acid 75 mg kg⁻¹ day⁻¹ (i.e. 25 mg kg⁻¹ every 8 h) and placebo. The main outcome measure was acute otitis media occurring within 8–12 days of initiating treatment.

Results Two hundred and three infants, aged 3 months–3 years with upper respiratory tract infection over 36 h and a history of recurrent acute otitis media were included over 8.5 months. Two children were lost to follow-up. Patient characteristics were similar in both groups. In the intention to treat analysis the frequency of acute otitis media was 16.2% (16/99) in the placebo group and 9.6% (10/104) in the amoxicillin/clavulanic acid group ($P = 0.288$). The difference between acute otitis media rates was 6.6% (one-sided 95% confidence interval of 14.3%). The occurrence of side-effects was similar in the amoxicillin/clavulanic acid and placebo groups.

Conclusions The difference in effectiveness between antibiotic and placebo was not greater than 14.3%, and we calculated that 94 children would need to be exposed to antibiotics to avoid six cases of acute otitis media. In view of the risk of development of resistance due to frequent exposure to antibiotics, our study supports the need for reduction in the administration of antibiotics in upper respiratory tract infection even in children at high risk of acute otitis media.

Keywords: acute otitis media, amoxicillin/clavulanic acid, children, randomized trial, upper respiratory tract infection

Introduction

Continuous antimicrobial prophylaxis for recurrent acute otitis media (AOM) has generally been considered effective but is not recommended because it acts as a natural selective pressure toward resistance [1]. Intermittent antimicrobial prophylaxis in OM-prone children initiated during an upper respiratory tract infection (URI) could be an alternative approach but its efficacy has not been demonstrated. URI is one of the most common paediatric diseases and its incidence in France is 5.5 million

attacks/year in children less than 7 years of age. Although acute URI is usually of viral origin, antibiotics are prescribed in 60% of children less than 7 years of age in France [2], in 43% in the UK, 44% in the USA and 46% in Germany. The rate of French antibiotic prescription increased by 115% between the 1980s and 1990s [3]. Risk factors for AOM, the most common complication of URI, are age less than 3 years, recurrent AOM, immunosuppression and day care with other children. Without antibiotics the frequency of AOM following URI is 7.4% in children without a history of AOM and 17% in children with a history of recurrent attacks of AOM [2, 4]. Several trials failed to demonstrate a reduction in duration of URI or AOM with amoxicillin, cotrimoxazole [5] or other older antibiotics [6]. In Cohen's study, the difference between AOM following URI with and without antibiotics (5.5% and 10%, respectively) could not be

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attributed to antibiotics, since their prescription was not controlled and therefore probably influenced by risk factors for AOM [2]. Two more recent trials failed to demonstrate efficacy of short-term antibiotic prophylaxis to prevent AOM. First, in a trial planned to demonstrate the superiority of amoxicillin/clavulanic acid (AMCL) over placebo in 104 children aged 1–4 years, without risk factors, AOM developed in 18% of those receiving AMCL initiated promptly after appearance of symptoms of URI and in 22% of those receiving placebo ($P = 0.59$) [7]. Second, in 70 children with 304 episodes of URI, and who had suffered their first AOM before 6 months of age, penicillin-V treatment during each URI did not reduce the number of attacks of AOM in comparison with placebo [8]. The lack of demonstration of prevention of AOM by antibiotics, their cost (\$26 for 8 days with AMCL) and their side-effects (2–10%) are not compensated for by the 24–48 h reduction in symptoms of URI that may result [9]. Antibiotic prophylaxis places selective pressure on bacterial ecology and contributes to the increase in resistance among respiratory pathogens which, more than all the foregoing arguments, raises the question of the relevance of antibiotic prescription for URI [10]. The emergence of resistant strains of *S. pneumoniae* (most often involved in severe infections) is a public health problem. Consequently antibiotics should not be prescribed for common URI (purulent nasal discharge, fever) [11]. They may be debatable for subjects at risk of AOM but no randomized, double-blind trial has been undertaken in this population. AMCL, recommended for AOM, is probably a likely candidate antibiotic because the bacteria involved in URI are the same as those involved in AOM, i.e. *S. pneumoniae*, *H. influenzae* and *M. catarrhalis*.

The main aim of this study was to assess the equivalence of AMCL and placebo in the prevention of AOM in children at high risk of AOM who develop URI.

Methods

The study was a multicentre, randomized, double-blind, equivalence trial in children treated by private paediatricians during the winter period (November–March). One randomization list per centre (i.e. each paediatrician) was established with random permuted blocks of size 2. The main end point was the occurrence of AOM based on physician assessment within 8–12 days after initiation of treatment. AOM was defined according to Paradise's criteria [12] by bulging, diffuse or localized inflamed tympanic membranes or spontaneous otorrhea.

The inclusion criteria were: age between 3 months and 3 years; acute URI, defined as bilateral clear or purulent nasal discharge with cough, fever $>38^{\circ}\text{C}$ in the preceding 48 h and no AOM; duration of symptoms of

URI present over more than 36 h but less than 5 days; recurrent AOM defined by a history of $\geq$ two attacks of AOM in the preceding 6 months in children less than 1 year of age or $\geq$ three AOM during the preceding 12 months in children older than 1 year of age; and informed parental consent. The exclusion criteria were lower respiratory infection; placement of tympanostomy tubes; sore throat; bloody rhinorrhea; antimicrobial therapy in the preceding 2 weeks; allergy to beta-lactam antibiotics or paracetamol; chronic treatment with anti-allergic agents or immunosuppressant drugs (except vitamins, fluoride); and chronic disease.

Amoxicillin (100 mg)/clavulanic acid (20 mg) was compared with placebo. Placebo syrup (prepared by SmithKline Beecham) was identical in appearance consistency and taste compared with AMCL syrup. The dose of AMCL was $75\text{ mg kg}^{-1}\text{ day}^{-1}$ (i.e. 25 mg kg^{-1} every 8 h) for 5 days. Treatment was administered orally. Bottles containing the volume of treatment required for 5 days were prepared and labelled in accordance with good clinical practice. The other treatments allowed were paracetamol on demand (not exceeding $60\text{ mg kg}^{-1}\text{ day}^{-1}$) and topical decongestants.

All children were re-examined 10 ± 2 days after inclusion. An earlier re-examination was performed whenever the parents suspected the development of AOM, or if worsening occurred (e.g. change in behaviour such as insomnia, anorexia, cough with vomiting, lack of smiling).

Sample size

AOM was estimated to develop in 15% of children receiving placebo. The maximum acceptable difference between the two treatments was fixed at 10%. This equivalence range was based on a clinically relevant outcome, i.e. the absolute percentage reduction in AOM should be greater than 10% to expose all otitis prone children with URI to antibiotics. Fixing α at 5% (one tailed analysis) and β at 20%, the number of children required in each group was calculated to be 158.

Analysis

Analysis was undertaken as intention to treat. Patients whose end point was not available were classified as not having AOM in the AMCL group and having AOM in the placebo group (maximum bias strategy in an equivalence trial). A per protocol analysis was also undertaken excluding children without the required history of recurrent AOM or with a treatment duration less than or equal to 3 days and patients lost to follow-up. The equivalence hypothesis was tested by a chi squared test with continuity correction in a one tailed analysis [13] and one

tailed 95% confidence intervals were estimated [14]. Comparison of paracetamol and antibiotic exposure and comparison of occurrence of side-effects were performed with the chi squared test. Risk factors for AOM were studied in all children except patients lost to follow-up, and independently of treatment administered. Univariate analyses were performed using the Wilcoxon test and Fisher exact test. Analyses were performed using SAS (SAS Institute Inc, Cary, NC).

The trial was undertaken in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice. The study was approved by the 'Comite Consultatif de Protection des Personnes dans la Recherche Biomedicale' of Tours. A Steering Committee set up before beginning the study, comprising two clinical physicians (a paediatrician and an otologist), a clinical pharmacologist and a biostatistician, was required to validate data, manage information and to make any final decision about the study.

Results

The study continued for a 3 month period during the winter of 1998–99 and a 6 month period during the winter of 1999–2000. A total of 203 patients were included by 30 private paediatricians. The rate of recruitment was not achieved because of difficulties experienced by paediatricians with the selection criteria of high risk of AOM patients (particularly the history of recurrent attacks of AOM), the low URI rates due to two mild winters, and new recommendations from the French Drugs Agency not to use antibiotics for URI. The per protocol population comprised 187 children (Figure 1).

The characteristics of the patients on inclusion were comparable in both groups, particularly in terms of risk factors for AOM (Table 1). In the intention to treat population the occurrence of uni or bilateral AOM at day 10 ± 2 was 16.2% (16/99) in children receiving placebo compared with 9.6% (10/104) in the group receiving AMCL ($P = 0.288$), i.e. a difference of 6.6% (one-sided 95% confidence interval of 14.3%). In the per protocol population the occurrence of AOM was 16.3% (15/92) and 10.5% (10/95) with placebo and AMCL, respectively ($P = 0.251$), i.e. a difference of 5.8% (one-sided 95% confidence interval of 14.0%). Paracetamol was taken by 76.5% (75/99) of children in the placebo group and 67% (69/104) of those in the AMCL group ($P = 0.14$) for a median (min; max) duration of 3 (1; 7) and 2 (1; 7) days, respectively. An antibiotic other than that used for the study was prescribed before day 10 ± 2 to 14.3% (14/99) of children in the placebo group and to 8.7% (9/104) of those in the AMCL group ($P = 0.22$).

Gastro-intestinal manifestations occurred in 24.2% of

children in the placebo group and 23.1% in the AMCL group while cutaneous side-effects occurred in 6.1% and 3.9%, respectively. One febrile seizure with benign resolution occurred in a 13 month-old child receiving placebo. The two patients who stopped treatment for side-effects related to treatment were in the AMCL group.

Risk of occurrence of AOM was analysed in 201 patients, 25 of whom had AOM (excluding the two patients lost to follow-up). No factors showed a significant influence on the occurrence of AOM in either group (Table 2).

Discussion

Our study is original because it is a double-blind randomized trial using amoxicillin and including URI patients at high risk of AOM. That only two patients were lost to follow-up (0.9%) is evidence of the quality of the study and the commitment of the investigators.

As the upper limit of the unilateral 95% CI was above the 10% considered to be equivalence, no conclusion could be drawn concerning equivalence between AMCL and placebo to prevent the development of AOM during URI. However, the upper limit of the confidence interval of the difference (14.3%) indicates that the difference could not exceed 14.3% (at the 5% significance level). The lack of demonstration of equivalence might be explained by lower number of patients than planned. However, even if the 316 children had been included as planned and if the rates of AOM had remained the same, the one-sided 95% confidence interval would have been 13.0% ($P = 0.236$), which would also have made it impossible to draw conclusions. To conclude statistically significant equivalence (reject the null-hypothesis) with the incidence of AOM observed in our study a sample of 1080 subjects would have been necessary. Paradoxically, in such a situation (i.e. with 1080 subjects, 16.3% and 9.6% AOM with placebo and AMCL, respectively) a statistically significant difference ($P = 0.001$) would also have been demonstrated in favour of antibiotics [14]. A difference of 6%, even if statistically significant, would not have been clinically relevant. Indeed, it would have been lower than the 10% considered to be a clinically relevant difference in our hypothesis, which therefore leads to the conclusion that it is not justified in terms of risk/benefit to expose 94 children to antibiotics to avoid six cases of AOM.

Although antibiotics have few immediate side-effects, they have ecological risks for individuals and society. Arguments on microbiological, clinical and epidemiological grounds in France, as in other European countries and Northern America, indicate that exposing a population to antibiotics increases resistance to antibiotics involving bacteria responsible for common infections (S.

Figure 1 Trial profile.

pneumoniae, *H. influenzae* and *M. catarrhalis*). For example, the resistance of *S. pneumoniae* to penicillin G in France increased from 0.5% (1984) to 32% (1994) in 10 years [15]. Moreover, under-dosing and use of antibiotics over too long a period appear to be qualitative and quantitative elements inducing selection of resistant strains, i.e. risk increased six-fold with doses lower than the recommended dose and risk increased 3.5-fold with treatment longer than 5 days [16]. However, of the two factors determining resistance to antibiotics (interindividual transmission and exposure to antibiotics) only exposure to antibiotics can be reduced, particularly by encouraging an appropriate use of antibiotics.

We did not find any risk factors for development of AOM, which is not surprising in that the trial population was already selected as at risk, particularly a history of repeated occurrence of AOM and the young age of the children.

Although we did not succeed in demonstrating equivalence between AMCL and placebo, we calculated that 94 children needed to be exposed to antibiotics to avoid six cases of AOM. These findings, combined with the ecological risks of frequent exposure to antibiotics, suggest that it is necessary to define ways of reducing prescription of antibiotics for upper respiratory tract infections with the risk of AOM.

Table 1 Characteristics on inclusion.

	Placebo n = 99	AMCL n = 104
Age (months)	17.9 ± 8.3	17.4 ± 8.8
Male	52 (52.5%)	60 (57.7%)
Weight (kg)	11.0 ± 2.5	11.0 ± 2.2
URI in previous 6 months	3 [0; 10]	3 [0; 10]
Adenoidectomy	3 (3.0%)	8 (7.7%)
Day care with other children	52 (52.5%)	56 (53.8%)
Passive smoking	32 (32.3%)	25 (24.0%)
GER	8 (8.1%)	9 (8.6%)
Breast feeding	35 (35.3%)	36 (34.6%)
Pacifier	51 (51.5%)	55 (52.9%)

AMCL: amoxicillin/clavulanic acid; URI, upper respiratory tract infection; GER, gastro-esophageal reflux. Results are expressed as median [min; max] for discrete data; number (%) for qualitative data; mean ± s.d. for continuous data.

Table 2 Risk factors for AOM. Results are expressed as mean ± s.d. for continuous data, median [min; max] for discrete data and number (%) for qualitative data.

	AOM (n = 25)	No AOM (n = 176)	P value
Age (months)	16.1 ± 8.1	18.0 ± 8.5	0.218
Sex M	15/25 (60.0%)	95/176 (54.0%)	0.670
URI in previous 6 months	3 [0; 7]	3 [0; 10]	0.514
AOM in previous 6 months	2 [0; 5]	3 [0; 6]	0.392
Adenoidectomy	2/24 (8.3%)	9/175 (5.1%)	0.626
Day care with other children	13/25 (52.0%)	95/176 (54.0%)	1.000
Passive smoking	4/25 (16.0%)	52/174 (29.9%)	0.233
GER	0/25 (0.0%)	17/176 (9.7%)	0.138
Breast feeding	7/25 (28.0%)	64/176 (36.4%)	0.506
Pacifier	12/25 (48.0%)	92/173 (53.2%)	0.672

URI, upper respiratory tract infection; AOM, acute otitis media; GER, gastro-esophageal reflux.

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