INHALED TOBRAMYCIN IN CHILDREN WITH ACUTE BACTERIAL RHINOPHARYNGITIS

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Received September 14, 2005 – Accepted February 7, 2006

Antibiotic abuse for treating rhinopharyngitis induces the occurrence of resistant bacteria. As topical drugs might reduce this phenomenon, the aims of our study were to evaluate inhaled tobramycin in children with acute bacterial rhinopharyngitis and to compare it with oral amoxicillin/clavulanate. The trial was conducted as randomized, parallel group and double blind. Children, aged 3-6 years, with acute bacterial rhinopharyngitis were treated with 15 mg of aerosolized tobramycin (Group A) or 50 mg/Kg of amoxicillin/clavulanate (Group B) twice daily for 10 days. The following parameters were assessed: nasal obstruction, mucopurulent rhinorrhea, post-nasal drip, adenoidal hypertrophy, tympanic inflammation, tympanogramm, rhinomanometry and cultures. Of 416 patients screened, 311 children (178 females and 133 males), median age 4.5 years, completed the study: 156 in Group A and 155 in Group B. Both treatments improved all parameters ($p<0.01$ for all). Intergroup analysis showed that inhaled tobramycin induced a better improvement versus amoxicillin/clavulanate concerning nasal obstruction ($p<0.05$), adenoidal hypertrophy ($p<0.01$), tympanic inflammation ($p<0.01$), rhinomanometry ($p<0.01$) and cultures ($p<0.05$). In conclusion, inhaled tobramycin may represent a valid treatment for acute bacterial rhinopharyngitis in children, as it is effective, safe, economic and simple to use.

Rhinopharyngitis is the most common disorder in children (1-2) and frequently causes complications, including otitis media, rhinosinusitis and lower respiratory tract infections (3-4). Even though upper respiratory infections (URIs) are usually sustained by viral infections, URIs are the leading reason for antibiotic prescription in children in U.S.A. (5). Antibiotic abuse often modifies normal saprophytic flora in rhinopharynx (6), thus inducing the occurrence of resistant bacteria (7). In this regard,

Key words: rhinopharyngitis, antibiotic therapy, inhaled tobramicin

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0394-6320 (2006)

long-term courses of antibiotics are the first cause of selecting resistant strains (8-9).

Upper airways constitute a pathophysiological unit and each inflammatory event, if not adequately treated, may spread towards other organs. Two main crucial areas are recognized: ostio-meatal complex (OMC) and rhinopharynx (RP). OMC is the natural site of drainage for anterior ethmoid, maxillar sinus and frontal sinus: the anterior rhinosinusal system. RP includes pharyngeal tonsil, rhino-tubaric-tympanic unit and spheno-ethmoidal recess (SER). The physiology of the upper respiratory tract is guaranteed by the patency of OMC and RP that is impaired during URI.

Intranasal inhalant therapy satisfies the requirements for restoring the patency and the drainage of OMC and RP. It achieves local higher drug concentrations, and consequently a lower drug dosage is possible which exerts prompt activity, removes watery secretions and increases tolerability (particularly suitable for children). In this regard, several studies evidenced the effectiveness of inhaled antibiotics in treating bacterial respiratory infections (10-19). Particularly, tobramycin has been demonstrated to be effective and safe when topically administered in adults with cystic fibrosis or URIs (11-13, 20-21). Thus, the aim of our study is to evaluate inhaled tobramycin in children with acute bacterial rhinopharyngitis and to compare it with oral amoxicillin/clavulanate.

MATERIALS AND METHODS

Study design

The trial was conducted as randomized, parallel group and double blind. Inclusion criteria were based on a documented diagnosis of acute bacterial rhinopharyngitis (positive culture for bacteria) and validated parameters. Children (aged 3-6 years) had to present at least 5 of these 7 parameters: nasal obstruction (22), mucopurulent rhinorrhea (23), post-nasal drip (24), adenoid hypertrophy (22), tympanic inflammation (24), impaired tympanogram (22) and abnormal rhinomanometry (25).

Exclusion criteria were anatomic anomalies (septal deviation, choanal atresia, etc), hypersensitivity to aminoglycosides and to β-lactamates, respiratory allergy, cystic fibrosis, renal failure, use of antibiotics and/or corticosteroids in the last 30 days and negative culture. All parents of enrolled children provided informed written consent. The study was approved by the Institutional Review Board. An adaptive randomization procedure was used to assign patients in a 1:1 ratio to receive tobramycin or amoxicillin/clavulanate.

Double-masked and double-dummy method was performed: oral taste-masked placebo was associated to patients taking tobramycin, whereas aerosol taste-masked placebo was associated with patients taking amoxicillin/clavulanate.

Cultures

A nasal swab was used with a sterile silicon-covered pad extracted at the tip only when close to the exudate in the rhinopharynx. Nasal swabs were plated onto the following media: blood-agar plate, CNA blood-agar, chocolate-agar plus isovitalex, (OXOID, Italy), Mac-Conkey agar and Brain-Heart Infusion agar. All plates were incubated for 24h at 37°C. Bacteria were identified by conventional techniques such as Gram stain, catalase and oxydase texts. Species identification was accomplished by API methods (BioMèrieux, Marcy L'étoile, France).

Drugs and monitoring

The treatment regimen consisted of 15 mg of aerosolized tobramycin (Group A) or 50 mg/Kg of amoxicillin/clavulanate (Group B), twice daily for 10 days. Tobramycin solution for inhalation (Tobi-Dompè S.p.A., Italy) was a sterile, pH-buffered solution containing 3 mg/ml tobramycin (preservative-free) in 5 mL of saline solution. Taste-masked placebo, chosen to mimic the taste of tobramycin, was 1.25 mg quinine sulfate in 5 ml of saline solution (NaCl 0.9%). The tobramycin was administered by the nasal device Rinowash (Markos-Mefar S.p.A., Italy), and the aerosol nebulizer with pneumatic compressor (1.5 bar per 5 L/min) (Moby-neb by Markos-Mefar S.p.A., Italy). During the study, the patients were visited at baseline (V1-the start of the trial) and after 10 days (V2-the end of the treatment). Nasal swab, clinical evaluation, fiberoptic endoscopy, impedenceometry and rhinomanometry were performed at each visit.

The following parameters were assessed: nasal obstruction (22) (graded as absent, continuous-daily or periodic), mucopurulent rhinorrhea (23) (evaluated as absent, reduced or unchanged after treatment), post-nasal drip (24) (evaluated as absent, reduced or unchanged after treatment), adenoidal hypertrophy (22) (graded as small, moderate or large, considering the distance between the vomer and the adenoid tissue), tympanic inflammation (24) (evaluated as absent, reduced or unchanged after treatment), tympanogramm (22) (graded as type A= compliance between 0 and 99 mm H_2O, type C1= compliance between 100 and 199 mm H_2O, type C2= compliance between 200 and 350 mm H_2O, or type B= absence of compliance), rhinomanometry (25) (graded as

normal=nasal resistance <1.2 Pa/mL/sec or abnormal= ≥1.2 Pa/mL/sec) and cultures.

The drugs were administered to the children by the parents who instructed the children to perform normal tidal breathing during aerosol-therapy. No other drugs were permitted during the study.

Statistical analysis

The statistical analysis was carried out using the program Statistic '98 Edition, StatSoft, Inc. The comparison between the proportions was computed under the approximation of normal distribution and testing the null hypothesis. For each symptom the efficacy of the two drugs was analysed valuing the reduction of the positive cases. A p value lower than 0.05 was considered as significant.

RESULTS

Of 416 patients screened, 354 met the eligibility criteria and received the study drugs; 177 patients received tobramycin (Group A) and 177 received amoxicillin/clavulanate (Group B). 311 patients (178 F and 133 M), median age 4.5 years, completed the study: 156 in Group A and 155 in Group B. The two groups were similar in respect to randomization stratum. There were no significant differences in baseline parameters, nasal obstruction, rhinorrhea, rhinomanometry, post-nasal drip, tympanic inflammation, adenoidal hypertrophy, tympanogram and cultures, between the two groups. Thus, the two groups were statistically homogeneous (Table I). Particularly, four groups of pathogens were identified: all strains were susceptible to the study drugs (Figure 1).

After treatment evaluation (day 10)

Compliance, as monitored by phial and tablet count, was similar in two groups: 87% of doses for Group A and 88% for Group B. Treatments were substantially well- tolerated in Group A without significant adverse events, whereas 12% of the children in Group B complained of nausea, 7% diarrhoea and 5% vomiting.

Intragroup analysis

In group A, inhaled tobramicyn induced a significant improvement of: nasal obstruction ($p<0.01$); rhinorrhea ($p<0.01$); post-nasal drip ($p<0.01$); adenoidal hypertrophy ($p<0.01$); tympanic inflammation ($p<0.01$); tympanogram ($p<0.01$); rhinomanometry ($p<0.01$); cultures ($p<0.01$) (Table II).

In group B, amoxicillin/clavulanate induced a significant improvement of: nasal obstruction ($p<0.01$); rhinorrhea ($p<0.01$); post-nasal drip ($p<0.01$; adenoidal hypertrophya ($p<0.01$); tympanic inflammation ($p<0.01$); tympanogram ($p<0.01$); rhinomanometry ($p<0.01$); cultures ($p<0.01$)(Tab III). Intergroup analysis (Fig. 2 and Tables IV-V).

Nasal obstruction

It was considered recovered if absent after treatment. 73.1% of patients of group A obtained recovery versus 61.3 % of group B ($p=0.03$).

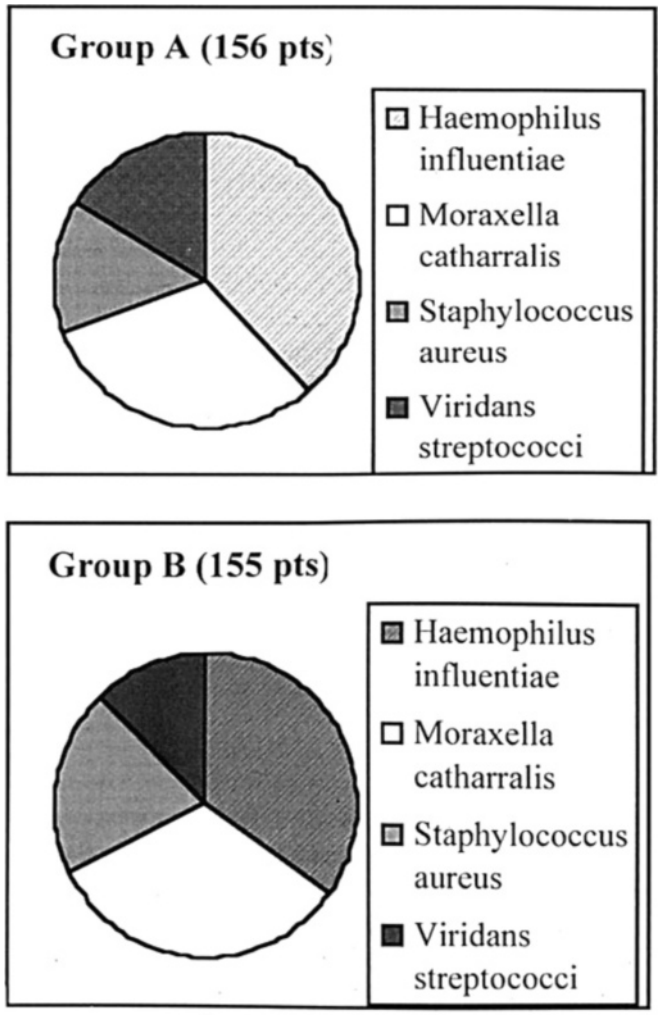

Fig. 1. *Bacterial cultures in Group A (topical tobramycin) and in Group B (amoxicillin/clavulanate) at baseline.*

Table I. *Evaluated parameters in Group A (inhaled tobramycin) and in Group B (amoxicillin/clavulanate) at baseline.*

Baseline parameters	Group A (156pts)	Group B (155pts)
Nasal obstruction	156	155
Continuous	135	132
Periodic	21	23
Rhinorrhea	153	149
Post-nasal drip	156	155
Adenoidal hypertrophy		
Small	22	19
Moderate	33	31
Large	101	105
Tympanic inflammation	140	148
Tympanogram		
Type A	13	15
Type C1	25	27
Type C2/B	118	113
Rhinomanometry (impaired)	152	152
Cultures (positive)	156	155

Rhinorrhea

It was considered recovered if absent after treatment. 68.6% of patients of group A obtained complete recovery versus 61.8% of group B (p=0.26).

Post nasal drip

It was considered recovered if absent after treatment. The patients recovered from post-nasal drip were 68.6% in group A and 56.8% in group B (p=0.05).

Adenoid hypertrophy

It was considered recovered if small after treatment. Considering patients with large or moderate adenoid hypertrophy at baseline, 74.6% of group A obtained a recovery versus 58.8 % of group B, with significant difference (p= 0.006).

Tympanic Inflammation

It was considered recovered if absent after treatment. The patients who recovered from tympanic inflammation were 75% in group A and 59.5% in group B (p=0.006).

Tympanogram

It was considered recovered if tympanogram was "type A" after treatment. Considering patients with baseline type C2/B or C1 tympanogram, 75.5% of group A obtained a complete recovery versus 65 % of group B (p=0.05).

Rhinomanometry

It was considered recovered if unilateral resistance at 150 Pa was less than 1.2 Pa/mL/sec after treatment. 76.3% of group A recovered versus 61.8% of group B (p=0.006).

Cultures

They were considered recovered if bacterial eradication was achieved after treatment. 73.1% of group A (114 children) obtained complete recovery versus 60.6% of group B (94 children) (p=0.02).

In patients with microbiological failure, persistence of the responsible pathogen was observed. However, there was no significant difference concerning type and frequency both of persistent and eradicated pathogens between the two groups.

Table II. *Evaluated parameters in Group A at V0 (baseline) and V1 (after treatment). + Positive cultures. * Eradicated cultures.*

Group A	V_1	V_2	Difference V_2 vs V_1
Nasal obstruction			P<0.01
Continuous	156	25	
Periodic	135	35	
Absent	21	95	
Rhinorrhea	153		P<0.01
Recovery		95	
Post-nasal drip	156		P<0.01
Recovery		88	
Adenoidal hypertrophy			P<0.01
Small	22	96	
Moderate	33	38	
Large	101	21	
Tympanic inflammation	140		P<0.01
Recovery		93	
Tympanogram			P<0.01
Type A	13	100	
Type C1	25	34	
Type C2/B	118	21	
Rhinomanometry	152		P<0.01
Recovery		95	
Cultures	156 +	114 *	P<0.01

DISCUSSION

This study provides evidence that the administration of inhaled tobramycin is better able to improve both clinical and functional outcomes and reduce adverse events than oral administration of amoxicillin/clavulanate in children with acute bacterial rhinopharyngitis. It is worthy of note that inhaled therapy is considered by the American Food and Drug Administration (F.D.A.) as first choice in treating lower airway infections (27). However, inhaled therapy is rarely prescribed for URIs.

The rhinopharynx constitutes an important anatomic and functional unit as impaired mucociliary clearance represents a main pathogenic factor in upper airway inflammations (28-29), followed by a bacterial overgrowth that, through post-nasal-drip, can diffuse to lower airways (30, 32). Acute rhinopharyngitis usually results from viral infection (28-29), whereas acute bacterial rhinopharyngitis is commonly caused by some

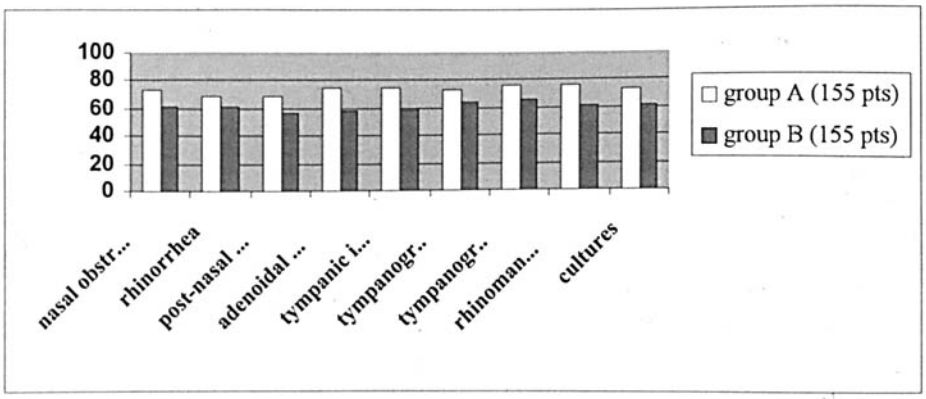

Fig. 2. *Percentage of recovery in group A and group B.*

Table III. *Evaluated parameters in Group B at V0 (baseline) and V1 (after treatment). + Positive cultures. * Eradicated cultures*

Group B	V_1	V_2	Difference V_2 vs V_1
Nasal obstruction			P<0.01
Continuous	155	25	
Periodic	132	35	
Absent	23	95	
Rhinorrhea	149		P<0.01
Recovery		95	
Post-nasal drip	155		P<0.01
Recovery		88	
Adenoidal hypertrophy			P<0.01
Small	19	96	
Moderate	31	38	
Large	105	21	
Tympanic inflammation	148		P<0.01
Recovery		93	
Tympanogram			P<0.01
Type A	15	100	
Type C1	27	34	
Type C2/B	113	21	
Rhinomanometry	152		P<0.01
Recovery		95	
Cultures	155 +	94 *	P<0.01

Table IV. *Evaluated parameters in Group A and group B at V2.*

Parameters	V_2	Group A (156pts)	Group B (155pts)
Nasal obstruction			
Continuous		15	25
Periodic		27	35
Absent		114	95
Rhinorrhea			
Recovery		108	95
Post-nasal drip			
Recovery		107	88
Adenoidal hypertrophy			
Small		121	96
Moderate		25	38
Large		10	21
Tympanic inflammation			
Recovery		120	93
Tympanogram			
Type A		120	100
Type C1		19	34
Type C2/B		17	21
Rhinomanometry			
Recovery		119	95
Cultures (eradicated)		114	94

Table V. *Percentage of recovery in group A and group B.*

Parameters	PERCETANGE OF RECOVERY	PERCETANGE OF RECOVERY	P value
	Group A (156pts)	Group B (155pts)	
Nasal obstruction continuos or periodic	73.1	61.3	0.03
Rhinorrhea	68.6	61.8	0.26
Post-nasal drip	68.6	56.8	0.05
Adenoidal hypertrophy large or moderate	74.6	58.8	0.006
Tympanic inflammation	75	59.5	0.006
Tympanogram Type C2/B TYPE C2/B or C1	 73.7 75.5	 64.4 65	 0.12 0.05
Rhinomanometry	76.3	61.8	0.006
Cultures	73.1	60.6	0.02

Society (36). The nasal shower Rinowash (Markos-Mefar S.p.A, Italia) is capable of nebulizing particles >18μ of diameter (37-38). This device shows selective drug distribution in rhinopharynx, high speed nebulization (1 mL/10 sec) and thecapability of removing nasal secretions (39).

There is evidence that an inhaled antibiotic (mainly aminoglycosides) (12, 15, 19) may be more effective than a systemic antibiotic if the drug has: dose-dependent bactericidal activity; no ciliotoxic effect; electrostatic positive storage. The inhaled tobramycin has all these characteristics (10-11, 14-15, 20-21) and the maximum non- ciliotoxic concentration that remains preserved also after nebulizing (17, 21) is <20% (40). Tobramycin is not nephrotoxic, in a few cases it causes allergy and it is very effective against many Gram- bacteria. The effectiveness of tobramycin is evident both after intratracheal (1.5 mg/Kg) and aerosol administration (10mg/mL for 15min) and its activity is persistent after 12 hours (>80%) with minimal systemic absorption (41). Furthermore, tobramycin has a low price, mainly concerning the duration of therapy (10-15-19). In addition, a long term study with inhaled tobramycin in patients with cystic fibrosis showed the lack of side effects, including bacterial resistance (the pathogen's MIC was unchanged after a 40 week treatment period) (10). As for all antibiotics, the efficacy of tobramycin may be limited by bacteria-resistance induced by plasmides (42). Therefore, the administration of inhaled tobramycin is usually recommended for 7-14 days.

This study compared two different therapies in children with acute bacterial rhinopharyngitis: inhaled tobramycin (nebulized by Rinowash) and oral amoxicillin/clavulanate, considered the "gold standard" for treating bacterial infections of upper airways (43). The findings showed that both treatments were effective and no patient showed antibiotic resistance. However, topical tobramycin was significantly better than oral amoxicillin/clavulanate in improving nasal obstruction ($p<0.05$), adenoid hypertrophy ($p<0.01$), tympanic inflammation ($p<0.01$), rhinomanometry ($p<0.01$) and cultures ($p<0.05$). It is to highlight that the activity on tympanic parameters is related to the influence of rhinopharynx disorders in otitis media. Thus, resolving rhinopharyngitis, otitis media may improve. Another interesting finding was the reduction of adenoid hypertrophy in tobramycin-treated children that may be sustained by its antiinflammatory activity.

In addition, inhaled tobramycin exerted a germicidal effect also on Gram+ bacteria (normally not sensitive to this molecule), probably due to the higher local concentration, about 1000 times the single bacterial's MIC, obtained with nebulized tobramycin (36, 38).

Finally, inhaled tobramycin was well tolerated, particularly the solution without phenols or bisulfites, potentially bronchoconstrictive agents (44), and provided good compliance.

In conclusion, the inhaled tobramycin may represent a valid treatment for acute bacterial rhinopharyngitis in children, as it is effective, safe, economic and simple to use.

The correct application of inhaled therapy needs a specific device for upper airways and suitable drugs for nebulization (such as those with specific physical-chemical characteristics). The abuse of systemic antibiotics for the treatment of acute rhinopharyngitis has caused, and continues to cause, antibiotic-resistance, across the western world. Thus, this study provides the first evidence that inhaled antibiotic therapy may be more effective than oral antibiotic treatment in children with acute bacterial rhinopharyngitis. Therefore, these findings should reduce ostracism to therapy with inhaled antibiotics. Of course, numerous studies need to be conducted to validate and confirm these results.

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