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Efficacy, safety and tolerability of 3 day azithromycin versus 10 day co-amoxiclav in the treatment of children with acute lower respiratory tract infections

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To compare the efficacy, safety and tolerability of a 3 day course of azithromycin with a 10 day course of co-amoxiclav in the treatment of children with acute lower respiratory tract infection (LRTI), 118 patients with community-acquired LRTI were included in a multicentre randomized double-blind, double-dummy study. The diagnosis of LRTI was based on the presence of respiratory signs and symptoms in combination with consolidation on a chest radiograph or clinical evidence of LRTI. Patients received oral azithromycin suspension (10 mg/kg/24 h) or placebo in one dose for 3 days and co-amoxiclav (45/11.25 mg/kg/24 h) or placebo in three doses for 10 days. Of 110 eligible patients, 56 and 54 patients, respectively, were treated with azithromycin or co-amoxiclav. The percentage of patients cured or clinically improved at days 10–13 (primary endpoint) was 91% for azithromycin and 87% for co-amoxiclav. This difference of 4% (90% confidence interval: –6%, +14%) was not statistically significant ($P = 0.55$). Significantly ($P = 0.01$) more related adverse events were found in the co-amoxiclav group. This was largely due to a higher percentage (43% versus 19%) of gastrointestinal complaints. A 3 day course of azithromycin (three doses) is as effective in the treatment of LRTI in children as a 10 day course of co-amoxiclav (30 doses). The azithromycin group had fewer adverse events. We conclude that azithromycin is an effective, safe and well-tolerated drug in the treatment of children with LRTI. An additional advantage is the easy administration and short duration of therapy.

Introduction

Azithromycin is a semi-synthetic azalide antibiotic, which differs from erythromycin by the substitution of a methyl group for nitrogen at position 9A in the 15-membered macrolide ring.[1] The advantages of azithromycin over erythromycin are: greater stability in the presence of acid, better absorption, fewer side effects, a better pharmacokinetic profile including high tissue levels, an expanded antimicrobial spectrum and a prolonged serum half-life.[1,2] The antimicrobial activity of azithromycin against Gram-positive bacteria is comparable to that of erythromycin. However, the *in vitro* activity against Gram-negative bacteria is improved with respect to erythromycin.[3] Azithromycin inhibits the most frequent bacterial pathogens of lower respiratory tract infections (LRTIs): *Haemophilus influenzae*, *Streptococcus pneumoniae*, *Moraxella catarrhalis*, *Mycoplasma pneumoniae* and *Chlamydia pneumoniae*.[4]

Co-amoxiclav is frequently given as treatment for LRTI in children. Compliance is often a problem as it is usually given three times a day for 10 days.[5–7] Because of the

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pharmacokinetic profile it is possible to administer azithromycin in a once-daily dose for 3 days. This is a great advantage in the treatment of ambulatory patients and, in the case of children, also for the parents.

The purpose of the current study was to compare the clinical efficacy, safety and tolerability of a 3 day course of azithromycin with a 10 day course of co-amoxiclav in children with acute LRTI. This is the first study of this kind to use a double-blind, double-dummy design.

Materials and methods

Study design

The study was designed as a multicentre, randomized, double-blind, double-dummy, comparative trial of the clinical efficacy of azithromycin versus co-amoxiclav in the treatment of children with acute LRTI.

The ethical review boards of all eight participating institutions approved the study protocol. Informed consent was obtained from the parents of all children.

Patients

Patients (age 3 months–12 years) with community-acquired LRTI were included between June 1995 and December 1998. One university hospital, the Sophia Children's Hospital, Rotterdam, and seven regional hospitals in the southwestern Netherlands participated in the study.

The diagnosis of LRTI was based on the presence of respiratory signs and symptoms in combination with a positive chest radiograph showing consolidation of at least a part of a lung lobe without loss of volume, or clinical evidence of LRTI according to the following definition: rectal or oral temperature $\geqslant$38°C, cough, leucocytosis $>$10 000 cells/mm^3 or 15% band forms and rales, rhonchi or signs of consolidation on physical examination.

Patients were excluded on the basis of the following: complaints of LRTI longer than 1 week, weight $>$40 kg, need for parenteral therapy, congenital malformations of the respiratory tract, foreign body aspiration, cystic fibrosis, bronchopulmonary dysplasia, congenital or acquired heart disease, severe retardation, immunodeficiency disorders, known hypersensitivity to β-lactams or macrolides, previous participation in this study, treatment with any investigational drug or azithromycin within 1 month before enrolment or concurrent therapy with ergotamine or digitalis glycosides.

Study drug

Patients were assigned randomly to treatment with oral azithromycin suspension (10 mg/kg/24 h) in a single dose for 3 days or co-amoxiclav suspension (45/11.25 mg/kg/24 h) tds for 10 days. Blinding of the study was maintained with matched placebo suspension: patients in the azithromycin group received co-amoxiclav placebo suspension tds for 10 days. Patients in the co-amoxiclav group received azithromycin placebo suspension in a single dose on the first 3 days.

Each centre was provided with study medication by the sponsor of this study (Pfizer B. V., Capelle a/d Yssel, The Netherlands). The combinations of azithromycin and co-amoxiclav active/placebo had been allocated randomly in blocks of six. Randomization was done at Imro Tramarko, Berghem, The Netherlands.

Clinical evaluation

Clinical signs and symptoms of LRTI were recorded before the start of treatment on day 1 (visit 1). Changes were monitored on days 3–5 (visit 2), on days 10–13 (visit 3) and on days 25–30 (visit 4). At all follow-up visits, adverse events, use of concomitant drugs and compliance with study medication were assessed.

Haemoglobin, haematocrit, white blood cell count and differential, platelet count and C reactive protein or sedimentation rate were determined at visits 1 and 4. At visit 1, oxygen saturation was measured transcutaneously.

Chest radiographs were obtained at visits 1 and 4. A paediatric radiologist (S. G. F. Robben) reviewed all radiographs.

On visits 2, 3 and 4, the patient's response to treatment was classified by the investigator as cured, clinically improved or failure. Cure was defined as disappearance of clinical signs and symptoms within the treatment period; improved was defined as subsiding of signs and symptoms but with incomplete resolution; failure was defined as unchanged or worsened clinical signs and symptoms. Patients in whom, according to the treating physician, it was necessary to stop the study medication and to commence other treatment were also classified as failures. Temperature was recorded twice daily by parents, taken rectally in the early morning and the evening. Patients were considered free of fever when their temperature was $<$37.5°C on two consecutive occasions. One month after the last visit, the parents were contacted by phone to inquire after the condition of the patient.

All outcome data for individual patients were reviewed before breaking the treatment code.

Safety

At visits 2, 3 and 4, adverse events were recorded and classified as mild, moderate, severe or life-threatening. The relationship to treatment was recorded as possibly related, probably related, certainly related, probably not related or certainly not related.

Compliance

The parents registered the doses of medication used on a diary card. Intake of $<$80% of the active medication was considered as non-compliance.

Bacteriology and virology

Blood cultures were taken. Sputum cultures were obtained when the child was able to expectorate sputum. The cultures were processed according to standard procedures. A nasopharyngeal aspirate was taken on the day of admission and 25–30 days later, using a standard procedure with 0.9% sodium chloride and a disposable mucus extractor (Unoplast; Maersk Medical, Denmark). Direct viral immunofluorescence assays were performed for respiratory syncytial virus (RSV), adenovirus, influenza A and B virus and parainfluenza virus 1, 2 and 3 followed by virus isolation for these viruses and also cytomegalovirus. PCR procedures were performed for *M. pneumoniae* and *C. pneumoniae.*

Serum samples collected at admission and 25–30 days later were used for serological analysis to detect antibodies against RSV, parainfluenzavirus type 1–3, adenovirus, influenza A and B virus, *M. pneumoniae* and *C. pneumoniae*. A four-fold antibody rise measured by complement fixation test or specific IgA, IgM and IgG enzyme immune assays between the sera was considered diagnostic.

Statistical analysis

The primary endpoint was cure or clinical improvement at visit 3 (10–13 days). Equivalence of both treatments was considered to be shown if the lower limit of the two-sided 90% confidence interval for the difference (azithromycin minus co-amoxiclav) of percentages of patients who reached the endpoint was greater than –10%. With an assumed cured/improved percentage of 95%, with 118 patients the power of the study to demonstrate equivalence equals 80%.[8] Percentages were compared using Fisher's exact test. Number of days until disappearance of fever and number of adverse events per patient were compared using the Mann–Whitney test. The limit of statistical significance was set at $P = 0.05$ (two-sided).

Results

A total of 118 patients were randomized, of whom 48 (41%) were enrolled by the university hospital. There were seven patients who did not meet the inclusion criteria. For another patient, the informed consent given by one parent was withdrawn by the other. The remaining 110 patients were evaluated for efficacy.

Fifty-six and 54 patients, respectively, were treated with azithromycin and co-amoxiclav. The two treatment groups were comparable (Table I). The median age in the group treated with azithromycin was 3.8 years versus 2.7 years in the group treated with co-amoxiclav. This difference was not statistically significant.

Three patients missed visit 3. As these three were all clinically improved at visit 2, and telephonic enquiry with parents showed that the child's condition was satisfactory, these children were classified as clinically improved for the main endpoint.

The proportion of patients who were cured or improved at visit 3 (10–13 days) was 91% for azithromycin and 87% for co-amoxiclav (Table II). Two patients, one in each group, were not evaluable for clinical outcome at visit 3. No statistically significant difference ($P = 0.55$) was observed between the two therapy groups in terms of clinical outcome at visit 3, with 90% confidence interval for the difference (azithromycin minus co-amoxiclav) of the cured/improved percentage ranging from –6% to +14%.

Five treatment failures occurred in the azithromycin group: two patients had additionally received a macrolide because of an infection with *M. pneumoniae* or suspicion of infection with *Bordetella pertussis*. One patient experienced nausea and vomiting which had led to a change to intravenous therapy. One patient refused to take the oral medication after 2 days and one patient had developed fever on day 9. Seven treatment failures were observed in the co-amoxiclav group: three patients were changed to intravenous medication because of nausea and vomiting, one patient developed pleural effusion, one patient developed fever on day 9 and one patient was not improved on day 10. One patient's mother did not trust the medication after 3 days and a change was made to other medication.

There was no statistically significant difference in clinical outcome at visit 3 in the azithromycin group ($P = 0.34$) or the co-amoxiclav group ($P = 1.00$) when we compared children older than 5 years with the younger ones.

On visit 4 (25–30 days), the percentage of cured/improved patients was 90% in the azithromycin group and 86% in the co-amoxiclav group (Table II). One of these cured patients, in the azithromycin group, developed a respiratory tract infection with bronchial obstruction 2 weeks after the last visit.

Seventy-four (77%) diary cards of the 96 patients who were cured/improved at visit 3 and who had fever at entry into study were evaluable for analysis of the temperature response. The median time for the temperature to return to normal in these patients was 3 days in the azithromycin group ($n = 39$). The median time in the co-amoxiclav group ($n = 35$) was 2 days (Table III). This difference was not statistically significant ($P = 0.08$).

Eighty-four (76%) patients had a second chest radiograph at visit 4 (Table III). There was no significant difference in chest radiograph outcome between the two treatment groups. Of the patients who were cured at visit 3, one patient in each group did not show improvement on the chest radiograph at visit 4.

There was no difference in clinical outcome between children presenting with or without a consolidation on the chest radiograph.

Ninety-four (85%) diary cards were available to assess compliance (Table III). One patient had taken only 30% of the co-amoxiclav. She was improved clinically on visit 2 after 2 days of therapy, with coughing as the only com-

Table I. Patient characteristics at baseline

	Azithromycin, $n = 56$	Co-amoxiclav, $n = 54$
Sex		
male	38 (68)	32 (59)
female	18 (32)	22 (41)
Age (years)	3.8 (0.3–12.4)	2.7 (0.3–10.8)
Presenting symptoms[a]		
cough	51 (91)	49 (91)
dyspnoea	34 (61)	25 (46)
sputum	22 (39)	18 (33)
fever	38.6 (37.0–41.0)	39.0 (35.2–41.5)
respiratory rate	40 (15–68)	42 (20–94)
rhonchi	20 (36)	21 (39)
rales	27 (48)	17 (31)
signs of consolidation	8 (14)	12 (22)
Medical history		
days of illness at presentation	3.0 (1.0–9.0)	4.0 (1.0–14.0)
URTI[b] in last 2 weeks	17 (30)	13 (24)
asthma	12 (21)	12 (22)
pneumonia	5 (9)	4 (7)
antibiotics in last week	8 (14)	4 (7)
Diagnosis		
clinical	8 (14)	11 (20)
positive chest radiograph	48 (86)	43 (80)
Infection parameters		
total white blood cell count ($>10^9$/L)	14.7 (5.3–50.5)	16.4 (4.7–50.3)
C-reactive protein (mg/L)	57 (1–256)	69 (3–377)

Data shown are numbers of patients (%) or median (range).
[a]Patients can have more than one symptom.
[b]URTI, upper respiratory tract infection.

Table II. Clinical response

	Visit 3		Visit 4	
Clinical response	azithromycin $n = 55$[a] (%)	co-amoxiclav $n = 53$[a] (%)	azithromycin $n = 51$[b] (%)	co-amoxiclav $n = 50$[c] (%)
Cure	41 (75)	37 (70)	45 (88)	42 (84)
Improved	9 (16)	9 (17)	1 (2)	1 (2)
Failure	5 (9)	7 (13)	5 (10)	7 (14)

Excluded (not evaluable): [a]one patient; [b]five patients; [c]four patients.

plaint. On visit 4, she was clinically cured. Compliance was adequate for all other patients.

Only patients who received at least one dose of study medication were included in the safety analysis. A total of 117 patients was analysed, because one patient (withdrawal of informed consent) did not receive any study medication. Fifty-six per cent (33/59) of the patients treated with azithromycin reported adverse events compared with 71% (41/58) in the co-amoxiclav group ($P = 0.13$) (Table III). The total number of adverse events in the azithromycin group was 47 and in the co-amoxiclav group 70; corresponding to mean numbers of 0.8 and 1.2 per patient, respectively. This difference was statistically significant ($P = 0.04$). Adverse events scored by the research physician as related (possible, probable, certain) to the study medication occurred in 24% versus 47% in the azithromycin- and

the co-amoxiclav groups, respectively ($P = 0.01$). This difference is due largely to a significantly ($P = 0.005$) increased incidence of gastrointestinal complaints in the co-amoxiclav group (43 versus 19%). The incidence of other relevant adverse events (rash, fever) did not differ significantly between the groups. No serious adverse events related to the study medication occurred.

In both groups a pathogen was identified in about 55% of patients. There were no differences between the two groups concerning microorganisms (viral, bacterial, atypical, mixed) that possibly caused disease. Table IV shows the aetiological agents found in both groups.

Discussion

In the present study, a 3 day course of azithromycin suspension (10 mg/kg/24 h) in one dose per day was as

Table III. Temperature, follow-up chest radiograph, compliance and adverse events by treatment group

	Azithromycin, *n* (%)	Co-amoxiclav, *n* (%)
Temperature response (return to normal)	39[a]	35[a]
median (days)	3.0 (2–11)	2.0 (2–10)
Chest radiograph visit 4	42[b] (75)	37[b] (69)
cured	35 (63)	28 (52)
improvement	6 (11)	8 (15)
no improvement	1 (2)	1 (2)
Compliance	49[c] (88)	45[c] (83)
non-compliant	0	1 (2)
compliant	49 (88)	44 (81)
Adverse events[d]		
gastrointestinal	12 (20)	28 (48)
rash	6 (10)	4 (7)
fever	2 (3)	2 (3)
total	33 (56)	41 (71)

Data shown are number of patients (%) or median (range).
[a]Patients with fever at entry and evaluable diary cards, excluding treatment failures.
[b]Treatment failures excluded.
[c]Patients with evaluable diary cards.
[d]Patients can have more than one adverse event.

Table IV. Aetiological agents by treatment group

	Azithromycin (*n*)	Co-amoxiclav (*n*)
No pathogen found	29	25
M. pneumoniae	4	3
C. pneumoniae	2	1
Influenza A virus	2	1
Respiratory syncytial virus	1	7
Parainfluenzavirus	1	0
Influenza B virus	1	0
Adenovirus	1	1
Cytomegalovirus	0	2
Rhinovirus	0	2
Mixed: MP or CP with other pathogen	8	7
Mixed: virus/virus	5	3
Mixed: bacteria/virus	2	1
Mixed: bacteria	0	1

MP, *M. pneumoniae*; CP, *C. pneumoniae*.

effective as a 10 day course of co-amoxiclav suspension (45/11.25 mg/kg/24 h) in three doses per day in the treatment of acute LRTI in children. The patients treated with azithromycin had significantly fewer adverse events than the patients treated with co-amoxiclav. This was mainly attributable to a significant difference in gastrointestinal complaints.

The clinical outcome in our study is comparable with those reported in previous studies.[5,9] In this, the first double-blind study, a 3 day course of azithromycin showed efficacy equal to a longer, more complex regimen of co-amoxiclav in children with LRTI.

Previous studies showed that azithromycin is well tolerated in children, with adverse events rates of 6–27%.[10–12] Children in the azithromycin group in this study experienced adverse events related to the medication in 24% of cases. It is not clear why the co-amoxiclav group reported such a high percentage (47%) of medication-related adverse events, as in previous studies this ranged from 11 to 31%.[5,10,11,13]

It is still difficult to detect rapidly the causative pathogen in children with acute LRTI and antibiotic treatment in children with LRTI is almost always empirical. Azithromycin is one of the newer macrolides, and provides a good choice for the treatment of LRTI in children. Furthermore, administration of azithromycin is attractive because of once-daily dosing and the short duration of therapy.

We conclude that a 3 day course of azithromycin (three doses) is as effective as a 10 day course of co-amoxiclav (30 doses) in the treatment of LRTIs in children. Azithromycin is better tolerated than co-amoxiclav and may be preferable to co-amoxiclav in children with LRTI because of its more convenient and shorter regimen.

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