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Sequential intravenous-oral amoxycillin/clavulanate (Augmentin) therapy in paediatric hospital practice

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The efficacy and safety of intravenous and sequential intravenous-oral clavulanate-potentiated amoxycillin therapy was evaluated in 71 hospitalized paediatric patients, one month to 16 years of age. The infections treated included peritonsillar abscess (2 patients), purulent tracheitis (1), acute epiglottitis (24), pneumonia (31), pansinusitis (4), mastoiditis (1), cellulitis (4), lymphadenitis (2) and pyelonephritis (2). The severity of disease was rated as moderate in 31 patients (44%), and as severe in 40 (56%). Bacterial pathogens could be cultured in 26 cases (37%). The response to therapy was prompt and followed by clinical cure in each patient. Adverse drug effects included phlebitis (in 6%), mild gastrointestinal complaints (6%), rash (4%) and transient neutropenia and elevation of transaminases (one case each). It is concluded that amoxycillin/clavulanate is effective and safe treatment for bacterial infections of the respiratory tract, urinary tract, skin or soft tissues in children.

Introduction

The combination of the β-lactamase inhibitor clavulanic acid with amoxycillin provides an attractive approach to increasing the clinical utility of amoxycillin in paediatric patients, since clavulanic acid protects amoxycillin against hydrolysis by β-lactamases produced with increasing frequency by many important bacterial pathogens causing paediatric infectious diseases (Hunter *et al.*, 1980; Reading, Farmer & Cole, 1983). Investigators at this institution have studied the pharmacokinetics of both intravenous and oral amoxycillin/clavulanate formulations in children and have suggested dosage schedules (Schaad, Casey & Cooper, 1983; Schaad, Casey & Ravenscroft, 1986). Several clinical trials with oral amoxycillin/clavulanate have demonstrated that this antimicrobial combination is effective and safe therapy for various childhood bacterial infections (Jeffries, Rose & Williams, 1983; Gooch *et al.*, 1985; Odio *et al.*, 1985; Jaffe *et al.*, 1985). However, published experience with intravenous amoxycillin/clavulanate in paediatric hospital practice is scant (Price & Horobin, 1985; Ploechl, Pirko & Huber, 1985). Therefore, this open, non-comparative study was conducted to evaluate the efficacy and safety of intravenous and sequential intravenous-oral amoxycillin/clavulanate in the treatment of hospitalized children with various bacterial infections of moderate to severe degree.

Patients and methods

Study patients

Infants and children aged one month to 16 years admitted to the Department of Paediatrics, University of Berne, for treatment of community acquired infections of suspected

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bacterial aetiology were candidates for study. The study protocol included the following disease localizations: upper and lower respiratory tract, soft and lymphoid tissue, and urinary tract. Patients with a history of allergy to β-lactam antibiotics or underlying renal or hepatic dysfunction were excluded. The study was approved by the Institutional Committee on Human Investigations, Department of Paediatrics, University of Berne, and informed parental consent was obtained.

Patient evaluation

Complete medical history, comprehensive physical examination and suitable laboratory, radiological and microbiological studies were performed on each patient. Patients with findings suggesting non-bacterial disease were excluded from enrollment. In-vitro susceptibilities of significant pathogens to amoxycillin/clavulanate, amoxycillin and other antimicrobial agents were determined by a standardized Kirby-Bauer paper disc technique.

Treatment

Amoxycillin/clavulanate (Augmentin) vials containing 550 mg (500 mg of amoxycillin plus 50 mg of clavulanic acid) or 1·1 g (1 g of amoxycillin plus 100 mg of clavulanic acid) were used. All patients were started on intravenous amoxycillin/clavulanate at a recommended dosage according to severity of disease of 110 to 220 mg of amoxycillin/clavulanate/kg body weight/day, divided into four equal doses administered as bolus iv injection over 2–5 min. Once an unequivocal clinical response had been established and provided that gastrointestinal function was normal, the patients were changed to oral amoxycillin/clavulanate therapy. Paediatric oral amoxycillin/clavulanate formulations (syrup sachets or bottled suspensions) were used and contained four parts of amoxycillin and one part of clavulanic acid. Recommended dosages were between 50 and 100 mg of amoxycillin/clavulanate/kg body weight/day, divided into three equal doses. Duration of therapy was decided by the physician responsible. The remaining medical therapy was according to standard procedures.

Evaluation of therapy

Clinical, bacteriological and radiological responses to treatment were evaluated in each patient. Clinical cure was defined as complete resolution of symptoms with significant improvement of physical signs. Follow-up bacteriological cultures were done at the discretion of the physician. Follow-up chest radiographs were performed in all pneumonia patients. Adverse or toxic reactions to amoxycillin/clavulanate were assessed by daily clinical observation and haematological and biochemical monitoring at the beginning and end of treatment.

Results

Patient characteristics and therapies

From March 1985 to February 1986 a total of 71 infants and children were enrolled in the study. Their sex and age distribution and the daily dosage and duration of iv and oral amoxycillin/clavulanate therapy are listed in Table I.

Table I. Patient characteristics, daily dosage and duration of amoxycillin/clavulanate therapy

Characteristic	No. patients (%)	Mean (range)
Sex		
Male	45 (63)	
Female	26 (37)	
Age		4 11/12 (1/12–15 9/12)
1–11 months	8 (11)	
1–6 years	44 (62)	
> 6 years	19 (27)	
Daily dosage of amoxycillin/clavulanate (mg/kg)		
iv (in 4 × /day)	71 (100)	174 (76–272)
po (in 3 × /day)	64 (90)	60 (23–110)
Duration of therapy (days)		
iv		4·6 (1–14)
po		7·2 (2–15)
Total		11·1 (5–25)

In 16 patients (23%) the medical history revealed an underlying disease potentially relevant to the outcome of the infection. Five patients with pneumonia and two with pansinusitis had psychomotor retardation. Gastrooesophageal reflux was present in four patients with pneumonia and congenital heart disease could have promoted pneumonia in two infants. There was one case each with the association of bilateral vesicoureteric reflux and pyelonephritis, surgically repaired cleft palate and epiglottitis, and acute lymphoblastic leukaemia and pneumonia.

Nineteen patients (27%) had received unsuccessful antimicrobial therapy either po (18 patients) or iv (one patient) prior to amoxycillin/clavulanate. In 15 cases the duration of oral antibiotic administration was only one (12 patients) or two days (three patients) and their clinical non-response was interpreted as due to inadequate duration or an unsuitable route. Three of these patients had received oral amoxycillin/clavulanate. The choice of an unsuitable antibiotic was felt to explain the clinical failure in two patients: one had received oral co-trimoxazole for cervical lymphadenitis, and one chloramphenicol for bronchopneumonia. In two patients, in-vitro resistance of the pathogen was the probable explanation: *Haemophilus influenzae* resistant to erythromycin causing lobar pneumonia in one of these, and *Escherichia coli* resistant to cefuroxime causing aspiration bronchopneumonia in the other.

Five patients (7%) received other antibiotics in addition to amoxycillin/clavulanate. Three patients with pneumonia and positive cold agglutinins received oral erythromycin until negative complement fixation tests for *Mycoplasma pneumoniae* were reported after 3, 7 and 10 days. One patient with severe, culture-negative pansinusitis and a subperiosteal abscess in the right orbital roof was concomitantly treated with clindamycin iv and the fifth patient with known bilateral vesicoureteral reflux who had developed severe pyelonephritis due to *E. coli* also received amikacin iv. This urine pathogen was sensitive *in vitro* to amoxycillin/clavulanate and amikacin, but resistant to amoxycillin.

In the 24 patients with acute epiglottitis immediate nasotracheal intubation was performed under deep inhalation anaesthesia as described in detail elsewhere (Gerber

& Pfenninger, 1986). Mean duration of intubation was 23·6 h with a range from 14 to 38 h. There was no complication related to anaesthesia or intubation procedures.

Infections

The various infections requiring antibiotic treatment and their severity are listed in Table II. The degree of illness was rated as moderate in 31 (44%) and as severe in 40 patients (56%).

Surgical drainage of pus was only necessary in the case of orbital subperiosteal abscess complicating pansinusitis. Thoracocentesis was performed in all six patients with pneumonia and pleural effusion (pleuropneumonia): sterile exudates were found and in no case was there empyema. There was one case of periorbital and three cases of buccal cellulitis.

Table II. Clinical details of cases

Diagnosis	No. patients (%)	Severity of disease	
		Moderate	Severe
Peritonsillar abscess	2 (3)	1	1
Purulent tracheitis	1 (1·5)	1	—
Acute epiglottitis	24 (34)	—	24
Pleuropneumonia	6 (9)	2	4
Lobar pneumonia	15 (21)	10	5
Bronchopneumonia	10 (14)	7	3
Pansinusitis	4 (5)	3	1
Mastoiditis	1 (1·5)	—	1
Cellulitis	4 (5)	4	—
Lymphadenitis	2 (3)	2	—
Pyelonephritis	2 (3)	1	1
Total	71 (100)	31 (44)	40 (56)

Bacteriology

Bacterial pathogens could be cultured from relevant samples in 26 patients (37%). The isolated pathogens, their source and in-vitro susceptibility, as well as the infections they caused are shown in Table III. All bacterial isolates were susceptible *in vitro* to amoxycillin/clavulanate but four strains were β-lactamase-positive and resistant to amoxycillin: one *Staphylococcus epidermidis* strain, two *E. coli* strains, and one *Klebsiella pneumoniae* strain.

Response to therapy

Response to amoxycillin/clavulanate therapy was prompt in each patient and clinical assessment at the end of treatment and at follow-up revealed cure in all cases. Follow-up radiographs in the patients with pneumonia, sinusitis and mastoiditis showed marked resolution of the pathologic radiographic signs before amoxycillin/clavulanate therapy was discontinued. Because of clinical cure, follow-up cultures were only performed in two urine (pyelonephritis) and two pus samples (mastoiditis, cellulitis): both urine and both clear aspirate samples were culture-negative.

Table III. Details of the isolated bacterial pathogens (n = 26)

Pathogen	Source	No.	Disc sensitivity[a] Amoxycillin	Augmentin	Infection
H. influenzae	Blood	15	S	S	Acute epiglottitis
	Tracheal aspirate	1	S	S	Lobar pneumonia
Streptococcus pneumoniae	Blood	2	S	S	Pleuropneumonia
	Pus	1	S	S	Mastoiditis
Str. pyogenes	Tracheal aspirate	1	S	S	Lobar pneumonia
Staph. epidermidis	Pus	1	R	S	Cellulitis (periorbital)
B. catarrhalis	Tracheal aspirate	1	S	S	Acute epiglottitis
H. parainfluenzae	Tracheal aspirate	1	S	S	Lobar pneumonia
E. coli	Tracheal aspirate	1	R	S	Aspiration bronchopneumonia
	Urine	1	R	S	Pyelonephritis
K. pneumoniae	Urine	1	R	S	Pyelonephritis

[a]S, Sensitive; R, resistant.

Safety

Clinical adverse effects attributed to amoxycillin/clavulanate were observed in 12 patients (17%). Phlebitis at the injection site in four patients required change of intravenous access. Four patients experienced gastrointestinal complaints (two with diarrhoea and vomiting, two with diarrhoea only). However, these were mild side effects, and in no case was medication discontinued. Three patients developed maculopapular rashes: at the end of therapy in two cases (days 8 and 14, respectively), and in one case manifest from day 4 to day 10 of treatment. One patient developed a generalized urticarial rash on the eighth day of treatment requiring cessation of therapy.

Complete laboratory monitoring at the beginning and at the end of treatment was performed in 38 patients (54%). Neutropenia developed in one patient with periorbital cellulitis (248 neutrophils/μl on day 6 of therapy) and resolved within three weeks. A four- and ten-fold rise respectively of the liver enzymes SGOT and SGPT was found in one patient with lobar pneumonia associated with recurrence of leukaemia and resolved partially after one week and completely after four weeks.

Discussion

Over the last ten years increasing numbers of β-lactamase-producing bacterial pathogens (*H. influenzae, H. parainfluenzae, Branhamella catarrhalis*, staphylococci and Enterobacteriaceae) have been isolated from paediatric patients with various infections. Management of these conditions requires an antimicrobial agent that is resistant to cleavage by the β-lactamases and effective against both Gram-positive and Gram-negative bacteria. In addition to satisfying these basic in-vitro requirements, amoxycillin/clavulanate has other major advantages: the amoxycillin component has a long record of extensive clinical use with favourable results; the two drug constituents amoxycillin and clavulanic acid are pharmacokinetically compatible after iv and oral administration and adequate dosage schedules have been established; finally, both intravenous and oral therapy are possible with the same antibacterial agents (Schaad *et al.*, 1983; Schaad *et al.*, 1986).

In the present non-comparative study the efficacy and safety of intravenous and sequential intravenous-oral amoxycillin/clavulanate therapy for various childhood bacterial infections were evaluated in 71 patients. An underlying disease was present in 23%, unsuccessful antimicrobial therapy prior to amoxycillin/clavulanate had been administered in 27%, and the degree of illness at hospital admission was rated as severe in 56% and as moderate in 44%. The response to amoxycillin/clavulanate therapy was prompt in each patient and all were cured of their infections.

These excellent clinical and bacteriological results with amoxycillin/clavulanate in paediatric hospital practice compare favourably with previous reports with oral amoxycillin/clavulanate in general paediatric practice (Jeffries *et al.*, 1983), in childhood pneumonia (Gooch *et al.*, 1985), otitis media (Odio *et al.*, 1985) and skin and soft tissue infections (Jaffe *et sl.*, 1985). Also the limited data reported with intravenous amoxycillin/clavulanate in paediatric infections (Price & Horobin, 1985; Ploechl *et al.*, 1985) are in agreement with the findings in this study.

Clinical adverse effects attributed to amoxycillin/clavulanate were infrequent and usually mild: in only one case of urticarial rash was cessation of therapy necessary. The observed 6% frequency of gastrointestinal complaints (diarrhoea with and without

vomiting) with amoxycillin/clavulanate lies at the lower end of frequencies reported elsewhere: 2·5% (Price & Horobin, 1985), 8% (Jeffries *et al.*, 1983), 9% (Jaffe *et al.*, 1985), 15% (Gooch *et al.*, 1985), and 24% (Odio *et al.*, 1985). A rash is observed in 1 to 5% of children who receive aminopenicillins (McCracken, 1983); in this study four patients (6%) developed rashes most probably related to drug therapy. There was one case each of transient neutropenia and temporary increase of hepatic enzymes. Whether the neutropenia and disturbed hepatic function were due solely to amoxycillin/clavulanate or to a multiplicity of factors is uncertain.

It is concluded that intravenous and sequential intravenous-oral amoxycillin/clavulanate are safe and highly effective treatments for paediatric patients admitted to hospital with respiratory tract, urinary tract, skin and soft tissue infections.

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