EVALUATION OF THE EFFICACY AND SAFETY OF PARENTERAL SULBACTAM/AMPICILLIN FOLLOWED BY ORAL SULTAMICILLIN FOR PAEDIATRIC INFECTIONS

E. MBONDA, F. DRESSE, F. GEUBELLE

Paediatric Department, University Hospital, University of Liège (Belgium)

Summary

The efficacy and safety of parenteral sulbactam/ampicillin followed by oral sultamicillin* has been evaluated in 41 children aged between 0.5 and 15 years presenting with various infections. Overall clinical and bacteriological success was achieved in 92% of evaluable cases; 97% of 22 pathogens isolated in these patients were eradicated. Adverse reactions were pain at the intramuscular injection site (7%) which was minimized by concurrent injection of lidocaine. Gastro-intestinal disturbances with soft stools were common during oral sultamicillin therapy. Laboratory tests remained normal. Parenteral sulbactam/ampicillin followed by oral sultamicillin is useful therapy for the treatment of serious non-life-threatening paediatric infections.

KEY WORDS: Paediatric infections, betalactamase, parenteral sulbactam/ampicillin, oral sultamicillin.

INTRODUCTION

Sulbactam is a semi-synthetic beta-lactamase inhibitor which, when combined with beta-lactam antibacterials extends their activity against bacteria normally resistant to the antibiotic because of the production of beta-lactamases. In combination with ampicillin, sulbactam extends the antibacterial activity of ampicillin to include beta-lactamase producing strains which would otherwise be resistant and increases the susceptibility of many sensitive strains of Gram-positive and Gram-negative aerobic bacteria and anaerobic bacteria. Sulbactam alone possesses only weak antibacterial activity against most bacterial species [1]. Sulbactam is poorly absorbed orally; after parenteral administration of sulbactam/ampicillin, sultamicillin, which is well absorbed after oral administration, may be given.

* UNASYN®

PATIENTS AND METHODS

1) *Patient selection:*

Forty-one children aged between 0.5 and 15 years and with clinical or microbiological evidence of infection were enrolled in the trial. Infections were classified in one of the following areas: respiratory tract (n=27), urinary tract (n=2), skin and soft tissue (n=7), gastro-intestinal (n=5).

We excluded from the study all patients with known hypersensitivity to penicillin, patients suspected of meningitis or with severe hepatic or kidney impairment, those with poorly controlled diabetes, those who demonstrated even partially a favourable response to another antimicrobial agent or who were taking concomitant antibiotics. Patients infected with organisms usually resistant to sulbactam/ampicillin *(Pseudomonas aeruginosa)* were also excluded.

2) *Confirmation of diagnosis*

Diagnosis in patients with respiratory tract infection was confirmed by bacterial isolation and chest X-ray findings. Blood cultures and serological studies to detect bacterial antigens and antibody to virus or *Mycoplasma pneumoniae* were carried out in four patients with pneumonia. The diagnosis of bacterial urinary tract infection was confirmed by positive culture of an uncontaminated urine specimen collected before initiation of sulbactam/ampicillin therapy; a count of >10 cfu/ml of urine was the criterion for infection. The bacterial aetiology of skin and soft tissue infection was established by isolation of bacteria from pus obtained by needle aspiration from the site of infection. Infectious diarrhoea was established by culture of an uncontaminated stool specimen and the isolation of relevant bacteria.

3) *Administration*

All 41 patients were treated with 50 mg sulbactam/kg and 100 mg ampicillin/kg per day; 24 received this combination by the intramuscular and 17 by the intravenous route. The mean duration of parenteral treatment was 2.8 days and the range of 2-4 days. The dose of oral sultamicillin was 50 mg/kg per day given in two divided doses; the mean duration of sultamicillin treatment was 13.2 days (range 9-18 days).

4) *Efficacy and safety*

Signs and symptoms of infection were recorded at baseline, on day 3, weekly and on the last day of treatment. Therapeutic efficacy was evaluated on the basis of the clinical resolution of signs and symptoms. In patients with urinary tract infection, bacteriological assessment was considered satisfac-

tory if a urine sample obtained on the third day of treatment, at the end of and 4 to 15 days after completion of treatment yielded no pathogen. For patients with respiratory tract infection, a satisfactory response was defined by the resolution of clinical signs and symptoms and of chest X-ray features. Patients with soft tissue and skin infections presented with disappearance of local and general signs of infection. There was a discrepancy in the results in patients with infectious gastroenteritis in whom we observed disappearance of general signs and symptoms of infection and persistance of diarrhoea for 3 to 5 days.

All patients were monitored for adverse effects both clinically and by laboratory investigations including determination of complete blood count, prothrombin time, alkaline phosphatase and liver enzymes, blood glucose, blood urea nitrogen and serum creatinine. All laboratory tests were performed before, during and after treatment.

RESULTS

Of 41 patients included, three failed to complete the planned study period (two of them were withdrawn because of side effects) and three patients were also excluded because of protocol violations. Thirty-five patients were therefore included in an analysis of efficacy. All but one were considered clinical cures (97%). One patient, although not cured, showed improvement at the end of the study. No clinical failure was reported. A rapid decrease in the severity of signs and symptoms was evident as the study progressed. All clinical symptoms disappeared after the baseline visit.

Side effects reported in 14 patients were tolerated with continued treatment. Gastro-intestinal side effects, all during oral therapy, included 8 patients (19.5%) with «soft stools» and one with vomiting. Three patients (7%) had pain at the injection site; one presented with thrombophlebitis and another with rash, both improved after treatment discontinuation.

Pathogens were isolated in 22 out of 41 patients. In some patients more than one pathogen grew in the culture and a total of 26 pathogens were isolated. Although all pathogens isolated had to be tested for susceptibility to sulbactam/ampicillin, in practice this was not done because of technical problems during the study. Table I shows the bacterial aetiology.

TABLE I:

Pathogens	Number of patients treated
Respiratory tract infections	
Streptococcus (beta-hemolytic)	8
Micrococcus	1
Klebsiella	1
Mycoplasma pneumoniae	1
Pseudomonas	1
Urinary tract infections	
Escherichia coli	2
Skin and soft tissue infections	
Staphylococcus aureus	4
Streptococcus mutans (hemoculture)	1
Proteus mirabilis	1
Gastro-intestinal infections	
Entamoeba coli	1
Campylobacter jejuni	3
Salmonella	1
Total	25
Number of patients	22

DISCUSSION

Beta-hemolytic streptococci (n=8) and *S. aureus* (n=4) were the most frequently encountered pathogens in the respiratory tract and skin and soft tissue infections respectively. Although *Pseudomonas* species was isolated in one instance, it was associated with *Klebsiella* infection of the respiratory tract; this *Pseudomonas* organism cultured from sputum was eradicated at the end of therapy. Overall evaluation of bacteriological efficacy was considered successful in 18 patients (90%). The two bacteriological failures *(Campylobacter)* did not correspond to the clinical course where signs and symptoms of infection had disappeared at the end of therapy.

Sodium sulbactam combined with ampicillin has been shown to be bactericidal for a wide spectrum of bacteria, in particular *Staphylococcus aureus, Hemophilus influenzae, Klebsiella, Proteus* species and *E. coli* [2]. It has also been effective in the treatment of infections in adults and older children [3].

Treatment of clinical infections in the children included in this study was started before the results of culture were available. The combination of sulbactam with ampicillin has a wide spectrum of antibacterial activity and is useful in the therapy of bacterial infections. This study included children

with infection due to Gram-positive and Gram-negative bacteria. Patients whose infections were not confirmed by positive culture findings had good clinical responses to therapy.

CONCLUSION

Parenteral sulbactam/ampicillin followed by oral sultamicillin is clinically and bacteriologically effective in paediatric infections of the urinary tract, skin and soft tissue, respiratory tract, ear, nose and throat as well as gastro-intestinal infections. It appears to be comparable in efficacy to various alternative regimens and to be well tolerated.

REFERENCES

[1] CAMPOLI-RICHARD, C.S., BROGDEN, N.R. — Subactam/ampicillin, a review of its antibacterial activity, pharmacokinetic properties, and therapeutic use. *Drugs*, **33**(6): 577-609 (1987).

[2] ENGLISH, A.R., RETSEMA, J.A., GIRARD, A.E., LYNCH, J.E., BARTH, W.E. — A beta-lactamase inhibitor extends the antibacterial spectrum of beta-lactams: Initial bacteriological characterization. *Antimicrob. Ag. Chemother.*, **14**: 414-419 (1978).

[3] LEES, L., MILSON, J.A., KNIRSCH, A.K., GREENHALGH, K. — Sulbactam plus ampicillin: Interim review of efficacy and safety for therapeutic and prophylactic use. *Rev. of Inf. Dis.*, **8**, suppl. 5: 644-650 (1986).

[4] SYRIOPOULOU, V., BITSI, M., THEODORIDIS, C., SAROGLOU, I., KRIKOS, X., TZANETOU, K. — Clinical Efficacy of Sulbactam/Ampicillin in Pediatric Infections caused by Ampicillin-resistant or Penicillin-resistant Organisms. *Rev. of Inf. Dis.*, **8**, suppl. 5: 630-633 (1986).

[5] WALD, E., REILLY, J.S., BLUESTONE, C.D., CHIPONIS, D. — Sulbactam/Ampicillin in the treatment of Acute Epiglottis in Children. *Rev. of Inf. Dis.*, **8**, suppl. 5: 617-619 (1986).

Address for correspondence: Pr F. GEUBELLE, Service de Pédiatrie, Hôpital Universitaire, Domaine Universitaire du Sart Tilman, B35; 4000 Liège 1 (Belgium).

RÉSUMÉ

L'efficacité et la sécurité du sulbactam/ampicilline par voie parentérale, suivi de l'administration orale de sultamicilline, ont été étudiées chez 41 enfants âgés de 0,5 à 15 ans, présentant diverses maladies infectieuses. Un succès global clinique et bactériologique a été observé dans 92% des cas évaluables; 97% des 22 micro-organismes pathogènes isolés chez ces patients ont été éradiqués. Les effets secondaires comportaient de la douleur à l'endroit de l'injection intramusculaire (7%), que la dilution avec de la lidocaïne a permis