A Multicentre, Randomized Comparative Study of 500 mg versus 1,000 mg Ceftazidime t.d.s. for Treatment of Gram-Negative Infections

Summary: A multicentre, randomized study was performed to compare the clinical and bacteriological efficacy of 500 mg ceftazidime i.v. t.d.s. with 1,000 mg ceftazidime i.v. t.d.s. for treatment of hospitalised, non-compromised patients with gram-negative infections. The study was conducted in ten hospitals in The Netherlands. Hospitalised patients with a suspected gram-negative lower respiratory tract infection, complicated urinary tract infection or septicaemia were included. Excluded were patients with neutropenia, limited life expectancy, or severe renal insufficiency as well as those on antibiotics in the 48 h prior to entry. Ceftazidime was administered via an intravenous infusion every 8 h. For patients with moderately impaired renal function the frequency was reduced to 12 h. Treatment was continued for as long as clinically indicated. Clinical response (cure, improvement or failure) and bacteriological response (elimination, persistence or non-evaluable) were assessed primarily by the investigator. Final assessments were made by a panel of experts without prior knowledge. In total 127 patients were randomized, 64 patients to the 500 mg group and 63 to the 1,000 mg group; 47 patients were excluded from evaluation, usually due to an incorrect diagnosis prior to randomization. Ultimately 37 patients of the 500 mg group and 43 patients of the 1,000 mg group were available for evaluation. Between these two groups of evaluable patients there were no significant differences in baseline characteristics, types of infection, isolated bacterial pathogens or treatment characteristics. There was no significant difference in either clinical or bacteriological efficacy. Therefore 500 mg ceftazidime i.v. t.d.s. can be considered optimal therapy for gram-negative lower respiratory tract infections, complicated urinary tract infections and septicaemia in hospitalised, non-compromised patients.

Introduction

Ceftazidime is a third generation cephalosporin with a broad antibacterial spectrum. In particular the intrinsic activity against gram-negative aerobic bacteria, including Pseudomonas aeruginosa, is high. It has been used successfully against a large variety of infections with gram-negative and gram-positive aerobic pathogens [1]. The initial intravenous dosage schedules for treatment of these infections were as high as 2,000 mg t.d.s. However, the potency of ceftazidime is much greater than that of older cephalosporins. Since concentrations of betalactam antibiotics that are much higher than maximally effective concentrations do not contribute more to the therapeutic efficacy it can be argued that the daily dose of ceftazidime should be much lower than a daily dose of 3 to 4 g, which is considered optimal for cefamandole or cefuroxime, even in severe infections [1]. This supposition is supported by experimental data obtained in vitro and from animal models [2, 3]. On the basis of this a priori information a standard dose of ceftazidime of 1 to 2 g t.d.s. must be considered far too high on all accounts, but only a few studies have been carried out to investigate the effect in man of lower dosages (e.g. ≤500 mg t.d.s.), and then only against (un)complicated urinary tract infections [4–9], lower respiratory tract infections [6, 10, 11] and skin and skin structure infections [12, 13]. The most extensive dose-response study in terms of patient numbers was performed by Parish et al. [13]. In this prospective, randomized study the efficacy of 500 mg and 1,000 mg ceftazidime t.d.s. was compared in 156 patients with cutaneous infections. Clinical cure or improvement was achieved in 98.7% of patients in each treatment group. These results at least do not refute the recommendation of a lower dose of ceftazidime. However, no studies on lower dosages for the treatment of patients with gram-negative septicaemia had been published. Therefore a pilot trial consisting of eight patients was conducted by one of us (H. M.); a dose of 500 mg t.d.s. was found to be effective against non-life-threatening infections in non-compromised patients. In a second trial consisting of 16 patients 500 mg t.d.s. was effective against various gram-negative infections. In these two single-centre trials a favourable clinical response was recorded for 87.5% and 94% of the patients, respectively [14].

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Since these preliminary results confirmed our proposition that 500 mg t.d.s. should be considered a maximally effective dose of ceftazidime, the present study was undertaken to come to the conclusion that ceftazidime 500 mg t.d.s. is indeed the optimal dose in non-compromised patients with gram-negative infections, if our null hypothesis, that the lower dose is not less effective, would not be rejected. The study was performed as a prospective, randomized, multicentre trial, the results of which have already been partly presented [14].

Patients and Methods

Ceftazidime (pentahydrate blended with anhydrous sodium carbonate, Glaxo, The Netherlands) was supplied in rubber capped vials containing 500 mg or 1,000 mg ceftazidime. Written or verbal approval of the study was obtained from the Ethics Committee or, if there was none, the Antibiotics Committee of the participating centres. Patients consented, either in writing or verbally, to participate in the study after a full explanation of the treatment options and the study objectives had been given. The study was designed as a prospective, randomized, parallel, comparative multi-centre study, treatment allocation being determined per centre by opening sealed envelopes in numerical order. The study was conducted in ten hospitals in The Netherlands from January 1989 until May 1990. Patient entry criteria, diagnosis and efficacy were assessed by two of us (H. M., and M. W. K.), who were unaware of the treatment used.

Patients: Included were hospitalised patients, aged 18 years and over, with a suspected gram-negative infection of the lower respiratory tract, a complicated urinary tract infection, gram-negative septicaemia, intraabdominal infection or a serious soft tissue infection with gram-negative microorganisms. A lower respiratory tract infection was defined by general signs and symptoms of infection and new or increased purulent sputum production, i.e. with bacteria and leukocytes on the Gram stain of washed sputum. A complicated urinary tract infection was defined by general signs and symptoms of infection, a urine culture of $\geq 10^5$ colonies/ml urine and leukocytes in the urine sediment. Septicaemia was defined by general symptoms of infection and a recognized pathogen isolated from blood cultures. Intraabdominal infection (including infection of the gall bladder, bile ducts, liver, spleen and pancreas) was defined by general signs and symptoms of infection. A serious soft tissue infection (e.g. necrotizing cellulitis) was defined by general signs and symptoms of infection as well as local inflammation of a soft tissue. General signs and symptoms of infection included fever, hypotension, tachycardia and indisposition.

Exclusion criteria were
- known allergic reactions to cephalosporins or previous anaphylactic reactions to penicillins,
- antibiotics administered in the 48 h prior to entry, unless there was proven inadequate response to these antibiotics,
- serious renal insufficiency (creatinine clearance $<30$ ml/min or serum creatinine $>200 \mu$mol/l),
- neutropenia (granulocytes $<500 \times 10^6$/l),
- limited life expectancy (death within 48 h) and
- pregnancy or lactation.

Patients meeting the entry criteria and giving informed consent to participate in the study were randomly assigned to one of the two treatment groups by sequential opening of the sealed envelopes. These envelopes were randomized in blocks of ten.

Treatment schedule: Ceftazidime at a dose of 500 mg or 1,000 mg was administered every 8 h via a slow intravenous infusion over a period of up to 30 min. For patients with moderate renal insufficiency (creatinine clearance 50 to 31 ml/min or serum creatinine 150 to 200 $\mu$mol/l) the frequency was reduced to every 12 h. If an anaerobic infection was also suspected, an i.v. dose of 500 mg metronidazole t.d.s. was added to the ceftazidime regimen. Intravenous therapy was continued for as long as clinically indicated.

Treatment was started after initial specimens were taken for microbiological culture and sensitivity testing but before the results were known. Other, non-antibacterial treatment was given as needed.

A clinical examination was performed not more than 48 h prior to the start of treatment. Brief demographic details were recorded together with data on the present infection, any underlying disease, and preceding medication, including antibiotics. Blood and urine samples for urinanalysis and haematological and biochemical analysis were collected. Appropriate specimens were taken for microbiological testing, including blood, urine specimens if a urinary tract infection was suspected and sputum specimens if a lower respiratory tract infection was suspected. During treatment clinical signs and symptoms, e.g. temperature and pulse, were assessed daily. All laboratory studies were repeated if clinically indicated. After discontinuation of ceftazidime a clinical examination was performed within 24 h to assess the patient’s clinical response to treatment. Again laboratory studies were repeated as indicated. In addition, bacteriological specimens (except for blood from patients who had responded) were collected 24–72 h after completing treatment.

The patient’s clinical response to treatment was recorded as cure, improvement or failure using the following criteria:

**Cure:** absence of clinical signs and symptoms of infection at the time of assessment;

**Improvement:** clinical signs and symptoms subsided significantly but with incomplete resolution of infection (e.g. related to underlying disease state);

**Failure:** no clinical response to therapy.

On the basis of microbiological culture and antibiotic susceptibility results the bacteriological response to treatment was recorded as elimination, persistence and non-evaluable, using the following criteria:

**Elimination:** absence of or clinically insignificant numbers of the original pathogen(s);

**Persistence:** continued isolation of the original pathogen(s) in clinically significant numbers;

**Non-evaluable:** neither clearance nor persistence (e.g. no sample could be taken).

Baseline characteristics and treatment characteristics of the different groups are presented as median values and ranges. Comparability of the groups with regard to infection types and isolated pathogens was assessed by means of the exact homogeneity test; differences in clinical and bacteriological response between groups were tested by means of an exact trend test and Fisher’s exact test, respectively. These exact tests are exact alternatives to...