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Double-Blind Randomized Study of 1 g versus 2 g Intravenous Ceftriaxone Daily in the Therapy of Community-Acquired Infections

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In a multicentre, double-blind, randomized study involving four general hospitals in Israel, the efficacy and safety of ceftriaxone 1 g/day i.v. was compared to that of 2 g/day i.v. in the treatment of moderate to severe community-acquired infections requiring hospitalization. Two hundred and twenty-two patients were enrolled; 112 received intravenous ceftriaxone 1 g/day, and 110 received 2 g/day. The two groups were matched demographically, and their mean APACHE II score (10 points) and mean duration of successful therapy (7 days) were identical. The sites of infection in the 1 g and 2 g groups respectively were lower respiratory tract in 57 versus 51 patients, urinary tract in 31 versus 40 patients, and soft tissue in 24 versus 19 patients. There were no significant differences in clinical outcome between the 1 g and 2 g groups, the outcome being cure in 91 % versus 86 % of patients, improvement in 3 % versus 3 % of patients, failure in 3 % versus 8 % of patients, and relapse in 3 % versus 3 % of patients. The findings of this study indicate that ceftriaxone 1 g/day is as effective as 2 g/day in the treatment of moderate to severe community-acquired infections. The low-dose form is a more economical means of treating these infections.

Ceftriaxone is a widely used cephalosporin which has a broad spectrum of bactericidal activity in vivo and in vitro against aerobic gram-positive and gram-negative bacteria (1, 2). It is distinguished from other third-generation cephalosporins by its comparatively long half-life of 8–10 h (3). Its activity in vitro has been shown against many organisms that are resistant to beta-lactams and aminoglycosides, while its effectiveness has been demonstrated clinically in a variety of bacterial infections both in hospitalized and in ambulatory patients. Ceftriaxone is useful for the treatment of serious community-acquired infections such as those due to *Streptococcus pneumoniae* or *Haemophilus influenzae*. From previous studies, the recommended dose of ceftriaxone is 1–2 g/day (3–9); however, the optimal dose in adult patients remains undefined. Recently, noncomparative studies have suggested that ceftriaxone, 1 g/day, is sufficiently efficacious against bacterial pathogens even in serious community-acquired infections (10–14). This randomized double-blind study compared the efficacy and safety of ceftriaxone 1 g/day i.v. versus the 2 g/day dose in combating community-acquired infections requiring parenteral therapy.

Patients and Methods

Study Design. This was a comparative, prospective, randomized and double-blind study performed at four centres in Israel. Randomization was balanced in blocks of ten patients to ensure equal distribution among the centres. Informed written consent was required before entry into the trial. Disease severity was assessed using the APACHE II score system which allows stratification of acutely ill patients and comparison of the efficacy of different forms of therapy (15).

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Inclusion Criteria. Only adult patients over 18 years of age who had a moderate to severe community-acquired infection requiring hospitalization and parenteral antibiotic therapy were enrolled in the study. Patient demographics are shown in Table 1. Common community-acquired infections among patients treated in this study included lower respiratory tract infection, urinary tract infection, and skin and soft tissue infection. Each patient was classified into one of these three groups depending on his/her infection site. Lower respiratory tract infection comprised pneumonia (new focal signs on physical examination of the chest, temperature > 38°C and radiographic evidence of a recent infiltrate) or acute bronchitis (presence of cough, purulent sputum and temperature > 38°C). Urinary tract infection was defined as bacterial growth > 10^5 cfu/ml in a urine specimen with compatible symptoms and pyuria. Soft tissue infection was defined as cellulitis/erysipelas (an area of acute cutaneous inflammation with or without a purulent exudate). Septicemia was defined as the presence of systemic symptoms and signs of sepsis, such as fever (temperature > 38°C), chills, tachycardia and a positive blood culture.

Exclusion Criteria. Exclusion criteria were hypersensitivity to cephalosporins, current pregnancy or breast-feeding, resistance of the pathogen to ceftriaxone, use of effective pre-entry antimicrobial therapy (assessed by improvement in any main clinical manifestation of infection), presence of meningitis, osteomyelitis, endocarditis, neutropenia, septic shock or assisted ventilation, predicted mortality within 48 h or an APACHE II score greater than 25.

Treatment. Ceftriaxone was given once daily intravenously in a dose of either 1 g or 2 g. Treatment was continued for a maximum of ten days unless adverse reaction necessitated discontinuation. Concomitant antibacterial treatment with metronidazole was allowed if a mixed aerobic and anaerobic infection was suspected. Drug safety was assessed throughout the study and efficacy determined during the follow-up period after treatment had finished. Compliance was monitored by checking drug records after completion of treatment. Oral antimicrobial therapy was prescribed during the follow-up period only if necessary.

Table 1: Baseline demographic data in the two groups of patients receiving ceftriaxone. Data are given as the mean (± SD), with the range in brackets[a].

	1 g/day group (n = 112)	2 g/day group (n = 110)
Age (years)	66 ± 18 (18–95)	62 ± 19 (20–92)
Male to female ratio	0.9	1
Weight (kg)	68 ± 14 (40–112)	69 ± 14 (47–150)
APACHE II score	10 ± 5.9[b] (0–24)	10 ± 5.9[b] (0–23)
Prior antibiotic therapy (number)[c]	29	29

[a] The p value was not significant for each comparison.
[b] Median value.
[c] Number of patients who received prior antibiotic therapy for this infectious episode.

Evaluation of Efficacy. Assessment of ceftriaxone efficacy was performed by monitoring the following variables: signs and symptoms relevant to the site of infection, temperature, total and differential leukocyte count, results of urinalysis, cultures of samples from the infection site and chest radiograph. Clinical efficacy was classified as cure (resolution of all clinical features of infection), improvement (resolution of only some clinical features), failure (no resolution of clinical features) and relapse. Microbiological efficacy was classified as eradication, persistence, relapse, colonization or superinfection (16). Cases were considered not assessable when evaluation of the clinical or bacteriological response was not possible because of early death of the patient (within the first 48 hours of treatment); all of these patients were excluded from the study. Further, no evaluation was made in cases of early withdrawal from the study, incomplete follow-up, resistance of the initial pathogen to ceftriaxone, or concomitant administration of other effective antimicrobial agents.

Evaluation of Safety. Patients were examined each day for the presence of clinical signs and symptoms suggesting adverse effects of the drug. Laboratory tests (complete blood count, blood urea nitrogen, serum creatinine, electrolyte levels, AST, ALT, bilirubin, alkaline phosphatase and urinalysis) were performed on day 4 after the start of treatment and at the end of the therapy. Clinical adverse events were classified as either minor or serious. Serious adverse events were those described as fatal, life-threatening, disabling or incapacitating, or those requiring prolonged hospitalization or leading to discontinuation of the drug.

Microbiological Tests. Serum ceftriaxone levels on day 4 of therapy were assayed by an agar disk diffusion method (16) using a sensitive *Bacillus subtilis* strain. Blood was obtained 30 min before (trough) and after (peak) intravenous administration of ceftriaxone. Cultures of samples from the site of infection were repeated on day 4 and at the end of therapy. In patients with urinary tract infection, additional cultures were performed one and three weeks after completion of therapy. In vitro antibiotic susceptibility tests were performed by a disk diffusion method (16). In patients with lower respiratory tract infection, serological tests for IgM and IgG antibodies against *Legionella* spp., *Mycoplasma pneumoniae* and *Chlamydia* spp. were performed using enzyme immunoassays.

Statistical Analysis. Student's t test and Fisher's exact test were used for comparison of the data. A sample size of 110 patients in each group was chosen to afford 90 % power to detect an absolute difference in cure rates of 15 %, assuming that the cure rate of ceftriaxone 2 g/day was 90 % and $x = 0.05$.

Results

During a 1-year period, 267 patients were recruited for the study, 222 of whom were eligible

for final evaluation. Of these patients, 112 received ceftriaxone 1 g/day and 110 ceftriaxone 2 g/day. In addition to ceftriaxone, 6 patients received metronidazole (2 in the 1 g ceftriaxone group and 4 in the 2 g ceftriaxone group).

Forty-five patients were excluded from the final evaluation due to early death (n = 6), allergic reactions (n = 2), refusal of therapy (n = 4) or violation of the protocol (n = 33). The protocol violations resulted from a negative urine culture in patients with urinary tract infection (n = 16), lack of fever in patients with soft tissue infection (n = 6), incomplete follow-up (n = 4), administration of additional antimicrobial agents other than metronidazole (n = 2), presence of noninfectious pulmonary infiltrates (n = 2) and presence of additional infections requiring exclusions from the study (typhoid fever, shigellosis and rickettsiosis). Of the excluded patients, 21 received ceftriaxone 1 g/day and 24 ceftriaxone 2 g/day. The sites of infection in the excluded patients were as follows: in the 1 g group, lungs (n = 4), urinary tract (n = 11) and soft tissue (n = 3); and in the 2 g group, lungs (n = 8), urinary tract (n = 9) and soft tissue (n = 3).

The sites of infection in the evaluable patients are shown in Table 2. The most commonly seen infections were those of the lower respiratory tract which occurred in a total of 108 patients. The specific lower respiratory tract infections seen in the 1 g ceftriaxone group were pneumonia (51 patients, of whom 3 also had pleural empyema) and bronchitis (6 patients). In the 2 g ceftriaxone group, the lower respiratory tract infections were pneumonia (n = 40), bronchitis (n = 8) and lung abscess (n = 3). The organisms responsible for lower respiratory tract infection were identified in 15 of 108 patients, the most common organism being *Streptococcus pneumoniae* (5 patients in the 1 g ceftriaxone group and 3 patients in the 2 g ceftriaxone group). Gram-negative aerobic microorganisms were isolated in seven patients with lower respiratory tract infection.

Table 2: Site of infection in patients receiving 1 g or 2 g ceftriaxone daily.*

	1 g/day group (n = 112)	2 g/day group (n = 110)
LRTI	57	51
UTI	31	40
STI	24	19
Septicemia and UTI	6	8
Septicemia and LRTI	3	4
Septicemia and STI	1	0

LRTI: lower respiratory tract infection, UTI: urinary tract infection, STI: soft tissue infection.
* The p value was not significant.

Serological tests for *Legionella* spp., *Mycoplasma pneumoniae* and *Chlamydia* spp. were performed in serum samples from 65 patients with pneumonia. Significant IgM titres were found in 10 of these patients (1 for *Legionella* spp., 2 for *Mycoplasma pneumoniae* and 7 for *Chlamydia* spp.). Clinical cure was reported in all of these patients after therapy with ceftriaxone 2 g/day (n = 4) or 1 g/day (n = 6). The possibility of co-infection with a susceptible bacterial pathogen, however, should not be overlooked.

A total of 71 patients with urinary tract infection were treated in this study. In the 1 g ceftriaxone group, 16 of 31 patients had pyelonephritis. In the 2 g ceftriaxone group, 25 of 40 patients had pyelonephritis. Bacteria isolated from patients with urinary tract infection were as follows: in the 1 g ceftriaxone group, *Escherichia coli* (n = 19), *Klebsiella* spp. (n = 3), *Proteus* spp. (n = 3) and other species (n = 6); in the 2 g ceftriaxone group, *Escherichia coli* (n = 33), *Klebsiella* spp. (n = 3), *Proteus* spp. (n = 1), *Enterobacter* spp. (n = 2) and other species (n = 12). Soft tissue infections were less commonly seen, affecting a total of 43 patients. All 24 patients in the 1 g ceftriaxone group had cellulitis/erysipelas (3 patients in the face and 21 patients in the extremities). In the 2 g ceftriaxone group, all 19 patients had cellulitis/erysipelas (2 patients in the face and 17 in the extremities).

The mean duration of ceftriaxone therapy was seven days in both the 1 g and 2 g groups. Mean serum ceftriaxone levels in the 1 g ceftriaxone group were 122.7 µg/ml (peak) and 27.4 µg/ml (trough). Mean serum levels in the 2 g ceftriaxone group were 189.9 µg/ml (peak) and 28.6 µg/ml (trough).

Table 3 shows the clinical and bacteriological outcome in the patients treated. Clinical cure was observed in 102 of 112 patients in the 1 g ceftriaxone group (91 %) and in 95 of 110 patients in the 2 g ceftriaxone group (86 %). Therapeutic failure, defined as an incomplete recovery after ten days of treatment, occurred in 12 patients, 8 with lower respiratory tract infection (2 in the 1 g group, 6 in the 2 g group), 2 with urinary tract infection (1 in each group), and 2 with soft tissue infections (both in the 2 g group). Clinical relapse occurred in 3 % of both the 1 g and 2 g groups.

Superinfection or colonization was observed in 13 patients, in 7 cases due to *Pseudomonas aeruginosa* (pneumonia [n = 2] or urinary tract infection

Table 3: Clinical and bacteriological outcome of ceftriaxone therapy.*

	No. of patients	
	1 g/day group (n = 112)	2 g/day group (n = 110)
Clinical outcome		
Cure	102 (91 %)	95 (86 %)
Improvement	4 (3 %)	3 (3 %)
Failure	3 (3 %)	9 (8 %)
Relapse	3 (3 %)	3 (3 %)
Bacteriological outcome		
Eradication	30	44
Persistence	0	1
Relapse	0	4
Superinfection or colonization	8	5

*The p value was not significant.

Table 4: Adverse events attributable to ceftriaxone therapy.

Adverse events	1 g/day group (n = 112)	2 g/day group (n = 110)
Abnormal liver function	5	5
Phlebitis	2	3
Other	3[a]	1[b]

[a] Leucopenia (n = 1), drug fever (n = 1), pruritus and eosinophilia (n = 1).
[b] Epileptic seizure.

[n = 5]). In addition, superinfection with *Enterobacter* spp., *Escherichia coli* and *Enterococcus fecalis* was seen in one patient with a urinary tract infection.

Adverse events attributable to ceftriaxone are shown in Table 4. Of the 19 adverse events, only one resulted in discontinuation of ceftriaxone therapy (cholestasis in a patient receiving ceftriaxone 1 g/day, with no evidence of biliary precipitation). None of the other patients who developed cholestasis had ultrasonographic evidence of biliary precipitation of ceftriaxone.

Discussion

Although once-daily ceftriaxone has previously been used in this population subset in outpatient and hospital settings (3, 6, 7, 13), the doses used have varied in the published studies, and some investigators reduced the dose during the course of treatment (17, 18). The clinical and bacteriological outcomes in the present study show that a parenteral dose of 1 g ceftriaxone once daily was as efficacious as a parenteral dose of 2 g once daily in the treatment of moderate and serious community-acquired infections. The cure rate was almost identical, being 91 % in the 1 g ceftriaxone group and 86 % in the 2 g group. In addition, there was no statistically significant difference in the numbers of patients in the two groups who improved on therapy or who relapsed.

The drug was tested in patients with a range of community-acquired infections, including lower respiratory tract, urinary tract and skin and soft tissue infection. The severity of infections was determined by the need for hospitalization and for parenteral treatment, and by an APACHE II score limited to 25 points. Applying these criteria, patients with common but not life-threatening moderate to severe community-acquired infections were selected.

A similar rate of clinical response and recovery was demonstrated for the three subgroups of infections. As initial cultures were frequently negative in many cases of respiratory and soft tissue infection, bacteriological follow-up was not possible. Such an inability to document a specific pathogen is relatively common, particularly in community-acquired infections of these sites (11, 17).

Among patients with urinary tract infection, the bacteriological eradication rate was particularly high. The incidence of superinfection (with *Pseudomonas aeruginosa)* was 6.5 % and 5 % in the 1 g and 2 g ceftriaxone groups, respectively. This is similar to the rate reported for other third-generation cephalosporins (19, 20).

As expected, mean peak serum ceftriaxone levels in the 2 g group were higher than those in the 1 g

group. Mean trough levels of ceftriaxone were comparable, however, in the two groups. A daily dose of 1 g yielded plasma levels that exceeded the expected MIC90 of pathogens commonly causing community-acquired infection (11, 13, 19).

No significant difference in the rate of adverse events between the two treatment groups was noted, and adverse reactions to ceftriaxone were generally mild. Except for one case of epileptic seizure which did not require drug discontinuation, side effects were similar in the two groups. The most commonly encountered adverse effect was elevated levels of liver enzymes, which was transient and not dose related. Infusion-site phlebitis was also seen in two and three patients in the 1 g and 2 g groups, respectively. Ceftriaxone therapy was discontinued in one case only, and no clinical evidence of persistent liver dysfunction was seen in this patient.

These data support the conclusion that 1 g/day of ceftriaxone is as efficacious as 2 g/day for the treatment of some moderate to serious community-acquired bacterial infections. A 1 g/day dose may be used for the empiric management of pneumonia, urinary tract infections, and skin and soft tissue infections even when sepsis is suspected. This lower parenteral dose offers economic benefits both in the hospital and in outpatient settings, halving the direct drug costs. In many hospitals, antibiotics, of which up to 50 % are cephalosporins, make up the largest share of the budget (11). Cephalosporins with high efficacy at lower doses are therefore likely to be of significant economic advantage.

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