A prospective open-label multicentre trial on the use of 1 g, once daily ceftriaxone in lower respiratory tract infections

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DE LOW, LA MANDELL. A prospective open-label multicentre trial on the use of 1 g, once daily ceftriaxone in lower respiratory tract infections. *Can J Infect Dis* 1994;5(Suppl C):3C-8C. This prospective, single open-label study was conducted in 14 Canadian centres to assess the efficacy of 1 g, once a day intravenous ceftriaxone treatment administered for a minimum of three days in patients with lower respiratory tract infection. There were 137 patients enrolled. Age varied between 19 and 95 years (mean 68 years). Most patients (91%) were diagnosed with community acquired pneumonia without bacteremia. Most of the cases (82%) were defined as moderate or severe. Patients received ceftriaxone treatment for an average of five days. Macrolides or metronidazole were administered concomitantly with ceftriaxone in 34 patients (25%). After a minimum of three days of ceftriaxone treatment, 59 patients (43%) were switched to oral antibiotics. Favourable treatment outcome was found in 92.9% and treatment failure (including relapse of infection) in 7.1% of patients. Evaluable patients accounted for 91% of patients enrolled in the study. Clinical cure and clinical improvement were achieved in 64.6 and 28.3% of the evaluable patients, respectively. Relapse of infection occurred in two patients (1.8%), and treatment failure was recorded in six cases (5.3%). Twelve patients (8.8%) died due to reasons unrelated to the study treatment. Three adverse event (hives, diarrhea and phlebitis at the injection site) were possibly related to the study drug. A cross-Canada in vitro susceptibility surveillance study of bacterial pathogens, frequently the cause of pneumonia, found ceftriaxone to have minimal inhibitory concentrations in 90% of isolates that would support such a dosing regimen, with the exception of *Enterobacter* species. These results support the use of 1 g, once daily ceftriaxone for the empirical treatment of pneumonia in those patients requiring hospitalization.

Key Words: Antimicrobial resistance, Ceftriaxone, Pneumonia

Essai prospectif, ouvert, multicentrique sur l'emploi de 1 g de ceftriaxone une fois par jour dans les infections respiratoires basses

RÉSUMÉ : Cette étude prospective, ouverte, simple a été menée auprès de quatorze centres canadiens en vue d'évaluer l'efficacité de 1 g de ceftriaxone administré une fois par jour par voie intraveineuse, pendant au moins trois jours chez des patients atteints d'infection respiratoire basse. Cent trente-sept patients y furent admis, âgés de 19 à 95 ans (moyenne 68 ans). La plupart des patients (91 %) avaient pour diagnostic une pneumonie extra-hospitalière, sans bactériémie. La plupart des cas (82 %) étaient jugés modérés à graves. Les patients ont reçu du ceftriaxone en moyenne durant cinq jours. Des macrolides et du métronidazole ont été administrés concomitamment avec le ceftriaxone chez 34 patients (25 %). Après un minimum de trois jours de traitement par ceftriaxone, 59 patients (43 %) sont passés à des antibiotiques

continued on next page

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oraux. On a observé des résultats favorables chez 92,9 % et un échec thérapeutique (y compris une rechute de l'infection) chez 7,1 % des patients. Les patients évaluable représentaient 91 % des patients admis à l'étude. La guérison clinique et l'amélioration clinique ont été atteintes chez 64,6 et 28,3 % des patients évaluable respectivement. La rechute de l'infection s'est produite chez deux patients (1,8 %), l'échec thérapeutique a été observé dans six cas (5,3 %). Douze patients (8,8 %) sont décédés de causes indépendantes du médicament à l'étude. Trois incidents défavorables (urticaire, diarrhée et phlébite au point d'injection) ont pu être associés au médicament à l'étude. Une étude épidémiologique pancanadienne de sensibilité *in vitro* portant sur les pathogènes bactériens fréquemment en cause dans la pneumonie a révélé que le ceftriaxone avait des concentrations inhibitrices minimales pour 90 % des isolats, ce qui appuierait l'emploi d'un tel schéma posologique, sauf en présence des *Enterobacter*. Ces résultats appuient l'emploi de ceftriaxone à raison de 1 g une fois par jour en traitement empirique de la pneumonie chez les patients qui doivent être hospitalisés.

INFECTIONS OF THE LOWER RESPIRATORY TRACT ARE AMONG the most common causes for antibiotic prescribing. Their diagnosis is often limited to clinical criteria, since microbiological information is frequently lacking. In the case of lower respiratory tract infections, the beta-lactamase stable parenteral cephalosporins (such as ceftriaxone) have become widely used to treat pneumonia in hospitalized patients, especially where Gram-negative enteric bacilli are of etiological importance.

The *in vivo* bactericidal activities of beta-lactams show minimal enhancement with increasing drug concentrations. The extent of bactericidal activity appears to depend more on the duration of exposure to drug levels above the minimal inhibitory concentration (MIC) than on the magnitude of antibiotic concentrations (1-4).

Ceftriaxone is a third-generation cephalosporin with a broad spectrum of activity against Gram-positive and Gram-negative pathogens causing lower respiratory tract infections (5,6). Its long half-life (7.65 h) results in serum concentrations at 24 h of greater than 10 µg/mL after a 1 g infusion (7). This level is well above the MIC₉₀ values for most respiratory pathogens, negating the need for using doses greater than 1 g daily. Despite this, doses of 2 g once daily or 1 g twice daily are often used for the treatment of pneumonia. To educate physicians about the utility of 1 g daily, we carried out a prospective open-label study in patients with lower respiratory tract infections. In addition, a cross-Canada *in vitro* surveillance study was carried out to determine if the activity of ceftriaxone against common respiratory pathogens continued to support such a treatment regimen.

PATIENTS AND METHODS

The study was designed as an open-label multicentre trial to evaluate the efficacy of 1 g, once daily ceftriaxone in patients with lower respiratory tract infections requiring hospitalization. The study was conducted over a seven-month period, between June 1993 and January 1994, in 14 Canadian centres: Queen Elizabeth Hospital, Charlottetown, Prince Edward Island; North York General Hospital, Toronto, Ontario; Hôtel-Dieu de St-Jérôme, St-Jérôme, Québec; Religious Hospitalers of St Joseph Health Centre of Cornwall Hôtel Dieu Hospital, Cornwall, Ontario; Mount St Joseph

Hospital, Vancouver, British Columbia; Valley Regional Hospital, Kentville, Nova Scotia; Royal Inland Hospital, Kamloops, British Columbia; Centre hospitalier St-Michel, Montréal, Québec; Western Memorial Regional Hospital, Corner Brook, Newfoundland; Regina General Hospital, Regina, Saskatchewan; Centre Honoré Mercier, Montréal, Québec; Kelowna General Hospital, Kelowna, British Columbia; Trenton Memorial Hospital, Trenton, Ontario; and Centre hospitalier Ste-Marie, Trois Rivières, Québec.

The study was approved by the institutional review board at each participating centre. Informed consent was obtained from each patient.

Patients who were treated with antimicrobial agents before entering the study were allowed to participate in the study only if the given treatment was found to be ineffective. Ceftriaxone had to be administered 1 g intravenously every 24 h for a minimum of three days, with a suggested course of three to five days. A macrolide antibiotic or metronidazole was allowed to be added to the treatment if so-called atypical pneumonia (caused by *Legionella* species, *Mycoplasma pneumoniae*, *Coxiella burnetii* and *Chlamydia pneumoniae*) or an anaerobic infection was suspected. No other antimicrobial agents were allowed during the first three days of the study. After three days of treatment with ceftriaxone, patients were allowed to be switched to oral antimicrobial agents. Hospital acquired pneumonia was defined as pneumonia developing after 48 h or longer of hospitalization for another problem.

Patients were allowed to be included in the study if they fulfilled the following criteria: were 18 years of age or older; had acute community or hospital acquired bacterial lower respiratory tract infections as indicated by a pretreatment roentgenogram with a pulmonary infiltrate thought to be due to infection; required hospitalization; and had not received an effective antibiotic within 72 h preceding admission to the study.

The study exclusion criteria were: allergy to penicillins or cephalosporins; a suspected *Pseudomonas aeruginosa* infection; febrile neutropenic patients; and patients requiring concomitant antibiotic therapy, other than a macrolide or metronidazole.

The patients were evaluated immediately before initiation of ceftriaxone therapy, after three to five and six

to nine days of treatment and two to four days after all antibiotic treatment was stopped. A follow-up evaluation was scheduled for patients who had residual signs or symptoms at the time of treatment termination. In addition to adverse event reporting, signs and symptoms (temperature, chills, chest pain, dyspnea, cough and breath sounds) were evaluated at the above observation times. Clinical responses were classified as: cure (clinical findings subsided within three to five days, with no evidence of infection for the balance of therapy); improvement (clinical findings subsided within three to five days, but with incomplete resolution of clinical evidence of infection); relapse (cured or improved within three to five days, followed by deterioration); failure (no apparent response to therapy); and unevaluable.

In order to determine in vitro activity of ceftriaxone against bacterial respiratory pathogens, consecutive nonduplicate clinical isolates of common aerobic Gram-negative rods and other respiratory bacterial pathogens were collected from 10 tertiary care centres across Canada until a predetermined number of isolates representing each pathogen was obtained. These were centres not participating in the clinical trial. Isolates were identified using standard methodologies (8) and frozen at -70°C in phosphate buffered glycerol. All isolates were subcultured twice before susceptibility testing. Isolates of *Moraxella catarrhalis* and *Streptococcus pneumoniae* were subcultured onto Columbia agar supplemented with 5% sheep blood. All isolates of *Haemophilus influenzae* were subcultured onto chocolate agar plates. Respiratory pathogens were incubated at 37°C in 5% carbon dioxide for 16 to 18 h. Isolates of *Enterobacteriaceae* species were subcultured onto MacConkey agar and incubated at 37°C in ambient air. Beta-lactamase production in *M. catarrhalis* and *H. influenzae* was detected using a nitrocefin-impregnated disc.

Broth microdilution was performed according to National Committee for Clinical Laboratory Standards guidelines (9). Microdilution panels were prepared by dispensing cation supplemented Mueller-Hinton broth containing twofold concentration increments of ceftriaxone in vitro into 96 well trays. Inoculum suspensions equal to a 0.5 McFarland standard were further diluted and added to the microdilution trays to achieve a final inoculum of 5×10^5 colony forming units/mL. Following inoculation, microdilution trays were incubated at 35°C in ambient air for 16 to 20 h. For isolates of *S. pneumoniae*, cation supplemented Mueller-Hinton broth was supplemented with 3% lysed horse blood and incubated at 35°C in ambient air for 20 to 24 h. For broth microdilution testing of *H. influenzae*, haemophilus test medium (HTM) was prepared from cation supplemented Mueller-Hinton broth supplemented with 15 g/mL NAD, 15 g/mL bovine hematin and 5 mg/mL yeast extract. Microdilution panels containing HTM were incu-

TABLE 1
Demographics and diagnosis of 137 enrolled patients

Features		Number (%)
Diagnosis:	Pneumonia without bacteremia	125 (91)
	Pneumonia with bacteremia	11 (8)
	Pleural empyema	1 (1)
Source of infection:	Community acquired	125 (91)
	Hospital acquired	12 (9)
Severity of infection:	Mild	25 (18)
	Moderate	85 (62)
	Severe	27 (20)

bated at 35°C in ambient air for 20 to 24 h. After incubation, the MIC was defined as the lowest concentration of ceftriaxone with no evidence of bacterial growth.

Escherichia coli ATCC 25922 and *P. aeruginosa* ATCC 27853 were used as control strains for broth microdilution testing using cation supplemented Mueller-Hinton broth alone. *H. influenzae* ATCC 49247 and *H. influenzae* ATCC 49766 were used as control organisms for panels containing HTM. *S. pneumoniae* ATCC 6306 was used as a control organism for panels supplemented with 3% lysed horse blood.

McNemar tests were used to evaluate the changes in symptoms from pretreatment to last evaluation. Kruskal-Wallis test was performed to detect differences in treatment outcomes as a function of diagnosis, source of infection and severity of infection.

RESULTS

There were 137 patients enrolled, of which 113 met the predetermined criteria for the efficacy-evaluable population. Patient characteristics are shown in Table 1. Reasons for excluding patients were: death (four); consent withdrawn (four); transfer to another hospital (two); pretreatment resistant pathogen (one); no infiltrate seen on roentgenogram (six); and treatment with a nonallowable concomitant antibiotic (nine). Twelve patients were unevaluable.

In the intent-to-treat population, the mean age was 68 years (range 19 to 95; $\text{SD} \pm 18$ years) and 48% were male. Community acquired pneumonia constituted 91% of cases. Twenty-eight patients (20%) received a total of 32 antibiotics before treatment: amoxicillin/ampicillin (eight); erythromycin/clarithromycin (five); cefaclor/cefuroxime (six); ciprofloxacin (three); trimethoprim-sulphamethoxazole (two) and other (eight). At the pretreatment evaluation, 47% of the patients had a temperature of 38.5°C or greater. Abnormal signs and symptoms were: chills (44%); cough (94%); productive cough (67%); chest pain (41%); dyspnea (81%); and abnormal breath sounds (88%) and rales (84%) on auscultatory examination. An abnormal white blood cell count was found in 82 patients (60%) (Table 2). Sputum samples were evaluable in 59 patients, with 29

TABLE 2

Frequency of abnormalities in signs, symptoms and investigations at various study phases in the intent-to-treat population

Features		Pretherapy Number (%)	Day 3 - 5 Number (%)	Day 6 - 9 Number (%)	Final Number (%)
Signs:	Temperature >38.5°C	64 (47)	12 (9)	4 (4)	0 (0)
	Abnormal breath sounds	120 (88)	78 (60)	37 (37)	24 (24)
Symptoms:	Chills	60 (44)	7 (5)	1 (1)	0 (0)
	Cough	129 (94)	91 (70)	35 (35)	18 (18)
	Productive cough	87 (67)*	38 (41)	6 (17)	2 (11)
	Chest pain	56 (41)	17 (13)	5 (5)	6 (6)
	Dyspnea	111 (81)	53 (41)	22 (22)	17 (17)
	Abnormal	84 (62)	39 (38)	13 (22)	2 (30)
White blood cell count:	Normal	52 (38)	63 (62)	46 (78)	5 (70)
	Infiltrates present	131 (96)	86 (86)	41 (71)	10 (43)
Chest x-ray:	Infiltrates absent	6 (4)	14 (14)	17 (29)	13 (57)
	If present:				
	Improved	—	44 (51)	32 (78)	9 (90)
	No change	—	27 (31)	8 (20)	1 (10)
	Worse	—	15 (17)	1 (2)	0 (0)

*Per cent of total patients with cough

TABLE 3

Clinical response to complete course of antibiotic therapy

Outcome	Intent-to-treat Number (%)	Efficacy-evaluable Number (%)
Clinical cure	78 (56.9)	73 (64.6)
Clinical improvement	37 (27.0)	32 (28.3)
Relapse	3 (2.2)	2 (1.8)
Failure	7 (5.1)	6 (5.3)
Impossible to evaluate	12 (5.8)	0 (0)
Total	137 (100.0)	113 (100.0)

positive and 30 with no pathogen identified. There were 32 possible bacterial pathogens isolated from 29 episodes of pneumonia. They included: *H influenzae* (11); *S pneumoniae* (10); *M catarrhalis* (five); *E coli* (two); *Klebsiella pneumoniae* (one); *Klebsiella oxytoca* (one); *Xanthomonas maltophilia* (one); and *P aeruginosa* (one). There were seven patients with bacteremic pneumonia. They included *S pneumoniae* (five); *H influenzae* (one) and *P aeruginosa* (one). Of the patients bacteremic with *S pneumoniae*, three were clinical cures (one) or clinical improvements (two); one was unevaluable and one died within 24 h of admission due to unrelated causes. The patient with *H influenzae* bacteremia was a clinical cure. The patient with *P aeruginosa* bacteremia had the same organism isolated from sputum and both were susceptible to ceftriaxone. This patient was a clinical cure.

Ceftriaxone treatment was administered to 135 patients intravenously and to two patients intramuscularly. The average duration of ceftriaxone treatment was 5.1 days (SD $\pm$ 2.9 days, range one to 18). Macrolides (erythromycin and clarithromycin) were administered to 34 patients and metronidazole to five patients during ceftriaxone treatment.

Following a minimum of three days of treatment with ceftriaxone, 59 patients (43%) were switched to antibiotics other than ceftriaxone. Of these patients, 53 were switched to oral antibiotics, while six continued to be treated intravenously. The most frequently used oral antibiotics were cefuroxime axetil (21 patients), ciprofloxacin (12 patients), cefaclor (nine patients) and cephalixin monohydrate (six patients).

Overall, the intent-to-treat and the efficacy-evaluable patient populations were statistically comparable with regard to the above variables.

The clinical efficacy assessments are presented in Table 3. Based on the intent-to-treat analysis approach, 57% of the patients were clinically cured and 27% showed clinical improvement. Relapse of infection was noted in three patients, while seven patients failed to respond to therapy. Clinical outcome could not be evaluated in 12 patients.

In the efficacy-evaluable population, favourable treatment outcome (clinical cure and improvement combined) was found in 93% and treatment failure (including relapse) in 7% of the patients (Table 3). Statistical tests were performed to determine whether treatment outcome was associated with initial diagnosis, severity and source of infection. Only the severity of infection was found to be a likely factor affecting the outcome of antibiotic therapy ($P=0.05$, Kruskal-Wallis test). Of the seven patients who failed to respond to treatment, all except one had moderate or severe infection.

The frequencies of abnormalities in signs and symptoms monitored at various study phases are shown in Table 2. Follow-up white blood cell count and chest x-ray were done only when indicated. At treatment termination, none of the patients had temperature greater than 38.5°C, and the frequency of other abnormal signs and symptoms varied from 8 to 24%. While

TABLE 4

In vitro activity of ceftriaxone against bacterial pathogens commonly associated with lower respiratory tract infections

Organism (number)	MIC (μ g/mL)*		
	50%	90%	Range
<i>Escherichia coli</i> (75)	≤ 0.50	≤ 0.50	≤ 0.50 - 1.0
<i>Klebsiella pneumoniae</i> (50)	≤ 0.50	≤ 0.50	≤ 0.50 - 128.0
<i>Proteus mirabilis</i> (50)	≤ 0.50	≤ 0.50	≤ 0.50 - 64.0
<i>Enterobacter cloacae</i> (25)	≤ 0.50	>128.0	≤ 0.50 - >128.0
<i>Serratia marcescens</i> (50)	≤ 0.50	1.0	≤ 0.50 - 32.0
<i>Klebsiella oxytoca</i> (50)	≤ 0.50	>128.0	≤ 0.50 - >128.0
Beta-lactamase negative <i>Haemophilus influenzae</i> (50)	≤ 0.06	≤ 0.06	≤ 0.06
Beta-lactamase positive <i>H influenzae</i> (25)	≤ 0.06	≤ 0.06	≤ 0.06
Beta-lactamase negative <i>Moraxella catarrhalis</i> (20)	≤ 0.06	≤ 0.06	≤ 0.06
Beta-lactamase positive <i>M catarrhalis</i> (30)	≤ 0.06	≤ 0.06	≤ 0.06 - 0.50
Penicillin susceptible <i>Streptococcus pneumoniae</i> (50)	≤ 0.06	≤ 0.06	≤ 0.06 - 0.50
Penicillin moderately susceptible <i>S pneumoniae</i> (25)	0.12	0.50	≤ 0.06 - 2.0
Penicillin resistant <i>S pneumoniae</i> (25)	0.50	1.0	0.12 - 1.0

MIC Minimal inhibitory concentration; *50% and 90%, MICs for 50 and 90% of isolates tested, respectively

lung infiltrates were present in most patients before the initiation of ceftriaxone treatment, after completion of antibiotic therapy only 10 of 23 patients who had chest x-rays done had infiltrates, of whom nine showed improvements. Twenty-two of the 24 patients required return for follow-up evaluations (two patients did not return). Respiratory signs and symptoms had resolved in all returning patients except one, for whom no further information was available.

Twenty adverse events in 19 patients were reported. Of the 20 adverse events, 14, one and five were classified as severe, moderate and mild, respectively. Twelve patients died due to reasons unrelated to the test drug. All severe events resulted in death, except one: 'aspiration of pill'. The three events probably related to test drug were hives (moderate), diarrhea (mild) and superficial phlebitis (mild) at the injection site. The three adverse events reported as possibly or remotely related to test treatment were oral thrush (mild), hypogastric fullness (mild) and pruritus on palms and soles (mild).

In total, 950 consecutive *Enterobacteriaceae* species and 175 other respiratory pathogens were collected from eight teaching centres across Canada in 1993. Of the consecutive *Enterobacteriaceae* species, 53% were speciated as *E coli*, 11% as *K pneumoniae*, 5% as *Serratia marcescens*, 4% as *Proteus mirabilis*, 3% as *Enterobacter cloacae*, 4% as *K oxytoca* and the remaining 20% was various other species of *Enterobacteriaceae*. Susceptibility testing of 525 isolates representing a random sample of each of the species was performed (Table 4).

DISCUSSION

In this open study to evaluate the efficacy of 1 g, once daily ceftriaxone, a favourable outcome was found in 83.9% of the intent-to-treat population and in 92.9% of the efficacy-evaluable population. These findings are

similar to those reported in other studies of the treatment of pneumonia in hospitalized patients (10). There are limitations to this study because clinical criteria used to diagnose pneumonia lack specificity (11-15). Our study entry criteria were those that clinicians would employ to make a diagnosis of pneumonia and are consistent with recently published guidelines for the conduct of clinical studies for anti-infective agents (10).

Although most of our patients had community acquired pneumonia, differentiation between community and hospital acquired pneumonia may no longer be valid. This has been called into question by Sapira et al (16), who suggested in a meta-analysis that adequate empirical syndromic treatment based solely on this classification was not possible.

Our in vitro data support the recommendation of 1 g of ceftriaxone once daily, with the exception of bacterial pneumonia suspected or proven to be due to *E cloacae*. The mechanism of resistance in *E cloacae* is due to chromosomally mediated class C beta-lactamase gene (*ampC*) (17). Rates of such resistance in *Enterobacter* species in Canada have been found to be greater than 16% (18). Development of this type of resistance during therapy should preclude the use of any cephalosporin for the treatment of such infections (19). The appearance of *K oxytoca* resistance to the cephalosporins is a more recent event and is thought to be due to chromosomal beta-lactamases (20). Therapy of infections with this organism should be guided by in vitro susceptibility testing of the isolate in question. Both *Enterobacter* species and *K oxytoca* are infrequent causes of bacterial pneumonia. Penicillin-resistant *S pneumoniae* remained susceptible to ceftriaxone. Although resistance of pneumococci to penicillin was previously found to be rare in North America (21,22), more recent studies have noted the rapid emergence of such resistance (23,24).

In conclusion, 1 g, once daily ceftriaxone appears to be an effective and well tolerated regimen for the treatment of lower respiratory tract infection.

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