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Treatment of Streptococcal Endocarditis With a Single Daily Dose of Ceftriaxone Sodium for 4 Weeks

Efficacy and Outpatient Treatment Feasibility

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Objective.—To evaluate the efficacy and safety of ceftriaxone sodium in the treatment of streptococcal endocarditis.

Design.—An open, multicenter, noncomparative study with a follow-up of patients for 4 months to 5 years.

Setting.—Internal medicine wards and outpatient clinics of hospitals of various sizes in three European countries.

Patients.—Fifty-nine patients with defined criteria for streptococcal endocarditis.

Intervention.—Ceftriaxone sodium administered at a once-daily dose of 2 g for 4 weeks.

Main Outcome Measures.—Clinical outcome and microbiological cure rate.

Results.—Among the 59 patients, 55 completed the treatment and were followed up for 4 months to 5 years. No patients showed evidence of relapse. Treatment was completely uneventful in 42 patients (71%). A cardiac valve was replaced in four patients (7%) receiving antimicrobial therapy and in six patients (10%) who had completed antimicrobial therapy. One of the 10 valves taken for culture at surgery was positive, but only for microorganisms that were different from the microorganism isolated before the treatment. The treatment had to be interrupted in four patients because of drug allergy. Other side effects were mild except for two cases of reversible neutropenia. The treatment was easy to administer: 27 patients (46%) had no permanent intravenous catheter at any time, seven patients (12%) had such a catheter for less than 4 days. Twenty-three patients (39%) were discharged from the hospital less than 2 weeks after admission.

Conclusions.—Ceftriaxone sodium administered at a once-daily dose of 2 g appears to be an effective and safe treatment of streptococcal endocarditis. In hospitals, this agent may be more convenient to administer than penicillin G with or without aminoglycosides. Some patients may even be treated as outpatients.

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ANTIMICROBIAL treatment of infective endocarditis (IE) has recently been reviewed by the Committee of the American Heart Association's Council on Cardiovascular Disease in the Young.[1] Streptococcal IE can be treated successfully either with high-dose parenteral administration of aqueous crystalline penicillin G for 4 weeks, or alternatively with a 2-week course of high dosages of penicillin combined with an aminoglycoside administered parenterally. With both types of treatment, the cure rate is better than 98%.[2] If a patient is allergic

For editorial comment see p 279.

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A complete list of the participants in the Infective Endocarditis Study Group appears at the end of this article.

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Table 1.—Minimal Inhibitory Concentration in Micrograms per Milliliter for Ceftriaxone Sodium and Penicillin of 60 Strains of Streptococci in 59 Patients

	No. of Strains	Ceftriaxone Sodium, μg/mL		Penicillin, μg/mL	
		MIC_{90}	Range	MIC_{90}	Range
Streptococcus sanguis	27	.125	.064-.25	.064	.016-.064
Streptococcus bovis	11	.064	.032-.125	.125	.125-.25
Streptococcus mutans	7	.032	.032	.064	.064
Streptococcus mitis	6	.125	.032-.125	.032	.032
Other streptococci	9	.032	.032-.125	.064	.032-.064

to penicillin, a first-generation cephalosporin or vancomycin hydrochloride can be given.

Ceftriaxone sodium, a third-generation cephalosporin, has excellent in vitro activity against *Streptococcus viridans* and nonenterococcal streptococci.[3] Because of its half-life of 6 to 9 hours, ceftriaxone administered once daily provides effective serum levels for 24 hours, both after intravenous (IV) and intramuscular (IM) injections.[4,5] This has permitted the treatment of severe infections with only one IV or IM injection daily.[6-8] This simplified regimen obviates the need for an IV access (except for the daily infusion), requires only one preparation of antibiotics daily, and consequently offers the possibility of home therapy for some patients.[6-8]

The purpose of the present study was to test the efficacy and safety of ceftriaxone sodium at a once-daily dose of 2 g (IV or IM) in monotherapy of IE due to ceftriaxone-susceptible streptococci. It was designed as an open, multicenter trial. The trial was noncomparative, since streptococcal IE has become a rare disease, and the results with penicillin treatment are well known.

PATIENTS AND METHODS

The criteria for diagnosis of IE were derived from those developed by Von Reyn et al.[9] Patients had to meet two conditions. First, at least two blood cultures (two bottles for each blood culture) obtained on two separate occasions had to be positive for nonenterococcal streptococcus. When only two or three blood cultures were obtained, all bottles had to be positive. When more than three blood cultures were obtained, at least 70% of them had to be positive. Second, patients must have had a new regurgitant heart murmur (or a definite change in a preexisting one) or a predisposing heart disease *and* vascular phenomena.

Patients were excluded from the study if they had received other antibiotics for more than 3 days, had allergic reactions to cephalosporins, or had severe renal impairment (creatinine clearance <0.167 mL/s).

Ceftriaxone sodium was administered at a daily dose of 2 g by short IV infusion (2 g diluted in 50 mL of 5% glucose) or by IM injections (2 g mixed with 1% lidocaine and injected in the gluteal muscles) for 4 weeks. The requirements for treatment by a permanent indwelling IV catheter were not strictly defined. When the condition of the patient permitted and there was an appropriate outpatient setting, patients were discharged from the hospital. They were asked to refrain from activities requiring permanent attention, such as driving a car.

Patients were assessed daily during hospitalization and at least once a week after discharge until the end of the treatment. Follow-up visits were carried out once between weeks 2 and 4, and again between 3 and 6 months after completion of treatment. Most patients were followed up for longer periods.

Serial laboratory investigations including hematologic and chemical analysis of the blood, urine analysis, blood cultures, and drug sensitivity tests were performed before, during, and after treatment.

The strains of streptococci isolated from blood cultures were identified by API 20 Strep system (Api System SA, France). The minimum inhibitory concentrations (MICs) were determined by the macro-tube dilution technique in Müller-Hinton broth.[3]

The study was approved by the ethical committee of the organizing institution (Lausanne, Switzerland).

RESULTS

Sixty-two patients with active, nonenterococcal streptococcal IE were included. Of these, three had to be excluded because they had received other antibiotics for more than 3 days before ceftriaxone therapy was started. Thus, 59 patients were evaluated. Five centers (Lausanne, Switzerland, Lyons, France, Bern, Switzerland, Brussels, Belgium, and Burgdorf, Switzerland) provided most of the cases, and eligible patients were included consecutively. The rest of the patients were provided by several hospitals under the direct supervision of the center at Lausanne.

Of the 59 patients, 41 were men and 18 were women. The median age was 59 (range, 19 to 87 years). The duration of symptoms before treatment ranged from 5 to 120 days, and six patients reported having symptoms for at least 3 months. Forty-six patients had a known underlying valvular or congenital cardiac abnormality. Infection affected the mitral valve alone in 28 patients (47%), the aortic valve alone in 20 patients (34%), mitral and aortic valves in five patients (8%), pulmonary valves in two patients (3%), and a ventricular septal defect in two patients (3%).

Sixty different strains of streptococci could be isolated from the 59 patients (Table 1). None was identified as a nutritionally deficient variant. All strains had MICs for ceftriaxone below 0.125 μg/mL, except for one strain of *Streptococcus sanguis* with a MIC of 0.25 μg/mL. The MICs for ceftriaxone were one dilution above the MICs of penicillin for all strains of streptococci except those of *Streptococcus bovis*, which were one or two dilutions below those for penicillin.

Twelve patients were treated with antibiotics other than ceftriaxone for 1, 2, or 3 days (four patients for each day) before the definite diagnosis of IE was established by blood culture results. These patients were then switched to ceftriaxone.

In four patients, the physician in charge decided to extend the treatment beyond 4 weeks: one patient presented with an associated spondylodiskitis (42 days), one had a spondylodiskitis and a cerebral mycotic aneurysm (60 days), one had a pacemaker (42 days), and one violated the protocol (42 days). In four patients, the treatment was interrupted because of adverse reactions to the drug: two patients developed an allergic rash and two had a second occurrence of fever, which was considered a drug reaction. For these patients, the treatment was continued with penicillin. The remaining 55 patients (93%) were followed up for 4 months to 5 years after the end of treatment. No patients presented with clinical signs or laboratory evidence of relapse. Three patients had a second episode of IE due to different microorganisms: one patient had a second episode of IE 4 years later due to a different strain of *S viridans*, another patient had a recurrence of endocarditis due to *Haemophilus influenzae* 1 year after the streptococcal episode, and a third patient is described below.

No patient died during treatment. One patient died suddenly 3 months after

completion of treatment. Blood cultures had been negative 1 month prior to death. No autopsy was performed.

Ten patients (17%) required cardiac surgery some time after the initiation of treatment. In eight of these patients, valve replacement was performed because of hemodynamic deterioration: two patients required the procedure during the course of the treatment (day 4 and day 23) and six required the procedure after its completion. All had signs of congestive heart failure before initiation of therapy. Two patients had valve replacements because of recurrent emboli (on day 7 and day 12). The valves removed at operation were negative for streptococcal infection in nine of 10 patients, as evidenced by direct microscopic examination and cultures. The 10th patient was an unusual case: he was treated with ceftriaxone sodium at 1 g per day for 6 weeks because of a protocol violation. The initial organism was *Streptococcus morbillorum* with an MIC of 0.125 μg/mL. He underwent dental extraction 4 weeks after initiation of therapy. On that occasion, he also received one dose of gentamicin sulfate. Three days after completion of treatment, he was profoundly neutropenic. He became febrile soon after and developed symptoms suggestive of multiple cerebral emboli, prompting an immediate valve replacement. Examination of the valve disclosed acute endocarditis. Cultures were positive for *Streptococcus mitis* and *Corynebacterium xerosis*. He was treated with penicillin and gentamicin for 6 additional weeks and eventually recovered.

Five patients developed emboli while receiving ceftriaxone. Blood cultures taken at the time of the episodes were sterile. Emboli affected multiple, small peripheral vessels in three patients (on days 3, 7, and 12) and a single major peripheral artery in two patients (on days 3 and 12). Two of the three patients with multiple emboli underwent cardiac valve replacement. Cultures taken of the excised valves were negative for streptococcal infection. Echocardiograms were performed on 51 (86%) of the 59 patients. Cardiac vegetations were seen in 22 (37%) of them and were detectable in only three of the five patients presenting with emboli.

Drug-related side effects were as follows: two patients experienced neutropenia, one on day 26 and the other 3 days after completion of a 42-day course of therapy (protocol violation). Complete blood counts returned to normal 5 to 7 days after cessation of ceftriaxone therapy. Pain and phlebitis at the site of IV injection occurred in six patients (10%), transient gastrointestinal discomfort in four patients (7%), superficial and transient *Candida* infection in three patients (5%), fever of presumably allergic origin in three patients (5%) (two prompting treatment interruption, both on day 15), rash in two patients (3%) (both prompting treatment interruption on days 2 and 10), dysgeusia in one patient (2%), and laboratory abnormalities in five patients (8%) (two with moderate hypereosinophilia, one with positive results of direct antiglobulin test and two with increases in aminotransferase levels). All side effects resolved either during therapy or after the end of treatment.

Many patients could be treated without a permanent indwelling IV catheter. In these patients, the drug was administered daily through the placement of a butterfly needle either as a short infusion or as a slow IV injection (Table 2). Twenty-seven patients (46%) had no permanent indwelling catheter at any time, seven (12%) had such a catheter for less than 4 days. In the other 21 patients, the IV line was maintained for more than 4 days either because of the concomitant administration of other medications or because the initial catheter was well tolerated and the physicians decided to maintain it for the administration of ceftriaxone. In seven patients, treatment was administered partially or totally by IM injections (for periods of 16, 16, 20, 24, 28, 28, and 52 days, the last patient being the one with spondylodiskitis and cerebral mycotic aneurysm). The IM injections were well tolerated. Twenty-three patients could be discharged from the hospital after less than 2 weeks: seven patients either were not hospitalized at all or were hospitalized for less than 2 days, two patients stayed for less than 7 days and 14 patients for 8 to 14 days. In these patients, the drug was administered either in the outpatient clinics of the participating hospitals or in the physicians' offices. In addition, seven patients were hospitalized for the entire course of treatment only because of the absence of outpatient treatment facilities.

Table 2.—Intravenous Requirements and Duration of Hospitalization of 55 Patients With Streptococcal Endocarditis Treated With One Daily Injection of 2 g of Ceftriaxone Sodium for 4 Weeks (51 Patients) or 6 Weeks (4 Patients)

Mode of Treatment, d	No. of Patients
Intravenous catheter	
None*	27
<4	7
≥4	21
Intramuscular injection	
7-52	7
Hospital stay	
<2	7
<7	2
<15	14
≥15	32†

*Drug was administered by short, once daily infusion.
†Includes 7 patients for which hospitalization beyond 2 weeks was due to nonmedical reasons.

COMMENT

Antibiotic regimens recommended by the American Heart Association for the treatment of streptococcal, nonenterococcal endocarditis require the administration of several IV or IM injections of the drugs daily,[1] thus, hospitalization is almost always unavoidable. In the present study, 59 patients were treated with ceftriaxone sodium administered once daily at a dose of 2 g by IV or IM injections. Drug allergy prompted the interruption of treatment in four patients. All 55 assessable patients responded clinically and microbiologically, and no relapse occurred after cessation of treatment. No patient died during treatment. Although this study was not comparative, the results are similar to those studies that reported using penicillin alone for 4 weeks or regimens of penicillin given with streptomycin sulfate for 2 weeks. These regimens anticipate a cure rate of at least 98%.[10-12] The present study also confirms and extends the results of a recently published study in which 30 patients were treated successfully with either 2 g of ceftriaxone sodium per day for 4 weeks or the same dosage for 2 weeks, and then given amoxicillin orally for 2 weeks.[13]

Eight (13%) of our patients required a valve replacement because of hemodynamic deterioration. All had some degree of cardiac failure on initiation of therapy. Cultures taken of the excised valves during or after treatment were sterile in all but one patient who had a second episode of endocarditis. The replacement rate is similar to that reported by some authors[11] but somewhat lower than the 29% reported by others.[14] Although the eligible patients coming to our study through the five main centers were included consecutively, some patients from the hospitals connected with the center at Lausanne may have been referred because the physicians knew about the possibility of outpatient treatment. Thus, there may have been some bias toward less severe cases included in the present study. This is also suggested by our low mortality rate and by the fact that only six patients (10%) reported having symptoms for more than 3 months, as compared with 18% to 20% of patients in other studies.[12,14]

The most severe side effect was neutropenia, which was observed in two patients (one of whom was treated for 42 days). This is a known side effect of penicillins and cephalosporins, which is

reversible within 5 to 7 days after discontinuation of therapy. It is observed in 2% to 4% of patients treated with these drugs, mostly after high dosage and prolonged use.[6,15] Thus, benzylpenicillin administered at a mean daily dose of 16.9 g had to be interrupted after 19 to 23 days in seven of 14 patients with endocarditis because of fever and neutropenia.[15] This underlines the necessity for regular hematological monitoring patients treated for more than 2 weeks with high dosages of β-lactam antibiotics. Other recorded side effects were mild and did not require withdrawal of treatment, except for allergic manifestations in four patients.

One of the main advantages of ceftriaxone relates to its pharmacokinetic properties, which have allowed treatment of severe infections with one daily administration by intermittent IV injection, heparin lock, or IM injection.[6-8] This obviates the risks and inconveniences inherent in any intravascular device and permits substantial cost savings in professional time necessary for drug administration and material costs, both for inpatients and outpatients.[6,7,13]

In the case of IE, patients eligible for outpatient treatment obviously need to be carefully selected. The most frequent complications of IE include congestive heart failure and emboli. Although hemodynamic deterioration may occur in any patient, this is more likely to affect patients who have some degree of heart failure on admission. Among the 91 patients with streptococcal IE reported by Wilson et al,[14] only one patient had progression of heart failure during therapy, and among the 16 who underwent aortic valve replacement, none had sudden-onset aortic insufficiency. In the present study, hemodynamic deterioration prompted valve replacement in only two patients who were undergoing therapy. Both had signs of cardiac failure at the time antibiotic therapy was started, and were kept in the hospital during the treatment. Therefore, careful evaluation of the cardiac function should allow the selection of patients who are at low risk for the development of cardiac insufficiency during outpatient treatment. Other cardiac complications, such as myocardial infarction or sudden death caused by occlusion of the coronary arteries by cardiac vegetations, are only rare complications of streptococcal IE.[11,16,17]

Arterial emboli are the second most common complications of IE. However, emboli mostly occur before or within the first few days after initiation of appropriate antibiotic therapy[18-20] and are less frequent in streptococcal IE than in IE due to more virulent microorganisms.[19,20] Moreover, the occurrence of major emboli is associated with the presence of large cardiac vegetations seen in echocardiograms,[21,22] so that it appears possible to select patients who are at low risk for such complication for outpatient treatment. Appropriate counseling for avoiding activities that may endanger the patient or other people in case of a sudden event during therapy is, nevertheless, indicated.

Infectious central nervous system complications, such as mycotic aneurysms or brain abscesses, may occur in IE. Due to its relatively good cerebrospinal fluid penetration, ceftriaxone should provide protection against such possibilities and may be a better choice than the first-generation cephalosporins currently recommended as alternative regimens to penicillin.[1]

It may be argued that the relatively narrow antimicrobial spectrum of penicillin is more appropriate for the treatment of IE due to sensitive microorganisms. However, it is unlikely that the use of a broad-spectrum antibiotic for the treatment of IE would contribute to the emergence of resistance to cephalosporins since streptococcal IE is a rare disease and the number of patients treated remains limited. The number of such patients may even be reduced with good compliance to antibiotic prophylaxis as emphasized in the recently revised recommendations of the American Heart Association.[23]

In conclusion, a 4-week course of a once-daily dose of ceftriaxone is efficacious and safe for the treatment of streptococcal endocarditis. It is easy to administer, requires only one daily injection, and permits outpatient treatment for selected patients. However, before considering outpatient treatment, the patients should be carefully evaluated and stabilized in the hospital.

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