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Right-Sided Endocarditis Caused by *Staphylococcus aureus* in Drug Abusers

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A prospective, open, and randomized study of right-sided endocarditis caused by *Staphylococcus aureus* in drug abuse patients is reported. The following parenteral treatments were compared. Group A patients were treated with 2 g of cloxacillin every 4 h and 1.5 mg of gentamicin per kg of body weight every 8 h for 2 weeks. Group B patients were treated with teicoplanin at 10 mg/kg/12 h on the 1st to 3rd days, 6 mg/kg/12 h on the 4th to 7th days, and 7 mg/kg/24 h on the 8th to 28th days. Drug abusers with bacteremia caused by *S. aureus* and suggestive signs of endocarditis were included. Clinical failures were observed in one patient in group A and in four of six patients in group B. Three patients in group B developed breakthrough bacteremia with teicoplanin-susceptible strains on days +6, +14, and +19. Serum teicoplanin levels and serum bactericidal titers showed a decrease in the 2nd week, when dosages received were 7 mg/kg/day. In conclusion, in treatment of right-sided endocarditis caused by *S. aureus* in drug abusers with teicoplanin, the use of dosages of 7 mg/kg/day is not recommended even if patients have received dosages of 12 mg/kg/day during the 1st week.

Right-sided endocarditis caused by *Staphylococcus aureus* in parenteral drug abusers is more amenable to a benign treatment than left-sided endocarditis, particularly in the absence of extensive pulmonary embolization (4, 15).

Results after 2 weeks of treatment with a combination of isoxazolyl penicillins and aminoglycosides are satisfactory in more than 90% of patients (6).

Nonintravenous therapy of right-sided endocarditis in drug abusers will be a help in the management of these patients. Preliminary studies with an oral combination of ciprofloxacin and rifampin are encouraging (9); however, in vitro studies have found that this combination can be antagonistic (23).

The more usual alternative is the use of glycopeptides: vancomycin and teicoplanin. Experience with vancomycin in endocarditis caused by *S. aureus* is unfavorable (22). On the other hand, two characteristics of teicoplanin are relevant in these patients: its special pharmacokinetics and its proven efficiency in endocarditis caused by gram-positive organisms (8, 11, 17, 18, 20).

To evaluate the efficiency of teicoplanin in right-sided endocarditis caused by *S. aureus* in parenteral drug abusers, a comparative study was conducted with the following two parenteral treatments: cloxacillin-gentamicin for 2 weeks (group A) and teicoplanin for 4 weeks (group B).

MATERIALS AND METHODS

This was a prospective, open, randomized (1 of group A:1 of group B), and parallel study.

Parenteral drug abusers with the following findings were included: (i) two or more blood cultures with isolation of methicillin-susceptible *S. aureus*, (ii) community-acquired infection, (iii) tricuspid regurgitation murmur, and (iv) clinical or radiological findings of septic pulmonary embolization or evidence of right-sided vegetations in transthoracic ecocardiography.

Patients were excluded from enrollment if any of the following criteria was met: (i) methicillin-resistant *S. aureus* in blood cultures, (ii) allergy to the antibiotics used, (iii) serum creatinine level higher than 220 nmol/liter (2.5 mg/dl), (iv) extrapulmonary metastatic foci (osteomyelitis, pericarditis, etc.) requiring surgery, (v) culture-proven meningitis, (vi) left-sided endocarditis, (vii) nonbiological valvular prosthesis or long-term catheter, (viii) polymicrobial infections, (ix) pregnancy, and (x) previous effective treatment in the last 72 h.

Patients in group A received simultaneously intravenous cloxacillin at 2 g/4 h and intravenous gentamicin at 1.5 mg/kg of body weight every 8 h for 2 weeks. Patients in group B received intravenous teicoplanin at 10 mg/kg/12 h on the 1st to 3rd days, 6 mg/kg/12 h on the 4th to 7th days, and 7 mg/kg/24 h on the 8th to 28th days.

Patients were evaluated daily. Routine analytical controls were obtained at weekly intervals.

For all patients, blood cultures were obtained 2 to 5 days and 2 to 4 weeks after the end of treatment and when clinically indicated. Usually, blood cultures were not obtained during the first 5 days of treatment, as this period is considered the natural duration of bacteremia in normally treated endocarditis (1, 16). Blood cultures were processed with BACTEC 860 A (Becton and Dickinson, Towson, Md.). Bottles were examined every 12 to 18 h to measure CO_2 concentration. Identification was done by standard methods. The MICs of teicoplanin, oxacillin, and gentamicin were determined by standard microdilution with Mueller-Hinton broth with cationic supplement (Oxoid, Basingstoke, United Kingdom).

Serum samples were obtained for all patients to determine the antibiotic levels and serum bactericidal titers (SBT) 20 min after administration (peak) and just before administration (trough). Once the steady state was reached, one sample was taken from group A patients and two samples were taken from group B patients, one in the 1st week and another in the 2nd week. Teicoplanin and cloxacillin levels in serum were determined by an agar diffusion bioassay with *S. aureus* ATCC 25922 as the indicator strain (2). Levels of gentamicin in serum were determined by the fluorescence polarization immunoassay method (TDx; Abbott Laboratories). SBT were determined by standard methods (13).

The following criteria of efficiency were used: for cure, microbiological eradication and satisfactory clinical response; for clinical failure, no response or worsening during treatment; for microbiological failure, positive blood culture after the 5th day; for microbiological relapse, positive blood culture after cessation of treatment.

RESULTS

Sixteen patients were included in the study; two of them were excluded from the final evaluation. One patient in group A developed *Streptococcus mitis* catheter-related bacteremia on day +12, which required a lengthening of therapy; the other, in group B, developed a generalized rash on day +3, which disappeared after discontinuation of teicoplanin. The other 14 patients were evaluated.

Pretreatment parameters (Tables 1 and 2). Five patients in each group were human immunodeficiency virus seropositive. Except for one patient in group A in stage C3 (5) with 27 CD4 lymphocytes per mm^3, all patients were in stage A or B and had >150 CD4 lymphocytes per mm^3. Most of them had had symp-

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TABLE 1. Clinical features, complementary studies, and evolution of cases of group A patients (cloxacillin and gentamicin)

Patient no.	HIV seropositive[a]	Immunological stage[b]	No. of CD4 lymphocytes/mm^3	Previous endocarditis[c]	Duration of symptoms (days)	Fever duration (days of treatment)	X-ray feature(s) (day of treatment)[d]	Transthoracic echocardiography[e]	MIC (μg/ml; against first strain) of:		Breakthrough bacteremia	Evolution of case
									Cloxacillin	Gentamicin		
1	+	A2	309	Y	2	1st	SPE + empyema (+1)[f]	MTI	0.5	0.2	N	Cured
2	+	A2	260	N	30	1st–5th	SPE + empyema (0)[f]	STI	0.2	0.2	N	Cured
3	−			N	2	1st–4th	SPE (0)	Normal	0.2	0.5	N	Cured
4	−			N	7	1st–3rd, 12th–14th	SPE (0), SPE (+12)	MTI	0.1	0.5	N	Clinical failure
5	+	B3	180	Y	14	1st	SPE (0)	MTI	0.2	0.2	N	Cured
6	+	B2	238	N	7	1st–6th	SPE (+3)	Not done	0.2	0.5	N	Cured
7	−			N	2	1st–8th	SPE + empyema (+2)[f]	Normal	0.5	1	N	Cured
8	+	C3	27	N	3	1st–9th	Pleural effusion (+3)	Not done	0.2	0.5	N	Cured

[a] HIV, human immunodeficiency virus.
[b] See reference 5.
[c] Y, yes; N, no.
[d] SPE, septic pulmonary embolism.
[e] MTI, moderate tricuspid insufficiency; STI, severe tricuspid insufficiency. All echocardiographies were done in the 2nd week.
[f] Pleural drainage was required.

toms for less than a week. Two patients in group A and one in group B (a carrier of a biological tricuspid prosthesis at the time of study) had suffered a previous endocarditis. One patient in group A and three in group B had severe tricuspid insufficiency by echocardiography.

Therapeutic efficiency (Tables 1 and 2). The difference in outcome for the two regimens did not achieve statistical significance ($P = 0.09$ by two-tailed Fisher's exact test), but given the impressive failure rate in the teicoplanin arm and the variance with expected outcome with effective regimens, the study had to be stopped.

Only one patient in group A showed a clinical failure (cured, seven of eight) on day +12, having chest pains and radiological infiltrates that required a lengthening of treatment for an additional week. Blood cultures did not demonstrate a microbiological failure.

In contrast, only two of six patients in group B were cured; one of them was treated on an ambulatory basis after day +8 and erroneously received dosages of 12 mg/kg/day for a second week to day +14. The other four patients had clinical failure with persistent fever and development of pulmonary embolism. These four patients had positive blood cultures; however, only three were considered to have microbiological failure with bacteremia after the 5th day (days +6, +14, and +19). The fourth patient developed hypotension, oliguria, and multiple pulmonary embolisms on day +4 that were consistent with the outcome of the study, as at that time blood cultures were positive.

Microbiological data. Initially, all strains isolated were susceptible to oxacillin, gentamicin, and teicoplanin (Tables 1 and 2). In patients with microbiological failure, the strains isolated from blood cultures required MICs identical to those required by strains isolated in the first episode (Table 2).

Group A showed discrepancies in antibiotic levels in serum which were probably due to the combinational nature of therapy. SBT were adequate in this group, with peak and trough levels usually above 1/32 and 1/8, respectively (Table 3).

Patients in group B (except patient 4, who received dosages of 12 mg of teicoplanin per kg per day for 2 weeks) showed a decrease in serum antibiotic levels in the 2nd week, when the dosages received were 7 mg/kg/day. Values of SBT in the 2nd week also showed decreases of 2 and 1 dilution in peak and trough levels, respectively (Table 4).

Adverse reactions. The small number of cases due to patient outcome makes the data on adverse reactions impossible to evaluate. A rash was observed in one patient in the teicoplanin group (excluded from clinical evaluation). No kidney or liver damage associated with antibiotic use was noted in any patient.

DISCUSSION

Teicoplanin is a glycopeptide with a half-life of 40 to 70 h, thus allowing a once-daily administration in the therapy of gram-positive infections, including endocarditis (8, 11, 17, 18, 20). Teicoplanin is therefore a therapeutic option for drug abusers, with a decrease of hospitalization and with treatment on an ambulatory basis.

Efficacy and therapeutic doses of teicoplanin in staphylococcal endocarditis are not yet established. This study shows the failure of teicoplanin in right-sided endocarditis caused by *S. aureus* in parenteral drug abusers at the chosen dosages. Because of the poor results reported with dosages lower than 6 mg/kg/day, dosages of 20 mg/kg/day for the first 3 days and 12 mg/kg/day for the next 4 days were used. Because of the reported cumulative effect of teicoplanin (3, 19), the dosage after the 8th day was decreased to 7 mg/kg/day. This cumulative effect was not observed in the present study. Serum antibiotic levels and SBT in the 2nd week were clearly lower than those observed in the 1st week (Table 4). The only patient who received dosages of 12 mg/kg/day for 2 weeks maintained high levels and was cured.

MICs of teicoplanin for *Streptococcus* spp. range from 0.008 to 3.1 μg/ml; however, MICs for *Staphylococcus* spp. range from 0.03 to 8 μg/ml (12). The slightly lower activity of teicoplanin against *Staphylococcus* spp. and the high protein binding (>90%) are the main causes of failure in low-dosage treatments (3 to 6 mg/kg/day) in endocarditis. Low-dosage treat-

TABLE 3. Serum antibiotic levels and SBT (peak and trough) in patients of group A

Patient no.	Dosage of cloxacillin; dosage of gentamicin	Level of cloxacillin/ level of gentamicin (μg/ml)		SBT	
		Peak	Trough	Peak	Trough
1	2 g/4 h; 80 mg/8 h	>100/5.25	50/0.8	1/32	1/16
2	2 g/4 h; 80 mg/8 h	35/16.6	25/5.5	1/128	1/64
3	2 g/4 h; 80 mg/8 h	13/3		1/16	1/4
4	2 g/4 h; 80 mg/8 h	54/4	22/0.2	1/64	1/32
5	2 g/4 h; 80 mg/8 h				
6	2 g/4 h; 80 mg/8 h	56.4/10.7	3.2/0.8	1/128	1/8
7	2 g/4 h; 80 mg/8 h	>100/5.9	22/0.4	1/128	1/8
8	2 g/4 h; 80 mg/8 h	>100/4.2	20/0.4	1/64	1/16

ments, however, are effective in other infections (3, 8, 11, 17, 18, 20).

Our study suggests the importance of retaining high dosages of teicoplanin in this severe infection. We agree with Wilson et al. (24), who recommend in endocarditis caused by *S. aureus* dosages of >12 mg/kg/day, as a trough concentration in serum of >20 μg/ml is needed; in our patients, this level was reached only, and not always, in the 1st week. Similar results have been obtained for osteomyelitis (11). Gilbert et al. (10), using dosages of 6 mg/kg/day preceded by initial dosages of 12 mg/kg/day, observed six failures in eight patients with endocarditis caused by *S. aureus* (four of four with left-sided endocarditis and two of four with right-sided endocarditis). A European study (8) reported a 79% success rate in 36 patients with endocarditis caused by gram-positive organisms; however, only 50% of patients with endocarditis caused by *S. aureus* responded well; all patients with treatment failure received low dosages (3.0 to 4.2 mg/kg/day).

A different factor that can be implicated in unfavorable results in drug abusers is the special pharmacokinetics of teicoplanin in these patients. Rybak et al. (21) demonstrated that teicoplanin levels in serum in parenteral drug abusers were clearly lower than those in healthy controls because of the higher clearance of teicoplanin due to an increase in glomerular filtration.

Other mechanisms associated with teicoplanin failure are

TABLE 4. Serum antibiotic levels and SBT (peak and trough) in patients of group B

Patient no.	Dosages of teicoplanin[a]	Level of teicoplanin (μg/ml)		SBT		Breakthrough bacteremia (day)	MIC (μg/ml) against first strain	MIC (μg/ml) against second strain	Evolution of case
		Peak	Trough	Peak	Trough				
1	12 mg/kg/day	74	12	1/32	1/8	Y (+19)	1	1	Clinical and microbiological failure
	7 mg/kg/day	65	11	1/16	1/4				
2	12 mg/kg/day	80	22	1/32	1/8	Y (+4)	1	1	Clinical failure[g]
3	12 mg/kg/day	>100	50	1/16	1/8	Y (+6)	0.5	0.5	Clinical and microbiological failure
	7 mg/kg/day	25	20	1/4	1/4				
4[b]	12 mg/kg/day	24	12	1/16	1/4	N	0.5		Cured
	12 mg/kg/day	35	9	1/8	1/4	N	0.2		Cured
5	12 mg/kg/day	28	17	1/64	1/16	Y (+14)	0.5	0.5	Clinical and microbiological failure
	7 mg/kg/day	20	4.8	1/16	1/8				
6	12 mg/kg/day	>100	80	1/128	1/64				
	7 mg/kg/day	72	7.8	1/32	1/8				

[a] Doses of 12 mg were administered on a twice-daily basis; doses of 7 mg were administered on a once-daily basis.

[b] This patient was treated as an outpatient after day +8 and received doses of 12 mg/kg/day on a once-daily basis.

TABLE 2. Clinical features, complementary studies, and evolution of cases of group B patients (teicoplanin)

Patient no.	HIV seropositive[a]	Immunological stage[b]	No. of CD4 lymphocytes/mm^3	Previous endocarditis[c]	Duration of symptoms (days)	Fever duration (days of treatment)	X-ray feature(s) (day of treatment)[d]	Transthoracic echocardiography[e]	MIC (μg/ml) against first strain	Breakthrough bacteremia (day)	MIC (μg/ml) against second strain	Evolution of case
1	+	A2	305	N	7	1st–17th	SPE (0), empyema + pneumothorax (+7),[f] SPE (+18)	MTI	1	Y (+19)	1	Clinical and microbiological failure
2	+	A2	320	N	3	1st–4th	SPE (0), SPE (+4)	MTI + tricuspid vegetation (1 cm)	1	Y (+4)	1	Clinical failure[g]
3	+	A3	150	N	5	1st–6th	SPE (+4), empyema (+6)[f]	STI + tricuspid and pulmonary vegetation (1.5 cm)	0.5	Y (+6)	0.5	Clinical and microbiological failure
4	−			Y	2	1st–3rd	SPE (+1)	Not done	0.5	N		Cured
5	+	A2	468	N	5	1st–4th	SPE (+2)	STI	0.2	N		Cured
6	+	B2	180	N	21	1st–6th, 12th–15th	SPE (+5), SPE (+13)	STI	0.5	Y (+14)	0.5	Clinical and microbiological failure

[a] HIV, human immunodeficiency virus.

[b] See reference 5.

[c] Y, yes; N, no.

[d] SPE, septic pulmonary embolism.

[e] MTI, moderate tricuspid insufficiency; STI, severe tricuspid insufficiency.

[f] Pleural drainage was required.

[g] Bacteremia during the first 5 days was not considered to be a microbiological failure.

resistance development (14) and poor diffusion of teicoplanin into vegetations (7). No patient in this study failed to respond because of resistant strains. Kaatz et al. (14) reported a case in which the MIC increased eightfold in a drug abuser who was treated with increasing doses of teicoplanin. Spontaneous resistance (constitutive) at concentrations 2 to 10 times above the MIC are detected in vitro with a rate of 10^{-7} to 10^{-9} (14). Maintaining high doses of teicoplanin in endocarditis is likely to avoid the development of resistance.

With dosages of 12 mg/kg/day, Greenberg reported that 28% of patients had drug fever and rash, which led him to stop teicoplanin administration (11). In our study, one patient developed rash; no other problems were noted.

In conclusion, the teicoplanin dosage in right-sided endocarditis caused by staphylococcal organisms is not yet established. Teicoplanin should not be used to treat serious staphylococcal infections, particularly endocarditis, until the minimum effective dosage can be identified. Treatments with dosages of 7 mg/kg/day in the 2nd week, despite administration of dosages of 12 mg/kg/day during the 1st week, showed a higher rate of clinical and microbiological failures. Other studies are needed to evaluate whether high dosages of teicoplanin or a combination of teicoplanin with other drugs (aminoglycosides, rifampin, etc.) are satisfactory without a disproportionate increase in toxicity.

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