J Infect Chemother xxx (2014) 1–4

Contents lists available at ScienceDirect

Journal of Infection and Chemotherapy

journal homepage: http://www.elsevier.com/locate/jic

Case report

Enterococcal endocarditis complicated with ruptured infected-intracranial aneurysm: With pharmacokinetic-pharmacodynamic documentation in proof of the successful antimicrobial treatment☆

Tosiharu Urakami [a], Yohei Hamada [a], Hiroki Magarihuchi [a], Hiroki Yamakuchi [a], Yosuke Aoki [a, b, *]

[a] Division of Infectious Disease and Hospital Epidemiology, Saga University Medical Center, Japan
[b] Depatment of International Medicine, Faculty of Medicine, Saga University, Japan

ARTICLE INFO

Article history:
Received 14 April 2014
Received in revised form
14 July 2014
Accepted 14 July 2014
Available online xxx

Keywords:
Endocarditis
Enterococcus
Infected intracranial aneurysm
Ampicillin
Pharmacokinetics-pharmacodynamics (PK-PD)

ABSTRACT

A 74-year-old man presented with sudden onset of aphasia and apraxia. Magnetic resonance image (MRI) of the brain disclosed a left frontal hemorrhage. The concomitant low grade fever suggestive of infection was unresponsive to cefazolin 1 g q12h, and refractory to piperacillin (PIPC) 2 g q8h. Blood culture grew enterococci, establishing together with echocardiography the diagnosis of infective endocarditis. The angiography revealed cerebral hemorrhage to have resulted from the rupture of the infected intracranial aneurysm. The antimicrobial therapy was switched to ampicillin (ABPC) 2 g q4h plus gentamicin (GM) 60 mg q8h. The positive blood culture was subsequently identified *Enterococcus faecium* to which the minimum inhibitory concentration (MIC) of PIPC, and ABPC was 16 mcg/mL, and 4 mcg/mL, respectively. The peak concentration of serum ABPC was 83.1, median 50.8, and trough 25.8 mcg/mL. Thus, the percent time > MIC for ABPC was 100%, and the time > minimum bactericidal concentration (MBC) as well. On the other hand, time > MIC for PIPC, was found nearly 30% in retrospective analysis using population pharmacokinetics. The neurological deficit of the patient was completely restored to the normal status after 4-weeks' antimicrobial therapy with ABPC plus GM, then he underwent cardiac surgery for valvular replacement, where microbiological culture of the resected valve was negative. The constellation of the clinical, pharmacological and microbiological outcome in our case provides scientific evidence that the antibiotic therapy given to our case is the best available strategy as an antimicrobial treatment of severe enterococcal endocarditis complicated by disseminated lesion as infected intracranial aneurysm.

1. Introduction

Infective endocarditis (IE) is a life threatening infection, manifesting systemic disease via hematogenous seeding of the infecting organism. Infected intracranial aneurysm (IIA) among others is the most serious complication of IE, with the reported incidence being 2%–5% [1,2]. Although the majority of community-acquired IE is caused by relatively limited numbers of bacteria such as staphylococci, streptococci, or enterococci, rapid determination of the antimicrobial susceptibility of the causative pathogen is of prime importance in order to put patients on the ideal antimicrobial treatment in a timely fashion. Enterococci accounting for 5–20% of IE poses a serious therapeutic concern because this pathogen is intrinsically resistant to most of the antibiotics currently available [3,4]. Although intravenous ampicillin 12g/24 h in 6 equally divided doses has been recommended as the first line regimen for the enterococcal endocarditis caused by penicillin sensitive strains [1], pharmacological principles of this recommendation have not been thoroughly explored in individual patients.

We report a case of successfully treated community-acquired enterococcal IE complicated with the infected intracranial aneurysm. The clinical and microbiological efficacies of the therapeutic

☆ This case report was selected for the chairperson-recommended paper at the 57th Western Japan Branch Meeting for The Japanese Society of Chemotherapy (Nov. 26 to 28, 2009, Nagoya Congress Center).

* Corresponding author. 5-1-1, Nabeshima, Saga 849-8501, Japan. Tel.: +81 952 34 2184; fax: +81 952 34 3294.
E-mail address: aokiy3@cc.saga-u.ac.jp (Y. Aoki).

http://dx.doi.org/10.1016/j.jiac.2014.07.011
1341-321X/

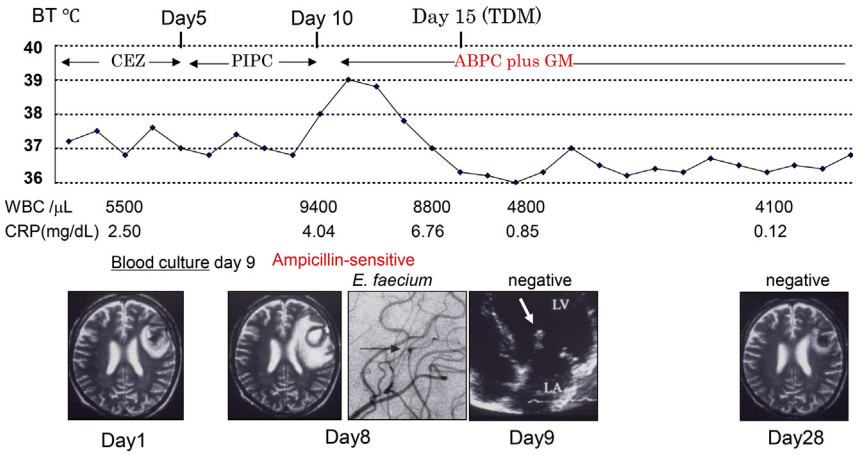

Fig. 1. Clinical course of the patient. MRI of the brain on the day 1, 8, and 28 are shown. The angiography of the brain disclosed pseudoaneurysm formation (day 8: black arrow) and echocardiography showed vegetation of the mitral valve (day 9: white arrow, LA: left atrium, LV: left ventricle). Aortic and mitral valve replacement was performed on the day 40.

strategy with penicillin antibiotics are discussed with special references to pharmacokinetic-pharmacodynamic profile.

2. Case report

A 74 year-old male patient suddenly developed aphasia and apraxia without complaining of headache or nausea. He was right-handed, previously in good health, except for the low grade fever of 2-weeks' duration prior to the presentation. His past medical history was not evident for the risk of atherosclerosis except for his age. His body temperature was 37.7 °C, pulse 92/min, and blood pressure 138/90 mmHg. The peripheral WBC count was 5800/μl, and C-reactive protein 2.5 mg/dL. The magnetic resonance imaging (MRI) of the brain showed a 2 cm hemorrhagic lesion at the periphery of the left temporo-frontal area, surrounded by minimum subarachnoid hemorrhage. The patient was admitted to the neurosurgery division and immediately put on hypertonic fluid therapy to lower the intracranial pressure. Because he had moderate grade of fever, cefazolin (CEZ) 2 g every 12 h was also started, then switched on the 5th day to piperacillin (PIPC) 2 g every 8 h for suspected bacterial infection of unspecified cause. On the 10th hospital day, he still manifested significant aphasia and fever. The follow-up brain MRI showed enlargement of the lesion, and the digital subtraction angiography (DSA) detected a 2 mm fusiform staining of the cortical branch of the precentral artery, suggesting the presence of pseudoaneurysm (Fig. 1). Upon consultation to infectious disease, two sets of blood culture were drawn while the patient was on intravenous PIPC, which yielded Gram-positive diplococcus suggestive of enterococci. Physical examination at this point of time revealed Levine III/VI systolic murmur at the apex, and diastolic murmur of the same magnitude over the midsternum. No mucocutaneous lesion suggestive of capillary damage was found. Neurological findings were not evident except for speech disturbance. The transthoracic echocardiography disclosed 10 mm vegetation of the anterior mitral leaflet and 8 mm vegetation of the right coronary cusp of the aortic valve. Since these findings were consistent with the definite diagnosis of IE [5], the cerebral hemorrhage was deemed to have resulted from the ruptured IIA.

The antimicrobial treatment was then switched from PIPC to a combination therapy of ampicillin (ABPC) 2 g every 4 h and gentamicin (GM) 60 mg every 8 h as a recommended therapy for native valve IE due to penicillin-sensitive enterococci [1]. The positive blood culture was identified as ampicillin-sensitive *Enterococcus faecium* (VITEK system; bioMerieux Japan) with the MIC of PIPC, ABPC, and GM determined by microdilution method (IA20MIC mkII; Koden Industry) being 16 mcg/mL, 4 mcg/mL, and 8 mcg/mL, respectively.

At the time of 25th ABPC administration, steady state serum concentrations of ABPC were measured by high performance liquid chromatography (HPLC) as previously reported [6]. The peak concentration of ABPC was 83.1 mcg/mL, a value that is very close to the one reported in a recent review [7]. The trough and the mean concentration was 25.8 mcg/mL, and 50.8 mcg/mL (Table 1). The pharmacokinetic parameters of ABPC were volume of distribution (VD) 0.45 L/kg (normal value: 0.3 L/kg), total clearance 10.3 L/h (normal value: 13.0 L/h) and half-life ($T_{1/2}$) 1.8 h (normal value: 1.0 h) [8]. Hence, the percent-time of dosing interval during which serum ABPC exceeds MIC (time above MIC; T > MIC) was apparently 100%. As shown in Fig. 1, the patient's became afebrile five days after starting ABPC plus GM therapy, and the follow up blood cultures turned negative.

The patient's aphasia also showed marked improvements in response to the combined antimicrobial therapy, which was in parallel with the marked resolution of the cerebral hemorrhage (Fig. 1). The intravenous ABPC and GM were continued for 6 weeks.

Table 1
Pharmacokinetic-pharmacodynamic analyses of ampicillin (patient's PK) and piperacillin (population PK).

	Ampicillin 2 g over 30 min, q4h	Piperacillin 2 g over 30 min, q8h	
Serum concentration (mcg/mL)	Peak 83.1 Trough 25.8 Mean 50.8	Peak 223[c]	
Total clearance	10.3 liter/h[b]	11.7 liter/h[c]	[1.36 × CLcr] + 1.50 (mL/min/kg)[d]
Volume of distribution (VD)	0.45 liter/kg[b]	11.8 liter[c]	0.18 liter/kg[d]
Half-life ($T_{1/2}$)	1.8 h	1.05 h[c]	0.93 h[d]
MIC against the *E. faecium* strain[a]	4 mcg/mL	16 mcg/mL	
% time > MIC	100%	32.4%[c,e]	20.1%[d,e]

[a] Minimum inhibitory concentrations were determined by microdilution method.
[b] Serum concentrations of ABPC were determined as describes previously [6]. Total clearance, VD, and $T_{1/2}$ of ABPC were determined based on the Sawchuk–Zaske method [17] with one compartmental model equations for intermittent intravenous infusion.
[c] Median value of PK parameters from 26 subjects [15].
[d] PK parameters [16].
[e] % time > MIC for PIPC = ln [Dose/(VD × MIC)] × [$T_{1/2}$/ln (2)] × [100/dosing interval].

Please cite this article in press as: Urakami T, et al., Enterococcal endocarditis complicated with ruptured infected-intracranial aneurysm: With pharmacokinetic-pharmacodynamic documentation in proof of the successful antimicrobial treatment, J Infect Chemother (2014), http://dx.doi.org/10.1016/j.jiac.2014.07.011