Implementation of Clinical Practice Policy on the Continuous Intravenous Administration of Amphotericin B Deoxycholate

Pasri Maharom MD*, Visanu Thamlikitkul MD*

*Department of Medicine, Faculty of Medicine Siriraj Hospital, Mahidol University

Background: *Systemic fungal infections have significantly increased. The mainstay of treatment is amphotericin B deoxycholate. A limitation of using amphotericin B includes infusion-related reactions and nephrotoxicity. A continuous infusion of amphotericin B was found to reduce nephrotoxicity and infusion-related reactions.*
Objective: *To implement clinical practice policy on the continuous intravenous administration of amphotericin B in the patients hospitalized in general medical wards at Siriraj Hospital.*
Method: *A one-page evidence-based clinical practice policy on continuous intravenous administration of amphotericin B was prepared and disseminated to all general medical wards in Siriraj Hospital. The information on the patients who received amphotericin B treatment between March 2004 and March 2006 was collected. The data were analyzed using descriptive statistics, univariate analysis and multiv ariate analysis as appropriate. A p-value of < 0.05 was considered statistically significant.*
Results: *Of 166 courses of amphotericin B treatment in 148 patients, 102 courses (61.4%) were given continuous intravenous administration of amphotericin B (CI group) and 64 courses (38.6%) were given conventional 4-to 6-hour intravenous administration (RI group). The mean age of the patients in the CI group was significantly greater than that in the RI group. The CI group had more patients with neutropenia with persistent fever whereas the RI group had more patients with HIV/AIDS and cryptococcal meningitis. The incidence of amphotericin B-related nephrotoxicity was 27.5% in the CI group compared with 39.1% in the RI group ($p=0.164$). Chills were observed in 6.9% of the patients in the CI group compared with 26.6% in the RI group ($p=0.001$). Overall mortality at the end of therapy was significantly higher in the CI group. However, most of the deaths in the CI group were unrelated to fungal infections or amphotericin administration.*
Conclusion : *Continuous infusion of amphotericin B was associated with a decrease in infusion-related reactions and tended to have less nephrotoxicity than those in the 4-to 6-hour infusion group.*

Keywords : *Continuous-infusion, Amphotericin B, Nephrotoxicity, Infusion-related reactions*

J Med Assoc Thai 2006; 89 (Suppl 5): S118-24
Full text. e-Journal: *http://www.medassocthai.org/journal*

Systemic fungal infections have significantly increased over the past 30 years[1-4]. Systemic opportunistic fungal infections constitute a leading cause of morbidity and mortality in neutropenic patients[5]. In addition, HIV-infected patients often have a variety of fungal infections, especially those who have CD4+ T lymphocyte counts of <50 cells/μL[6,7]. The common causative agents in HIV-infected patients include *Cryptococcus neoformans*, *Histoplasma capsulatum*, and *Penicillium maneffei* [8].

The mainstay of treatment for these patients is amphotericin B deoxycholate despite it being associated with significant drug-related adverse effects, especially infusion-related reactions, [9-11] and nephrotoxicity [12,13]. Over the past few years, several randomized trials revealed different strategies to reduce AmB-induced renal toxicity. These strategies included sodium supplementation,[14,15] concurrent administration of low-dose dopamine,[16] correction of potassium depletion[17] and slow infusion rates. Many recent

Correspondence to : *Visanu Thamlikitkul, Department of Medicine, Faculty of Medicine Siriraj Hospital, Phone 02-412-5994 E-Mail : sivth@mahidol.ac.th*

clinical trials of new antifungal agents have observed better outcomes and lower drug-related toxicity[18-22]. However, amphotericin B remains a cornerstone of antifungal therapy for patients with opportunistic fungal infections. Recently, continuous infusion of amphotericin B has been found to reduce the incidence of nephrotoxicity and infusion-related reactions, compared with traditional administration of the same amount of the drug over 4–6 h[23-26] as well as the results from local randomized controlled study conducted at Ramathibodi Hospital [27]. This mode of administration of amphotericin B seems to be effective in reducing the adverse effects of amphotericin B [28] and is feasible in our setting. This prompted us to implement clinical practice policy based on continuous intravenous administration of amphotericin B deoxycholate in the patients hospitalized in the general medical wards at Siriraj Hospital.

Material and Method

A one-page evidence-based clinical practice policy on continuous intravenous administration of amphotericin B containing a description of the problem of using amphotericin B, recommendation on using continuous intravenous administration of amphotericin B, grade of recommendation and references was prepared. The clinical practice policy on continuous intravenous administration of amphotericin B was circulated to 10 general medical wards at Siriraj Hospital in March 2004. The decision to use continuous infusion or 4-to 6-hour infusion of amphotericin B was made by the responsible attending physicians. The use of medications to prevent infusion-related reactions was decided by attending physicians. The study was approved by the ethics committee on human research of the Faculty of Medicine, Siriraj Hospital. We collected the information on the patients who received amphotericin B who had serum creatinine <3 mg/dl. The patients who needed amphotericin B could receive a continuous infusion (CI group) or 4-to 6-hour infusion (RI group) of amphotericin B. In the patients who received continuous infusion of amphotericin B, amphotericin B at the appropriate dosage was added in 500 ml of 5% glucose without any additives and given intravenously as a continuous infusion over 24 hours. Medications to prevent any infusion-related reaction and intravenous saline were administered whenever appropriate.

Infusion-time was recorded in all cases. All infusion-related conditions were recorded including chills, nausea, vomiting, and phlebitis. Serum creatinine was measured at least twice a week and creatinine clearance (CrCl) was calculated by the Cockcroft-Gault formula[29]. Renal impairment was defined as a doubling of baseline serum creatinine and was calculated as a creatinine ratio (peak serum creatinine during amphotericin B administration/baseline serum creatinine).

The number of patients required for this study was assessed by the assumption that a rate of renal impairment in the CI group was 20% $\pm$ 7.5%. That was clinically less than 40% observed in hospitalized patients in the Department of Medicine who received 4-hour amphotericin B infusions in 2002, where 110 courses of CI would be needed at the two-sided significance level of 5%. Multivariate logistic regression analysis was used to adjust for potential confounding variables with regard to renal impairment and outcome. A Mann-Whitney U-test was used for median comparisons.

Results

Baseline characteristics

Of 166 courses of amphotericin B treatment in 148 patients, 102 courses (61.4%) in 91 patients were given by continuous intravenous administration of amphotericin B (CI group) and 64 courses (38.6%) in 57 patients were given by conventional 4-to 6-hour intravenous administration (RI group). The demographics of the patients in both groups are shown in Table 1. There were no significant differences in gender, duration of treatment or total dose of amphotericin B. However, the patients in the CI group were older than those in RI group (40 (15-74) vs 36 (16-68) years, p = 0.03) and had less HIV/AIDS than those in the RI group (21.6% vs 40.6%, p = 0.01). The number of patients in the CI group who received amphotericin B due to neutropenia with refractory fever was significantly greater than that in the RI group, 64.7 % vs 42.2% (p = 0.007) as shown in Table 2. Cryptococcal infections were more common in the patients in the RI group when compared with those in the CI group (34.4% vs 17.7%, p = 0.02). The baseline serum BUN was higher in the CI group than in the RI group (16.4 $\pm$ 14.5 mg/dl vs 13.9 $\pm$ 8.8, p = 0.03), but the baseline values of serum creatinine and calculated creatinine clearance were not significantly different between both groups. The use of medications to prevent infusion related reactions did not differ between the CI group and the RI group.

Outcomes

Nephrotoxicity, infusion-related reactions, and

Table 1. Demographic data of the patients

	Infusion rate		
	CI group (n = 91)	RI group (n = 57)	p-value
Median age, years (range)	40 (15-74)	36 (16-68)	0.03
Female, No. (%) of the patients	42 (41.2)	28 (43.8)	0.43
Median (range) days of treatment	11 (1-147)	14 (5-121)	0.11
Median (range) mg accumulative dose	400 (60-1880)	645 (180-5820)	0.17
Diagnosis, no.(%) of the patients			
- HIV/AIDS	22 (21.6)	26 (40.6)	0.01
- Acute myeloid leukemia	40 (39.2)	24 (37.5)	
- Non-Hodgkin's lymphoma	12 (11.8)	2 (3.1)	
- Acute lymphocytic leukemia	8 (7.8)	4 (6.3)	
- Severe aplastic anemia	6 (5.9)	1 (1.6)	
- Chronic myeloid leukemia	5 (4.9)	3 (4.7)	
- Others	9 (8.8)	4 (6.3)	
Concurrent treatment of nephrotoxic drugs	56 (54.9)	30 (46.9)	0.40
- Aminoglycosides	30 (29.4)	20 (31.3)	
- Vancomycin	14 (13.7)	4 (6.3)	
- Both	12 (11.8)	6 (9.4)	
- Others	1 (1)	0 (0)	

Table 2. Indications for amphotericin B treatment

	CI group (102 courses in 91 patients)	RI group (64 courses in 57 patients)	p-value
Refractory fever in neutropenia (ANC < 500/cumm) *	66 (64.7%)	27 (42.2%)	0.005
Cryptococcal infection	18 (17.7%)	22 (34.4%)	0.02
Aspergillus infection	8 (7.9%)	9 (14.1%)	
Penicillium infection	4 (3.9%)	0	
Histoplasma infection	2 (2%)	2 (3.1%)	
Mucormycoses	2 (2%)	1 (1.6%)	
Candidemia	2 (2%)	2 (3.1%)	
Cladophialophora bantiana brain abscess	0	1 (1.6%)	

* ANC means absolute neutrophil count

clinical outcomes of the patients are shown in Table 3. The nephrotoxicity was observed in 27.5% in the CI group and 39.1% in the RI group ($p = 0.2$), the relative risk of nephrotoxicity of the CI group when compared with that in the RI group was 0.70 (95% CI 0.45 to 1.09) and the relative risk reduction was 30% (95% CI -12% to 56%). The incidence of chills was 6.9% in the CI group and 26.6% in the RI group ($p = 0.001$), the relative risk was 0.26 (95% CI-0.11 to 0.59) and the relative risk reduction was 74.1%. There was no significant difference between nausea of 6.9% in the CI group and 12.5% in the RI group ($p = 0.169$) and phlebitis 22.5% in the CI group and 18.8% in the RI group ($p = 0.352$). Treatment failure was found in three patients with invasive aspergillosis who received continuous infusion of amphotericin B. Overall mortality at the end of therapy was significantly higher in the CI group (34.1%) than in the RI group (17.5%) ($p=0.05$), the relative risk was 1.35 (95% CI 1.06 to1.72). However most of the deaths in the CI group were unrelated to fungal infections. Chances of survival were significantly associated with age, febrile neutropenia, cryptococcal meningitis and AIDS from univariate analysis as shown in Table 4. However, a multivariate analysis

Table 3. Nephrotoxicity, infusion-related reactions and clinical outcomes of the patients

	CI group (102 courses in 91 patients)	RI group (64 courses in 57 patients)	p-value	Relative risk (95% CI)
Nephrotoxicity	28 (27.5%)	25 (39.1%)	0.16	0.70 (0.45-1.09)
Infusion related reactions				
- chills	7 (6.9%)	17 (26.6%)	0.001	0.26 (0.11-0.59)
- nausea	7 (6.9%)	8 (12.5%)	0.34	0.55 (0.21-1.44)
- phlebitis	23 (22.5)	2 (18.8)	0.352	1.20 (0.64-2.24)
Treatment failure	3 (2.9%)	0	0.3	not available
Overall mortality	31 (34.1%)	10 (17.5%)	0.05	1.35 (1.06-1.72)
Death due to fungal infections	2 (2.2%)	2 (3.5%)	0.6	0.6 (0.1-6.4)
Death due to other causes	29 (31.9%)	8 (14%)	0.02	2.8 (1.1-7.5)

Table 4. Univariate and multivariate analyses of overall mortality

	Outcome		Univariate analysis		Multivariate analysis	
	Survival	Death	p-value	OR (95%CI)	p-value	OR (95%CI)
Age > 36 year	54 (64.3%)	30 (35.7%)	0.021	0.78 (0.64-0.94)	0.057	
Febrile neutropenia	54 (65.1%)	29 (34.9%)	0.042	0.80 (0.66-0.97)	0.706	
AIDS	38 (88.4%)	5 (11.6%)	0.009	1.34 (1.13-1.60)	0.008	0.252 (0.091-0.696)
Cryptococcal meningitis	30 (90.9%)	3 (9.1%)	0.013	1.36 (1.15-1.61)	0.346	
Continuous infusion of amphotericin B	60 (65.9%)	31 (34.1%)	0.046	0.80 (0.66-0.97)	0.099	

revealed only AIDS was significantly associated with mortality, and continuous infusion of amphotericin B had not contributed to mortality.

Discussion

The clinical practice policy on continuous intravenous infusion of amphotericin B deoxycholate used in our study was based on the evidence from a randomized controlled study comparing continuous infusion of amphotericin B with 4-hour infusion regarding the incidence of the nephrotoxicity and infusion-related reactions [22]. The nephrotoxicity was decreased from 38% to 15% and infusion-related reactions from 63% to 20%. Subsequent studies also confirmed the safety and efficacy of continuous infusion of amphotericin B [23-26]. Therefore, our study was not intended to repeat any randomized controlled study, but rather to gain further knowledge. The implementation of the clinical practice policy in our study was only meant to raise awareness of the prescribers by disseminating such a clinical practice policy and the decision to use continuous infusion or 4-hour infusion of amphotericin B was made by the responsible attending physicians. As a result, only 61.4% of amphotericin B treatments followed the recommendation in the clinical practice policy. This observation confirmed the previous findings that dissemination of the guidelines was less effective than multifaceted interventions [30-31]. Since our study was not a randomized controlled trial, many important factors relevant to the severity of infection and prognosis of the treatment were not balanced between the group receiving continuous infusion of amphotericin B and that receiving 4-hour infusion. The patients in the CI group were older and had neutropenia with refractory fever significantly more often than those in the RI group. On the other hand, HIV/AIDS and cryptococcal meningitis were greater in the RI group. All these different factors seemed to be unfavorable for the patients in the continuous infusion group.

The incidence of nephrotoxicity in the RI group was 39%, comparable to 38% observed in the randomized controlled study. However, it was 27.5% in the CI group, higher than 15% observed in the randomized controlled study. As a result, the incidence of the nephrotoxicity of the patients in the CI group was not significantly different from that in the RI group. This could be explained by the small sample size since the relative risk reduction of nephrotoxicity was 30%.

We did not include fever as an infusion-related reaction because most of the patients who were receiving amphotericin B had fever at the beginning of amphotericin B infusion. Superficial thrombophlebitis from chemical irritation in the continuous infusion regimen was not significantly greater than that in the RI group.

Treatment failure was found in three patients in the CI group. All of them had invasive aspergillosis and two of them were switched to voriconazole therapy. These failures might not be related to continuous infusion of amphotericin B since it is well recognized that many patients of invasive aspergillosis do not respond well to amphotericin B deoxycholate. If these three patients had received 4-hour infusion of amphotericin B, they would not have responded to the treatment either. The overall mortality in the CI group was found to be significantly higher than that in the RI group. However, most of the deaths in the CI group were unrelated to fungal infections or continuous infusion of amphotericin B. The subgroup analyses of the mortality group revealed that the significant difference was confined to deaths from other causes. These observations might be due to the differences in many important factors of the patients between the CI group and the RI group mentioned earlier. Multivariate analysis also confirmed that continuous infusion of amphotericin B was not associated with an increase in mortality.

Conclusion

Continuous infusion of amphotericin B was associated with a decrease in infusion-related reactions and tended to have less nephrotoxicity than 4-to 6-hour infusion.

Acknowledgements

The authors wish to thank Mr. Sutthipol Udompanthurak for statistical analyses and The Thailand Research Fund for supporting the study.

References

1. Beck-Sague C, Jarvis WR. Secular trends in the epidemiology of nosocomial fungal infections in the United States, 1980-1990. National Nosocomial Infections Surveillance System. J Infect Dis 1993; 167: 1247-51.
2. Bodey G, Bueltmann B, Duguid W, Gibbs D, Hanak H, Hotchi M, et al. Fungal infections in cancer patients: an international autopsy survey. Eur J Clin Microbiol Infect Dis 1992; 11: 99-109.
3. McNeil MM, Nash SL, Hajjeh RA, Phelan MA, Conn LA, Plikaytis BD, et al. Trends in mortality due to invasive mycotic diseases in the United States, 1980-1997. Clin Infect Dis 2001; 33: 641-7.
4. Richardson MD, Kokki MH. Diagnosis and prevention of fungal infection in the immunocompromized patient. Blood Rev 1998; 12: 241-54.
5. Kuderer NM, Dale DC, Crawford J, Cosler LE, Lyman GH. Mortality, morbidity, and cost associated with febrile neutropenia in adult cancer patients. Cancer 2006; 106: 2258-66.
6. Chang LW, Phipps WT, Kennedy GE, Rutherford GW. Antifungal interventions for the primary prevention of cryptococcal disease in adults with HIV. Cochrane Database Syst Rev 2005; CD004773.
7. Kaplan JE, Masur H, Holmes KK. Guidelines for preventing opportunistic infections among HIV-infected persons—2002. Recommendations of the U.S. Public Health Service and the Infectious Diseases Society of America. MMWR Recomm Rep 2002; 51: 1-52.
8. Benson CA, Kaplan JE, Masur H, Pau A, Holmes KK. Treating opportunistic infections among HIV-exposed and infected children: recommendations from CDC, the National Institutes of Health, and the Infectious Diseases Society of America. MMWR Recomm Rep 2004; 53: 1-112.
9. Gallis HA, Drew RH, Pickard WW. Amphotericin B: 30 years of clinical experience. Rev Infect Dis 1990; 12: 308-29.
10. Goodwin SD, Cleary JD, Walawander CA, Taylor JW, Grasela TH Jr. Pretreatment regimens for adverse events related to infusion of amphotericin B. Clin Infect Dis 1995; 20: 755-61.
11. Grasela TH Jr, Goodwin SD, Walawander MK, Cramer RL, Fuhs DW, Moriarty VP. Prospective surveillance of intravenous amphotericin B use patterns. Pharmacotherapy 1990; 10: 341-8.
12. Deray G. Amphotericin B nephrotoxicity. J Antimicrob Chemother 2002; 49(Suppl 1): 37-41.
13. Girois SB, Chapuis F, Decullier E, Revol BG. Adverse effects of antifungal therapies in invasive fungal infections: review and meta-analysis.

Eur J Clin Microbiol Infect Dis 2006; 25: 138-49.
14. Arning M, Scharf RE. Prevention of amphotericin-B-induced nephrotoxicity by loading with sodium chloride: a report of 1291 days of treatment with amphotericin B without renal failure. Klin Wochenschr 1989; 67: 1020-8.
15. Heidemann HT, Gerkens JF, Spickard WA, Jackson EK, Branch RA. Amphotericin B nephrotoxicity in humans decreased by salt repletion. Am J Med 1983; 75: 476-81.
16. Camp MJ, Wingard JR, Gilmore CE, Lin LS, Dix SP, Davidson TG, et al. Efficacy of low-dose dopamine in preventing amphotericin B nephrotoxicity in bone marrow transplant patients and leukemia patients. Antimicrob Agents Chemother 1998; 42: 3103-6.
17. Bernardo JF, Murakami S, Branch RA, Sabra R. Potassium depletion potentiates amphotericin-B-induced toxicity to renal tubules. Nephron 1995; 70: 235-41.
18. Dupont B. Overview of the lipid formulations of amphotericin B. J Antimicrob Chemother 2002; 49 (Suppl 1): 31-6.
19. Herbrecht R, Denning DW, Patterson TF, Bennett JE, Greene RE, Oestmann JW, et al. Voriconazole versus amphotericin B for primary therapy of invasive aspergillosis. N Engl J Med 2002; 347: 408-15.
20. Johnson PC, Wheat LJ, Cloud GA, Goldman M, Lancaster D, Bamberger DM, et al. Safety and efficacy of liposomal amphotericin B compared with conventional amphotericin B for induction therapy of histoplasmosis in patients with AIDS. Ann Intern Med 2002; 137: 105-9.
21. Jorgensen KJ, Gotzsche PC, Johansen HK. Voriconazole versus amphotericin B in cancer patients with neutropenia. Cochrane Database Syst Rev 2006; CD004707.
22. Leenders AC, Daenen S, Jansen RL, Hop WC, Lowenberg B, Wijermans PW, et al. Liposomal amphotericin B compared with amphotericin B deoxycholate in the treatment of documented and suspected neutropenia-associated invasive fungal infections. Br J Haematol 1998; 103: 205-12.
23. Hiemenz JW. Amphotericin B deoxycholate administered by continuous infusion: does the dosage make a difference? Clin Infect Dis 2003; 36: 952-3.
24. Imhof A, Walter RB, Schaffner A. Continuous infusion of escalated doses of amphotericin B deoxycholate: an open-label observational study. Clin Infect Dis 2003; 36: 943-51.
25. Peleg AY, Woods ML. Continuous and 4 h infusion of amphotericin B: a comparative study involving high-risk haematology patients. J Antimicrob Chemother 2004; 54: 803-8.
26. Uehara RP, Sa VH, Koshimura ET, Prudente FV, Tucunduva LT, Goncalves MS, et al. Continuous infusion of amphotericin B: preliminary experience at Faculdade de Medicina da Fundacao ABC. Sao Paulo Med J 2005; 123: 219-22.
27. Banpamai O. Comparison of amphotericin B deoxycholate induced nephrotoxicity between 6-hour versus 24-hour continuous infusion: a randomized controlled trial. Research Report submitted to Infections Diseases Association of Thailand, 2004.
28. Eriksson U, Seifert B, Schaffner A. Comparison of effects of amphotericin B deoxycholate infused over 4 or 24 hours: randomised controlled trial. BMJ 2001; 322: 579-82.
29. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron 1976; 16: 31-41.
30. Grimshaw JM, Thomas RE, MacLennan G, Fraser C, Ramsay CR, Vale L, et al. Effectiveness and efficiency of guideline dissemination and implementation strategies. Health Technol Assess 2004; 8: iii-iv, 1-72.
31. Gross PA, Pujat D. Implementing practice guidelines for appropriate antimicrobial usage: a systematic review. Med Care 2001; 39: II55-69.

การใช้ยาแอมโฟเทอริซินบีหยดเข้าหลอดเลือดดำอย่างต่อเนื่องใน 24 ชั่วโมงตามนโยบายเวชปฏิบัติ

ภาศรี มหารมณ์, วิษณุ ธรรมลิขิตกุล

วัตถุประสงค์: *เพื่อทราบผลการใช้ยาแอมโฟเทอริซินบีหยดเข้าหลอดเลือดดำอย่างต่อเนื่องใน 24 ชั่วโมงตามนโยบายเวชปฏิบัติในผู้ป่วยสามัญ ภาควิชาอายุรศาสตร์ โรงพยาบาลศิริราช เนื่องจากพบมีหลักฐานว่าการใช้ยาดังกล่าวลดพิษต่อไตได้*

วัสดุและวิธีการ: *เตรียมนโยบายเวชปฏิบัติเรื่องการใช้ยาแอมโฟเทอริซินบีหยดเข้าหลอดเลือดดำอย่าง ต่อเนื่องใน 24 ชั่วโมงแทนการใช้ยา 4-6 ชั่วโมง และเผยแพร่นโยบายเวชปฏิบัตินี้แก่แพทย์ที่หอผู้ป่วยสามัญ ภาควิชาอายุรศาสตร์ ตั้งแต่เดือนมีนาคม พ.ศ. 2547 ถึงมีนาคม พ.ศ. 2549 นำข้อมูลมาวิเคราะห์ด้วยสถิติเชิงพรรณนา, การวิเคราะห์ univariate และ multivariate*

ผลการศึกษา: *มีการใช้ยาแอมโฟเทอริซินบีทั้งหมด 166 ครั้งในผู้ป่วย 148 ราย การใช้ยาในผู้ป่วย 102 ครั้ง (64%) เป็นการใช้ยาอย่างต่อเนื่อง 24 ชั่วโมง (CI) ส่วนอีก 64 ครั้ง (38.6%) ใช้ยา 4-6 ชั่วโมง (RI) อายุเฉลี่ยและภาวะไข้ในขณะที่มีเม็ดเลือดขาวต่ำในกลุ่ม CI มากกว่ากลุ่ม RI ส่วนกลุ่ม RI มีผู้ป่วยเอดส์ และเยื่อหุ้มสมองอักเสบจากเชื้อคริบโตคอคคัสมากกว่ากลุ่ม CI พบอัตราการเกิดพิษต่อไต 27.5 % ในกลุ่ม CI เทียบกับ 39.1% ในกลุ่ม RI (p = 0.164) ผลข้างเคียงโดยเฉพาะอาการสั่นขณะให้ยา 6.9% ในกลุ่ม CI เทียบกับ 26.6% ในกลุ่ม RI (p = 0.001) และพบอัตราตายรวมในกลุ่ม CI มากกว่ากลุ่ม RI อย่างมีนัยสำคัญ แต่เป็นอัตราตายจากสาเหตุอื่นที่ไม่ใช่จากการได้รับยาแอมโฟเทอริซินบีหยดเข้าหลอดเลือดดำอย่างต่อเนื่อง*

สรุป: *การนำแนวทางเวชปฏิบัติใช้ยาแอมโฟเทอริซินบีหยดเข้าหลอดเลือดดำอย่างต่อเนื่องใน 24 ชั่วโมง มาใช้ในภาควิชาอายุรศาสตร์สามารถลดปฏิกิริยาของยาได้และมีแนวโน้มที่จะลดพิษต่อไตได้มากกว่าการใช้ยาหยดเข้าหลอดเลือดดำใน 4-6 ชั่วโมง*