Research Article

EVALUATION OF CEFOPERAZONE/SULBACTAM AND VITAMIN K USE IN PATIENTS WITH BACTERIAL INFECTIONS

THEERAPONG SEESIN[1]*, PITIPONG PENGSUPSIN[1], SARAWUT WEESAPHEN[1], PEERAYA SRIPHONG[1], UAEPONG LIMPAPANASIT[2], SIRIN BHONGCHIRAWATTANA[3]

[1]Department of Clinical Pharmacy, Faculty of Pharmacy, Mahasarakham University, Kantharawichai, Maha Sarakham, Thailand. [2]Department of Internal Medicine, Mahasarakham Hospital, Muang Maha Sarakham, Maha Sarakham, Thailand. [3]Department of Pharmacy, Mahasarakham Hospital, Muang Maha Sarakham, Maha Sarakham, Thailand. Email: theerapong.s@msu.ac.th

ABSTRACT

Objective: The objectives of this study were to evaluate the effects of Vitamin K use for bleeding or coagulopathies prevention and to assess the occurrence of drug-related problems in patients receiving cefoperazone/sulbactam.

Methods: The prospective study was conducted between January and April 2018 at 5 general medicine wards in Mahasarakham Hospital, Thailand. Patients above 18 years of age with bacterial infections who received cefoperazone/sulbactam concurrent with Vitamin K were included. Rate of bleeding, coagulopathies, and drug-related problems were evaluated.

Results: Forty-three eligible patients enrolled in this study. Most were women (72.1%), average ages were 64.7 years old and 93.0% had comorbidities (most were diabetes, hypertension, and chronic kidney disease). High doses of cefoperazone/sulbactam have been used in 35 patients (81.4%). Gastrointestinal bleeding occurred in one patient (8.3%), 24 patients had prolonged prothrombin time (55.8%), and 8 patients had prolonged activated partial thromboplastin time (18.6%). Anticipated risk factors were not associated with bleeding. Drug-related problems were missing of dose adjustment for cefoperazone/sulbactam in patients with renal impairment (4.7%), drug interactions between warfarin and Vitamin K (4.7%), and drug allergy (2.3%).

Conclusion: This study found that cefoperazone/sulbactam aggravated bleeding and coagulopathies despite using Vitamin K for prevention. We support the use of Vitamin K for the prevention of bleeding in high-risk patient such as elderly who receive cefoperazone/sulbactam.

Keywords: Cefoperazone/sulbactam, Vitamin K, Bleeding, Coagulopathies.

INTRODUCTION

Cefoperazone is a beta-lactam antibiotic containing N-methylthiotetrazole side chain which may aggravate hypoprothrombinemia and bleeding by inhibiting hepatic Vitamin K epoxide reductase [1]. This medication is available in Thailand as combination with sulbactam; a beta-lactamase inhibitor. Previous study reported the use of cefoperazone in patients with bacterial infections caused prolonged prothrombin time 3.6 times compared to ceftizoxime and ceftazidime [2]. The use of Vitamin K for the prevention of bleeding or hypoprothrombinemia in patients receiving cefoperazone is controversy [3,4]. This study was performed to evaluate the effects of Vitamin K use for bleeding prevention and to assess the occurrence and character of drug-related problems in patients receiving cefoperazone/sulbactam at general medicine wards, Mahasarakham Hospital, Thailand.

METHODS

The prospective study was conducted between January and April 2018 at 5 general medicine wards in Mahasarakham Hospital, Thailand. Patients above 18 years of age with bacterial infections who received cefoperazone/sulbactam at least one dose concurrent with Vitamin K were included in the study. Patients with a history of allergic reactions to cefoperazone/sulbactam and Vitamin K, coagulation laboratory data missing or presented with health problems that interfere the evaluation of bleeding conditions such as severe skin lesion, and patients presented with other bleeding conditions such as gastrointestinal bleeding and intracranial hemorrhage before receive cefoperazone/sulbactam were excluded from the study. Data were obtained by patient profiles review and clinical observation. Rate of bleeding events and coagulation laboratory abnormalities, risk factors affected coagulopathies, and drug-related problems were evaluated. The descriptive statistics including percentage and mean were used to determine demographic data and rate of events. Chi-square test was used to determine the association between coagulopathies and risk factors. The research protocol has been reviewed and accepted by ethical committees of Mahasarakham University and Mahasarakham Hospital.

RESULTS

There were 43 eligible patients enrolled in the study. Most patients were female (72.1%) and average age was 64.7 years old. Indication for the use of cefoperazone/sulbactam was pneumonia mostly, and most patients received this medication in high dose (81.4%). Demographic data of the patients are presented in Table 1.

There was one patient experienced gastrointestinal bleeding (2.3%). Prolonged prothrombin time occurred in 24 patients (55.8%) and prolonged activated partial thromboplastin time occurred in 8 patients (18.6%). Risk factors related to bleeding such as concurrent use of antithrombotics (warfarin, unfractionated heparin, enoxaparin, and aspirin), renal impairment, and hepatic impairment were not associated with coagulopathies (Table 2).

Drug-related problems occurred in 5 patients (11.6%) including no dose adjustment for cefoperazone/sulbactam in patients with renal

Table 1: Demographic data of eligible patients

Demographic data	n=43 (%)
Sex	
Male	12 (27.9)
Female	31 (72.1)
Age (mean±SD)	64.7±15.9
Comorbidities	
Diabetes mellitus	12 (27.9)
Hypertension	24 (55.8)
Chronic kidney disease	12 (27.9)
Dyslipidemia	21 (48.8)
Gouty arthritis	1 (2.3)
Myocardial infarction	1 (2.3)
Heart failure	2 (4.65)
None	3 (7.0)
Abnormal aspartate aminotransferase (>200 IU/L)	6 (14.0)
Abnormal alanine aminotransferase (>200 IU/L)	4 (9.3)
Abnormal serum creatinine (>2 mg/dl)	11 (25.6)
Concurrent use of medication affected bleeding	
Warfarin	2 (4.65)
Unfractionated heparin	1 (2.3)
Enoxaparin	1 (2.3)
Aspirin	8 (18.6)
Duration of cefoperazone/sulbactam use (days)	6.9±4.3
Indication of cefoperazone/sulbactam	
Pneumonia	36 (83.7)
Septicemia	5 (11.6)
Urinary tract infections	1 (2.3)
Intra-abdominal infections	1 (2.3)
Dose of cefoperazone/sulbactam (1:1 ratio)	
≤3 g/day	8 (18.6)
>3 g/day	35 (81.4)

Table 2: Risk factors related to bleeding or coagulopathies

Risk factors	Exposed patients		Unexposed patients		Odds ratio (95% CI)
	Total	Outcome (%)	Total	Outcome (%)	
Warfarin use	2	1 (50.0)	41	23 (56.1)	1.27 (0.1–21.8)
Heparin use	1	1 (100)	42	23 (54.7)	1.83 (1.4–2.4)
Enoxaparin use	1	1 (100)	42	23 (54.7)	1.83 (1.4–2.4)
Aspirin use	8	3 (37.5)	35	21 (60.0)	2.50 (0.5–12.1)
AST>200 IU/L	6	4 (66.7)	37	20 (54.1)	0.58 (0.1–3.6)
ALT>200 IU/L	4	2 (50.0)	39	22 (56.4)	1.29 (0.1–10.1)
SCr>2 mg/dl	11	8 (72.3)	32	16 (50)	0.37 (0.1–1.7)

AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, SCr: Serum creatinine, CI: Confidence interval

impairment (4.7%), warfarin and Vitamin K interaction (4.7%), and allergy to cefoperazone/sulbactam (2.3%).

DISCUSSION

There was still a lack of evidence to confirm clinical significant of cefoperazone/sulbactam-induced bleeding and coagulopathies. Our findings support this hypothesis because there were 2.32% of bleeding, 55.8% prolonged prothrombin time, and 18.6% prolonged activated partial thromboplastin time occurred despite using Vitamin K to prevent. Risk factors that have been anticipated the coagulopathies in this study were concurrent use of antithrombotics, hepatic impairment, and renal impairment, but the results showed no statistically significant. Another risk factor proposed to be associated with coagulopathies was the quite high average age of patients (64.7 years). However, the trend of using this medication in Thailand is rising because of an emerging of multidrug-resistant pathogens such as *Acinetobacter baumannii* [5]. Because of some evidence has showed the efficacy of sulbactam in high dose against this bug, the use of cefoperazone/sulbactam in high-dose was followed which might increase the rate of coagulopathies [6-7]. The dose of cefoperazone/sulbactam over 3 g was used about 81.4% in this study and might lead to develop drug-related problem in the manner

of dosage adjustment in 2 renal impairment patients which has been resolved by pharmacist interventions.

Other drug-related problems were drug interactions and drug allergy. Interactions between warfarin and Vitamin K became significant because of antagonism properties and need to be monitored closely. Drug allergy occurred as it was common side effects of beta-lactams, and the pharmacist had a role to manage this case by review timeline of medications use, assess the possibilities, and gave the intervention to physicians.

CONCLUSION

This study found bleeding and coagulopathies occurred in patients receiving cefoperazone/sulbactam despite concurrent use of Vitamin K. We support the use of Vitamin K to prevent these events, especially for high-risk patient such as elderly.

REFERENCES

1. Shearer MJ, Bechtold H, Andrassy K, Koderisch J, McCarthy PT, Trenk D, *et al.* Mechanism of cephalosporin-induced hypoprothrombinemia: Relation to cephalosporin side chain, Vitamin K metabolism, and vitamin K status. J Clin Pharmacol 1988;28:88-95.

2. Strom BL, Schinnar R, Gibson GA, Brennan PJ, Berlin JA. Risk of bleeding and hypoprothrombinaemia associated with NMTT side chain antibiotics: Using cefoperazone as a test case. Pharmacoepidemiol Drug Saf 1999;8:81-94.
3. Katukuri GR, Maddala RN, Ramamoorthi K, Hande M. Cefoperazone induced gastrointestinal bleeding. J Clin Diagn Res 2016;10:OD10-1.
4. Rockoff SD, Blumenfrucht MJ, Irwin RJ Jr., Eng RH. Vitamin K supplementation during prophylactic use of cefoperazone in urologic surgery. Infection 1992;20:146-8.
5. Apisarnthanarak A, Mundy LM. Mortality associated with pandrug-resistant *Acinetobacter baumannii* infections in Thailand. Am J Infect Control 2009;37:519-20.
6. Chu H, Zhao L, Wang M, Liu Y, Gui T, Zhang J, *et al.* Sulbactam-based therapy for *Acinetobacter baumannii* infection: A systematic review and meta-analysis. Braz J Infect Dis 2013;17:389-94.
7. Qin Y, Zhang J, Wu L, Zhang D, Fu L, Xue X, *et al.* Comparison of the treatment efficacy between tigecycline plus high-dose cefoperazone-sulbactam and tigecycline monotherapy against ventilator-associated pneumonia caused by extensively drug-resistant *Acinetobacter baumannii*. Int J Clin Pharmacol Ther 2018;56:120-9.