Be Careful with Adverse Events Caused by Cefoperazone-Sulbactam

Xianshi Zhou,^{a,b} Fanwei Wu^c

^aEmergency Department, Guangdong Provincial Hospital of Chinese Medicine, Guangzhou, China

^bGuangdong Provincial Key Laboratory of Research on Emergency in TCM, Guangzhou, China

^cFamous Doctor Hall, Bao'an TCM Hospital Group, Shenzhen, China

We read with great interest the article by Liu et al. (1) in an issue of *Antimicrobial Agents and Chemotherapy*. The article concluded that the clinical efficacy of 2 g cefoperazone-sulbactam every 12 h was noninferior to 2 g cefepime every 12 h for patients with hospital-acquired pneumonia/health care-associated pneumonia. Although the study sounds interesting, some important issues should be discussed.

First, Liu et al. should be commended for performing intent-to-treat (ITT) analysis and per-protocol analysis to reduce biases. However, their data set of ITT analysis was questionable. ITT analysis is a statistical method that compares the data between the study groups and control groups after the subjects have been randomly allocated, irrespective of protocol deviations, participant compliance, or withdrawal in each group (2, 3). In the article by Liu et al., after the original random allocation, there were 79 and 87 patients in the cefoperazone-sulbactam group and the cefepime group, respectively; thus, ITT analysis should include 79 and 87 patients in each arm rather than 71 and 83 shown in Table 1. What is more, Table 2 shows that data from only 55 and 64 patients in each group were included to analyze the treatment duration in different treatment arms; thus, we wonder why data were missing for some subjects.

Second, compared with the cefepime arm, the cefoperazone-sulbactam arm had a lower body mass index (BMI) after randomization ($P < 0.05$); then, we wonder whether the randomization was complete. As BMI might affect the mortality of the patients with pneumonia and alter the blood concentration and efficacy of the antibiotics (4), we suggest the authors adjust the variable of BMI in their analysis to make their results more persuasive.

Third, the differences in the ratio of adverse events (AEs) in the two arms should not be ignored. According to Table 4, the death rate in the cefoperazone-sulbactam arm was twice more than in the cefepime arm (37.8% versus 18.2%). The proportion of serious adverse events (SAEs) was almost 3 times in the former arm than the later arm (15.2% versus 5.7%). Considering the many SAEs in the cefoperazone-sulbactam arm, we suggest the safety of cefoperazone-sulbactam should be checked and verified in future large sample studies.

Last, we appreciate Liu et al. for their innovative work, but further studies are needed before any rigorous conclusions can be made.

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We declare that all the authors have participated in the conception or preparation of this manuscript.

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Address correspondence to Fanwei Wu, wfwis09000@126.com.

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