Killing Activity of Ceftazidime and Sulfamethoxazole/Trimethoprim against *P. pseudomallei*

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Treatment regimens of *Pseudomonas pseudomallei* infection, melioidosis, are still controversial due to the variation in the treatment outcome. However, general guideline may be established as such that potent agents, alone or in combination are required for septicemic melioidosis, whereas single agent of long duration is adequate for localized, chronic form of the disease. The combined regimens of several drugs has been investigated, in vitro and in vivo, and various effects as additive, synergistic and antagonistic effects were reported. The antagonistic effect of ceftazidime and sulfamethoxazole/trimethoprim (SMZ/TMP) has been advocated, even the clinical outcome of such combination did not support the notions. This report investigated the killing effect of ceftazidime and SMZ/TMP for *P. pseudomallei* using standard killing curve. The in vitro activities, albeit their limited explanatory potential of in vivo phenomenon, render crude guideline of antimicrobial choice.

**MATERIALS AND METHODS**

Three recent clinical isolates of *P. pseudomallei* strains No. 14, 24, 28 were obtained from hospitalized patients with septicemic melioidosis. Those strains were kept under -70°C prior to the experiment. Standard powder of ceftazidime was gift from Glaxo and that of SMZ/TMP was purchased from Sigma Chemical Co. The concentrations of one-fourth of the MIC₅₀ were used. The bacteria were grown overnight in Mueller-Hinton broth at 37°C. The standard time-kill curves were performed using the starting inoculum of approximately 10⁷ cfu/ml. At times of 0, 2, 4, 6 and 24 hours, samples of 0.1 ml from the antibiotic-organism mixture were serially diluted and plated. The results were read as mean ± SD of the cfu/ml against time period. The control curves of *P. pseudomallei* growth was performed in the Mueller-Hinton broth. The effects of drug combination were interpreted as synergistic, additive and antagonistic using standard criteria.

**RESULTS**

The concentrations of ceftazidime or of SMZ/TMP at one-fourth of the MIC₅₀ had no killing effect for *P. pseudomallei*. However SMZ/TMP seemed to be more potent, as the starting inoculum remained the same at time 2 to 6 hours. At time 24 hours, the bacterium had regrowth in the medium containing either ceftazidime or SMZ/TMP. *P. pseudomallei* in the medium containing ceftazidime plus SMZ/TMP had similar growth curve as in the medium containing only SMZ/TMP at times 2 to 24 hours and did not show antagonistic effect.

Figure depicted the growth curve of *P. pseudomallei* in medium containing ceftazidime, SMZ/TMP and the combination of both agents.
Figure 1 Time-kill curves of *P. pseudomallei* in ceftazidime (○), SMZ/TMP (■), and the combination of both agents (□) at the concentration of 1/4 x MICs.

DISCUSSION

The result of this study demonstrated that the combination of ceftazidime and SMZ/TMP did not show in vitro antagonistic effect. It is claimed that adding the third agent to the combination of SMZ and TMP would result in losing the bacteriostatic and bactericidal actions of the latter two drugs. Eickhoff et al found that the adding of tetracycline, chloramphenicol or kanamycin to SMZ/TMP combination resulted in losing of bacteriostatic and bactericidal effect of the latter combination. We found different effects of various drug combinations, with only antagonism between chloramphenicol and SMZ/TMP. The difference in methods employed may be the explanation. It is evident then, that the effect of drug combination may manifest differently depending on several factors. The most important factor may be the drug concentration and its dynamicity. The use of continuous culture system may be more relevant to clinical situation. The objective for adding the third agent to SMZ/TMP in treating melioidosis may not be the need for bacterial synergy. Instead, the pharmacological synergy, in which each drug acting on different parts of infected anatomic sites is a requisition. This may be mandatory in the treatment of melioidosis, in which the bacterium causing the disease may involve different anatomic sites, and the intracellular survival of this agent may be one of the important anatomic site. The adding of the third agent to SMZ/TMP should, therefore, depend on the objective of the treatment based on the pharmacology of each agent.

REFERENCES