STABILITY OF CEFTAZIDIME IN NORMAL SALINE SOLUTION AFTER EXPOSURE TO LIGHT

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Abstract. Bactericidal activity of ceftazidime is determined by the time that concentrations in tissue and serum are above the MIC for the pathogens during the dosing interval. Thus, the most effective mode of administration of ceftazidime is continuous infusion. However, this agent is light sensitive which may result in instability when administered by this method without protection from light. Until now we have had no data to demonstrate the stability of this drug during continuous infusion. Therefore, the objective of this study was to provide such data. One gram of ceftazidime was mixed with 1,000 ml normal saline and exposed to two 36 watt fluorescence lights for 24 hours. The distance between ceftazidime solution and light source was 1 meter. Twenty samples (1 g-ceftazidime in normal saline) solution were evaluated. The mean ceftazidime concentrations in normal saline solution were decreased by only 1.69%, 4.44% and 7.19% after 6, 12 and 24 hours after exposure to light, respectively. Therefore, we conclude that the reduction of drug concentration was not considered to be significantly high, and this agent can be administered by continuous infusion.

INTRODUCTION

The most effective mode of administration to optimize the bactericidal effect of parenteral antibiotics for the treatment of infections is dependent on the drug class (Craig and Ebert, 1992). For instance, the bactericidal activity of β-lactam antibiotic is not maximized by increasing the peak drug serum concentration to MIC ratio because the bacterial killing of these drugs is concentration independent. Its bactericidal activity is determined by the time that concentrations in tissue and serum are above the MIC for the pathogen during the dosing interval. If the concentrations of antibiotics decrease to below the MIC, bacterial growth is resumed immediately since these drugs have no significant post-antibiotic effect, as seen with aminoglycosides (Craig and Ebert, 1992; Benko *et al*, 1996; Nicolau *et al*, 1996). Therefore, the ideal method to maintain the time that the β-lactam antibiotic is above its MIC for a pathogen would be to administer the agent by continuous infusion (Craig and Ebert, 1992). Moreover, this method of administration allows a reduction in the amount of the antibiotics used per day (Craig and Ebert, 1992; Benko *et al*, 1996; Nicolau *et al*, 1996).

Ceftazidime, a β-lactam antibiotic, is commonly used for the treatment of nosocomial gram negative bacilli infections, particularly *Pseudomonas aeruginosa* infection (Richards and Brogden, 1985). This agent is light sensitive (Branhart, 1990) which may result in instability when administered by continuous infusion without protection from light. However, until now we have had no data to demonstrate the stability of this drug during continuous infusion. Thus, the objective of this study was to provide such data.

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METERIALS AND METHODS

Drug and chemicals

Ceftazidime was generously donated by Glaxo (Thailand) as pure powder. Ceftazidime (Fortum) was purchased from Glaxo (Thailand).

Hydrochlorothiazide was purchased from Sigma Chemical Company (St Louis, MO, USA). All of the solvents were high-performance liquid chromatography (HPLC) grade.

Study design and samples collection

One gram of ceftazidime and 1,000 ml normal saline solution were mixed together and exposed to two 36 watt fluorescence light for 24 hours. The distance between the ceftazidime solution and light source was 1 meter. The concentration of ceftazidime in the solution was measured at 6, 12 and 24 hours after exposure to light. Twenty lots of (1 g-ceftazidime in normal saline) solution were evaluated. Results were expressed as mean ± SD, and statistical comparisons were made using the Wilcoxon signed-ranks test.

Ceftazidime assay

The concentration of ceftazidime was determined by reverse-phase HPLC by the modified method of Hwang *et al* (1984). Briefly, the samples were diluted 10-fold by mobile-phase solution, and hydrochlorothiazide was used as an internal standard. The diluted samples (25 μl) were injected, using an automated injection system (Waters 717 plus Autosampler, Waters, Milford, MA, USA), onto a μBON DAPAK C_{18} column (Waters). The mobile phase was composed of water : acetonitrile : acetic acid (93:6:1, v/v), pH 4, at a flow rate of 2 ml/minutes. The column effluent was monitored by UV detection (Waters 486) at 254 nm. The standard curve, with ceftazidime concentrations ranging from 25 to 100 μg/ml, was shown to be linear and the coefficient of variation was 5% in the ceftazidime assay. The limit of detection was 250 ng/ml.

RESULTS

The mean ceftazidime concentrations in normal saline solution gradually decreased after exposure to light as shown in Fig 1 and Table 1.

DISCUSSION

The serum concentrations of ceftazidime administered by intermittent injections are variable and trough levels may fall below the MIC even when using the maximum recommended dose (Craig and Ebert, 1992; Benko *et al*, 1996; Nicolau *et al*, 1996). This

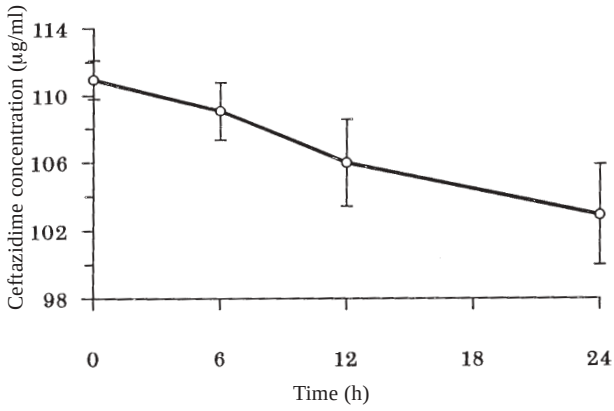

Fig 1–Mean ± SD concentrations of 1 g of ceftazidime in 1,000 ml normal saline solution after 6, 12 and 24 hours exposure to fluorescence light.

Table 1
Ceftazidime concentrations in normal saline solution (mean ± SD) after exposure to fluorescence light and % decrease as compared to drug concentrations at time 0.

Time after exposure to light	Ceftazidime concentrations	% Decrease
0 hours	110.93 ± 1.12	-
6 hours	109.05 ± 1.74	1.69[a]
12 hours	106.00 ± 2.56	4.44[a]
24 hours	102.95 ± 2.96	7.19[a]

[a]$p < 0.05$ compared to ceftazidime concentrations at time 0.

may result in therapeutic failure and the emergence of antibiotic resistance. Previous studies in a rabbit model of *Pseudomonas aeruginosa* endocarditis showed that ceftazidime resistance developed if drug concentrations fell below the MIC for 61% of the dosing interval (Fantin *et al*, 1994). Therefore, the administration of a loading dose of ceftazidime followed by continuous infusion should solve this problem. This method of drug administration would be suitable to maintain ceftazidime concentrations in serum and tissue above the MIC for most of the dosing interval. However, ceftazidime is light sensitive. During the administration of this agent by continuous infusion without protection from light, it may become unstable, and drug concentrations may be lower than therapeutic levels. Our present study showed that ceftazidime in normal saline solution was unstable when exposed to light. Drug concentrations were reduced 1.69%, 4.44% and 7.19% after 6, 12 and 24 hours after exposure to light respectively, but the reduction of drug concentrations were not considered to be significantly high. Therefore, this agent can be administered by continuous infusion. We recommend that ceftazidime in normal saline solution should be prepared every 8-12 hours.

ACKNOWLEDGEMENTS

This work was supported by the Songklanagarind Hospital Foundation. We thank Dr Jimmy Rich Ray for checking our English.

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