In Vitro Interactions Between Cotrimoxazole and Doxycycline in Burkholderia Pseudomallei: How Important is this Combination in Maintenance Therapy of Melioidosis?

Dear Editor,

Melioidosis is a serious community-acquired infection endemic in Southeast Asia and northern Australia, and is particularly prevalent in northeast Thailand. The treatment of septicaemic melioidosis is problematic having not only a 40% fatality rate but also a 23% relapse rate after the completion of antibiotic therapy.[1,2] In Thailand, current treatment recommendations include administration of intravenous ceftazidime or a carbapenem for 10–14 days followed by cotrimoxazole plus doxycycline for 12–20 weeks.[3] As an in vitro study indicated that either trimethoprim (TMP) or sulfamethoxazole (SXT) antagonized the antibacterial activity of doxycycline,[3] we still do not know the rationale of cotrimoxazole plus doxycycline for treating melioidosis. The present study was undertaken to assess the antibacterial activity of doxycycline, cotrimoxazole and their combination on Burkholderia pseudomallei, the causative microorganism of melioidosis. Ten strains of B. pseudomallei, isolated from patients with confirmed melioidosis infection at the Srinagarind Hospital, Khon Kaen, Thailand, were used in this study. All isolates had same cotrimoxazole susceptibility, with minimum inhibitory concentrations (MICs) of 2.38 µg/mL (TMP/SXT) determined by a broth microdilution method follow the guidelines of the NCCLS.[4] For doxycycline susceptibility, MICs ranged between 0.5 and 2 µg/mL. Experiments were conducted using a method modified from the time–kill study described by Smith et al.[5] A bacterial suspension was prepared from an overnight broth culture in 30-mL culture bottles containing 10 mL pre-warmed cation-adjusted Mueller–Hinton broth with the required concentration of antimicrobial (4 x MIC) to give an initial bacterial inoculum of ca. 5 x 10⁷ CFU/mL. All culture bottles were incubated for up to 24 h at 37°C on a 150 rpm shaking waterbath. Viable counts were carried out after 0, 2, 4, 6, 8, 12 and 24 h of incubation. All experiments were repeated three times and carried out within biosafety level 3 containment. The change in log₁₀ colony count at each sampling time point from the starting inoculum was calculated and then the time–kill curve was constructed. A bactericidal effect was defined as a > 3 log₁₀ reduction in CFU/mL compared with the initial test inoculum within 24 h.

All strains exposed to cotrimoxazole showed the maximum bactericidal activity at 24 h, with a mean ± SD of 2.5384 ± 1.1103 log₁₀ reduction, but only two of 10 strains showed a bactericidal effect. Experiments performed with doxycycline showed negligible changes and implied a bacteriostatic effect. All strains exposed to cotrimoxazole plus doxycycline showed a mean ± SD of 1.4214 ± 0.4738 log₁₀ reduction, which is less than cotrimoxazole alone, and implied an antagonistic effect of doxycycline to cotrimoxazole as shown in Fig. 1. The present study suggested that cotrimoxazole monotherapy is better than doxycycline monotherapy or cotrimoxazole plus doxycycline for eradication therapy of melioidosis. Our finding supported an unacceptable relapse rate of doxycycline monotherapy for maintenance phase therapy.[2] The results of the present time–kill experiments should be integrated and confirmed in clinical trials in patients infected with B. pseudomallei.

Acknowledgements

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References

1. Chaowagul W, Chierakul W, Simpsom AJ, Short JM,
Dear Editor,

I read with interest the article "Prostatic abscess by Staphylococcus aureus in a diabetic patient" [1] published in the Oct–Dec 2008 issue of the Indian Journal of Medical Microbiology. The article describes a rare case of prostatic abscess. However, several aspects of the article need to be set in the correct perspective so that the practice of clinical microbiology in India is enriched. Infections with S. aureus are common in diabetics. The prostatic abscess with S. aureus is most probably haematogenous. A blood culture taken from the patient would have been very useful. Prostatic abscess is unlikely to be the primary pathology and the source is likely to be elsewhere (endocarditis, disciitis or osteomyelitis). In any case, these sources or complications need to be ruled out.

Treatment with penicillinase-resistant penicillins (ß-lactam antibiotics, such as β-lactamase inhibitors) given intravenously is the treatment of choice for S. aureus infections. [2] These penicillins concentrate sufficiently in the prostrate in the presence of inflammation to achieve a time-dependent killing. Analysing the pharmacokinetics and pharmacodynamics of ciproßloxacin in S. aureus infections of the prostate, the Cmax/MIC ratio (the maximal tissue concentration of the drug divided by the MIC) achieved is about 8–20. Being a concentration-dependent drug, ciproßloxacin needs to have a much higher Cmax/MIC ratio to achieve adequate cure. In addition, S. aureus rapidly develops resistance through mutations on ciproßloxacin monotherapy. [3] For these reasons, ciproßloxacin should not be used in the treatment of S. aureus infections.

The authors do not mention the duration of antibiotic treatment. Although the abscess was drained, antibiotics for at least 4 weeks are needed to achieve complete cure. Cefotaxime should not be tested against S. aureus, should not be reported and S. aureus infections should not be treated with it. Reporting wrong antibiotic susceptibilities will only encourage improper use of antibiotics.

REFERENCES