Pharmacokinetic-pharmacodynamic target attainment and clinical outcomes in patients treated with oral flucloxacillin plus probenecid

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Abstract

Aim Oral flucloxacillin may be co-administered with probenecid to increase flucloxacillin concentrations and increase attainment of pharmacokinetic-pharmacodynamic (PK-PD) targets. The aims of this study were to describe outcomes of patients treated with oral flucloxacillin plus probenecid as follow-on therapy from initial intravenous treatment, and to identify optimal dosing regimens when treating infections caused by susceptible Gram-positive organisms. Methods We performed a prospective observational study of adults treated with oral flucloxacillin 1000 mg and probenecid 500 mg 8-hourly (with food) for proven or probable staphylococcal infections. We developed a population pharmacokinetic model of free flucloxacillin concentrations within Monolix, in order to estimate probability of PK-PD target attainment (fT>MIC), and used Monte Carlo simulation to explore optimal dosing regimens. Results The 45 patients (73% male) had a median (range) age of 49 years (20 – 74), weight of 90 kg (59 – 167), fat free mass (Janmahasatian) of 65 kg (38 – 89) and eGFR (CKD-EPI) of 89 mL/min/1.73m2 (41 – 124). The most common infections were osteomyelitis (n=18, 40%) and septic arthritis (n=12, 27%). Forty patients (89%) were cured 30 days after completion of therapy. 10 (22%) experienced nausea which did not require treatment alternation. Free flucloxacillin clearance depended on allometrically-scaled fat free mass, and increased by 1% for each unit increase in eGFR. Conclusion Oral flucloxacillin and probenecid was well-tolerated and efficacious. Patients with higher fat free mass and eGFR may require four times daily dosing and/or therapeutic drug monitoring to ensure PK-PD target attainment.

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