**THE EFFECT OF PROBENECID, WITH AND WITHOUT FOOD, ON ORAL FLUCLOXACILLIN PHARMACOKINETICS IN VOLUNTEERS**

**Authors:**

Everts RJ1, Begg EJ2, Zhang M2,3, Turnidge J4, Chambers ST5

1 Department of Medicine, Nelson Hospital, Nelson, New Zealand

2 Department of Medicine, University of Otago-Christchurch, Christchurch, New Zealand

3 Toxicology, Canterbury Health Laboratories, Christchurch, New Zealand

4 Departments of Pathology, Paediatrics and Molecular and Biomedical Sciences, University of Adelaide, Australia

5 Department of Pathology, University of Otago-Christchurch, Christchurch, New Zealand

**Introduction:**

Probenecid inhibits renal tubular secretion of flucloxacillin. This study was undertaken to accurately measure the effect of probenecid on unbound flucloxacillin pharmacokinetics, with and without food.

**Methods:**

An open-label, three-part, cross-over study in 11 healthy volunteers aged 18 to 33 years was undertaken. Fasting subjects received flucloxacillin 1 g orally alone, flucloxacillin 1 g orally with probenecid 500 mg orally, then flucloxacillin 1 g orally with probenecid 500 mg orally with a standard meal, on three separate days one week apart. Timed peripheral blood samples were taken over 12 hours following flucloxacillin ingestion and total and free plasma concentration of flucloxacillin were measured by liquid chromatography/tandem mass spectrometry (LC-MS/MS) in a batch.

**Results:**

Probenecid significantly reduced flucloxacillin clearance and increased the AUC. Food prolonged the time to maximum flucloxacillin plasma concentration but had no significant effect on AUC. The mean time of free flucloxacillin above 0.5 mg/L (MIC90 for methicillin-susceptible *Staphylococcus aureus*) was 1.9 hours for flucloxacillin alone without food, 3.8 hours for flucloxacillin and probenecid without food, and 4.2 hours for flucloxacillin and probenecid with food.

**Conclusion:**

Based on these data and the results of other published pharmacokinetic and pharmacodynamic studies, twice-daily probenecid-boosted oral flucloxacillin with meals should have similar efficacy to the standard four-times daily oral flucloxacillin taken on an empty stomach for mild gram-positive bacterial infections. Similarly, three-times daily probenecid-boosted oral flucloxacillin may offer an alternative to outpatient IV infusion of flucloxacillin for moderate gram-positive bacterial infections.

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