Canterbury District Health Board
Te Poari Hauora ō Waitaha

Clinical Pharmacology Bulletin

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Probenecid to extend the plasma half-life of beta-lactam antibiotics

Probenecid was introduced in the 1950's to reduce the renal elimination and extend the plasma half-life of penicillins. This effect is exploited therapeutically in the treatment of cellulitis and other infections. This bulletin will focus on the use of probenecid to extend the plasma half-life of beta-lactam antibiotics.

Mechanism

In the kidney, probenecid reduces the active tubular secretion of drugs by inhibiting organic anion transporters (OATs) in the basolateral membrane of the proximal tubular cells. Thus the clearance of organic anion drugs with a high fu (e.g. ≥ 0.9; fraction excreted unchanged in the urine) will be reduced leading to an increase in plasma concentration and extended half-life of drugs such as the penicillins and cephalosporins (see table below). Some cephalosporins with lower fu's (e.g. ceftriaxone fu =0.5) and/or those that do not undergo significant active tubular secretion (e.g. ceftazidime, ceftriaxone) are not affected by probenecid to the same extent.

Dosage

General beta-lactam treatment

Adults: Probenecid 500mg may be given up to four times daily.
Child ≥ 2 years: Initially 25mg/kg, then 10mg/kg every 6 hours.

Uncomplicated gonorrhoea

1g as a single dose at the same time as oral beta-lactam antibiotic or ≥ 30 minutes before parenteral beta-lactam.

Patients with renal impairment may not require the addition of probenecid to extend the half-life of the beta-lactam antibiotic, because the renal impairment itself prolongs the half-life.

Side effects

The most common adverse events are headache and nausea. Less common (<1%) include sore gums, flushing, headache, dizziness, urinary frequency, anaemia and alopecia.
Rare effects (<0.1%) include hepatic necrosis, hypersensitivity reactions (including anaphylaxis, pruritus, urticaria, fever, Stevens-Johnson syndrome), nephrotic syndrome, haemolytic anaemia, leucopaenia and aplastic anaemia.

Contraindications/precautions to the use of probenecid

Blood dyscrasias, uric acid renal stones, gout (initiate once acute attack has subsided), hypersensitivity to probenecid or any of excipients and children < 2 years. Probenecid is not usually recommend in patients with a history of peptic ulcer disease, pregnancy, breastfeeding and renal impairment (<30mL/min).

The effect of probenecid on other drugs			
Interacting drug	**Mechanism**	**Clinical Importance†**	**Management**
Lorazepam, nitrazepam	Inhibits the glucuronidation by the liver, ↑ half-life	Important	Consider dose reduction of the interacting drug and monitor for increased adverse effects.
Meropenem Methotrexate	↓ renal clearance, ↑ plasma concentration, ↑ half-life		
Cephalosporins#(cephalexin, cefazolin, cefuroxime, cefaclor, cefotaxime, ceftazidime) Ciprofloxacin, norfloxacin Dapsone Ganciclovir, valganciclovir Loop diuretics (e.g. furosemide) Mycophenolate NSAIDs Nitrofurantoin Oseltamivir Paracetamol Penicillins (amoxicillin, flucloxacillin, piperacillin + tazobactam) Zidovudine	↓ renal clearance, ↑ plasma concentration ↑ half-life	May be important	Monitor for increased plasma concentrations or adverse events of the interacting drug. Loop diuretics: Monitor for reduced efficacy. Zidovudine: Reduce dose by 50% only on days co-administered with cidofovir + probenecid.
Aciclovir, valaciclovir Captopril, enalapril Fexofenadine	↓ renal clearance, ↑ plasma concentration, ↑ half-life	Minimal importance	As a precaution, monitor for increased adverse events of the interacting drug
Cidofovir	↓ nephrotoxicity	Combination used clinically	Combination used clinically to decrease risk of nephrotoxicity
The effect of other drugs on probenecid			
Aspirin (>325mg)	↓ probenecid effectiveness	Important for large doses of aspirin	Avoid regular antiinflammatory doses of aspirin. Occasional analgesic doses appear to produce minimal interference.
Pyrazinamide	↓ probenecid effectiveness	May be important	Larger doses of probenecid may be required.
Allopurinol	↑ probenecid concentrations	Minimal importance	No action required

† may be greater in those with renal impairment or in the presence of other drugs that compete for renal excretion such as penicillins or cephalosporins
# Concomitant use of probenecid has no significant effect on ceftriaxone or ceftazidime. We are not aware of any interaction data on cefepime.