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Pharmacokinetic medicines interactions with probenecid

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. It is also used for gout prophylaxis, in light of its uricosuric effects.

Probenecid is a competitive inhibitor of organic anion transporters in the kidney. Organic anion transporters (OATs) mediate the uptake of medicines from the plasma into the kidney. Probenecid inhibits these OATs, and hence will increase the concentration of any concomitantly administered medicines that are OAT substrates. Probenecid also inhibits glucuronidation, which increases concentrations of medicines that are metabolised this way. The table below highlights examples of interactions that can occur with probenecid:

Interacting medicine	Interaction details *	Management
Aciclovir, valaciclovir	OAT inhibition 33% decrease in clearance 50% increase in concentrations	No change to usual management but consider dose reduction if high dose treatment is typically used for the indication e.g. HSV encephalitis
Allopurinol	OAT inhibition Reduced reabsorption of oxypurinol (active metabolite) from urine Increased oxypurinol clearance 40% decrease in oxypurinol concentrations	This combination is used therapeutically for gout due to the additive hypouricaemic effects
Aspirin (doses > 325 mg)	Decreased probenecid effectiveness for gout	Avoid regular anti-inflammatory doses of aspirin. Occasional doses appear to produce minimal interference
Baricitinib	OAT inhibition 69% decrease in clearance 3-fold increase in concentrations	Consider 50% dose reduction of the interacting medicine, or consider stopping probenecid
Captopril, enalapril	Likely OAT inhibition 73% decrease in enalapril/enalaprilat clearance 50% increase in concentrations	No change to usual management
Cephalosporins (cefalexin, cefazolin, cefuroxime, cefaclor, cefotaxime, ceftazidime)	OAT inhibition 73% increase in concentrations of cefalexin	Interaction exploited therapeutically
Ciprofloxacin, norfloxacin	OAT inhibition 60% decrease in clearance 74% increase in concentrations	No change to usual management
Dapsone	Likely OAT inhibition 25-50% increase in plasma concentrations	Consider 25-50% dose reduction of the interacting medicine
Fexofenadine	OAT inhibition 70% decrease in clearance 53% increase in concentrations	No change to usual management

Interacting medicine	Interaction details *	Management
Ganciclovir, valganciclovir	OAT inhibition 20% decrease in clearance 50% increase in concentrations	Consider 25-50% dose reduction of the interacting medicine Monitor for signs and symptoms of toxicity Monitor plasma concentration of interacting medicine if possible
Lorazepam, nitrazepam	Glucuronidation inhibition 45% decrease in clearance 2-fold increase in half-life Increased concentrations of interacting medicine	Consider 50% dose reduction of the interacting medicine
Loop diuretics (e.g. furosemide)	OAT inhibition 70% reduction in clearance Increased systemic concentrations, and decreased urine concentrations.	Monitor for reduced efficacy and titrate furosemide to effect
Meropenem	OAT inhibition Increased half-life 43-55% increase in concentrations	Consider 25-50% dose reduction of the interacting medicine
Methotrexate	Likely OAT inhibition Increased half-life 2-4-fold increase in plasma concentrations	Consider 50-75% dose reduction of the interacting medicine
Mycophenolate	Mechanism unclear Concentrations increase, magnitude unclear	Consider increased monitoring of mycophenolate concentrations
Nitrofurantoin	Likely OAT inhibition Likely 50% decrease in clearance Likely 2-fold increase in concentrations	No change to usual management
Naproxen	Glucuronidation inhibition Decrease in clearance 50% increase in naproxen concentrations	Consider 50% dose reduction of the interacting medicine
Oseltamivir	OAT inhibition 50% decrease in clearance 2.5-fold increase in concentrations	No change to usual management
Paracetamol	Possibly glucuronidation inhibition 50% decrease in clearance Increase in concentrations	Consider 50% dose reduction of the interacting medicine
Penicillins (amoxicillin, flucloxacillin, piperacillin + tazobactam)	OAT inhibition 50-70% decrease in clearance 4-fold increase in benzylpenicillin concentrations	Interaction exploited therapeutically

*concentrations refer the area under the concentration-time curve (AUC)

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