

## Drug Interactions with probenecid

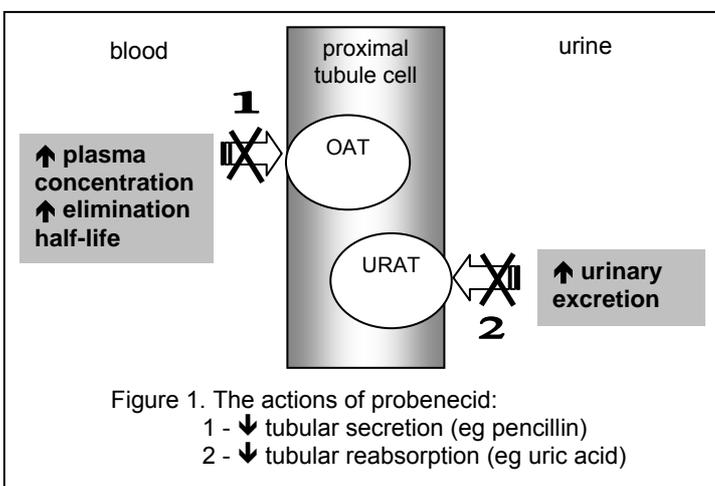
Probenecid was introduced in the 1950's to reduce the renal elimination and extend the plasma half-life of penicillins. This use continues to the present day. It was subsequently found that probenecid lowers serum uric acid concentrations and it has been used extensively as a uricosuric agent for the prevention of gout. This bulletin will discuss drug interactions with probenecid that may be therapeutically useful or undesirable.

### Drug transporters

The action of probenecid results from the inhibition of membrane transporters. Transporters control the cellular influx of nutrients and the efflux of cellular waste. Several are also known to transport drugs and are found in the kidney, liver, gut wall and other sites. They are important for drug absorption, distribution and excretion and usually have a protective or detoxifying role.

### Renal transporters and probenecid (Figure 1)

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. This results in reduced drug clearance and elevated plasma drug concentrations of substrate drugs. By contrast, the uricosuric action of probenecid results from the inhibition of urate transporters (URATs) in the apical membrane of the proximal tubule, decreasing uric acid reabsorption.



### Drug interactions

**Reduced renal clearance:** The renal clearance of drugs that undergo tubular secretion via OAT transporters may be reduced by probenecid (Table 1). The significance of the interaction will depend on the therapeutic index of the drug, the patient's renal function and whether other elimination pathways exist. For example, the plasma concentrations of methotrexate may be elevated 3-4 fold by the co-administration of probenecid and severe toxicity has been reported. By contrast, the renal clearance of captopril has been found to be reduced by 44% with the co-administration of probenecid. However, as other elimination pathways exist, the total clearance of captopril is only reduced by 19% (unlikely to be clinically significant).

Probenecid also reduces the renal clearance of several  $\beta$ -lactam antibiotics. This effect is exploited therapeutically in the treatment of cellulitis and other infections. Co-administration of probenecid allows for longer dosing intervals for some cephalosporins and penicillins.

**Reduced renal toxicity:** Probenecid reduces the accumulation of nephrotoxic drugs in the proximal tubule cells. Co-administration of probenecid is now recommended to reduce renal damage from the antiviral drug cidofovir.

**Altered diuretic effect:** Co-administration of loop diuretics and probenecid has been shown to result in altered diuresis. The mechanism is unclear, but may involve the inhibition of loop diuretic tubular secretion by probenecid.

**Other possible mechanisms:** Probenecid may inhibit the glucuronidation of some drugs, though data are limited. This may explain the reduced clearance of NSAIDs and some benzodiazepines by probenecid.

**The effect of other drugs on probenecid:** Aspirin (>325mg) and pyrazinamide diminish the uricosuric activity of probenecid, most likely by reducing the active tubular secretion of uric acid from the blood into the tubules. This results in elevated serum uric acid concentrations but reduced uric acid in the renal tubule, where probenecid exerts its uricosuric effect.

Table 1. The effect of probenecid on other drugs	
↓ renal clearance, ↑ plasma concentration or ↑ half-life	
aciclovir	fexofenadine
captopril	ganciclovir
carbapenems (eg meropenem)	loop diuretics (altered diuresis)
cephalosporins (not ceftazidime & ceftriaxone)	methotrexate
ciprofloxacin	oseltamivir
dapsone	penicillins (many)
enalapril	zidovudine
Other documented effects	
cidofovir - ↓ nephrotoxicity	
cisplatin - may ↓ nephrotoxicity (conflicting data)	
some benzodiazepines (eg lorazepam) - ↓ clearance (mechanism unclear)	
some NSAIDs (eg naproxen) - ↓ clearance (mechanism unclear)	
The effect of other drugs on probenecid	
aspirin (>325mg) - ↓ probenecid effectiveness	
allopurinol - ↑ probenecid plasma concentrations	
pyrazinamide - ↓ probenecid effectiveness	

### Summary

Probenecid has the propensity to interact with a large number of drugs. Many relatively small hydrophilic drugs (<500 daltons) may be OAT substrates. However, the study of drug transporters is a relatively new field and OAT substrates are being continually identified. Recent discoveries include, amongst others, losartan and adefovir, which may be candidates for clinically important interactions with probenecid.