Fluclouxacinillin: a weak inducer of drug metabolism

Fluclouxacinillin is an antibiotic used to treat skin infections, respiratory tract infections and other infections caused by fluclouxacinillin-sensitive organisms (e.g., osteomyelitis, urinary tract infection, diabetic foot infections) [1]. The usual oral dosage is 250 mg 4 times daily. For osteomyelitis, endocarditis: fluclouxacinillin is given up to 8 g daily in divided doses 6 to 8 hourly [1].

Clinical evidence for the fluclouxacinillin inducing effect

Fluclouxacinillin is mainly eliminated renally and was shown to be neither a substrate nor an inhibitor of cytochromes P450 (CYP) or P-glycoprotein (P-gp) [2]. However, at high concentrations, fluclouxacinillin has been shown to induce CYP3A4 and P-gp, both in vitro and in a rat study, likely due to the activation of pregnane-X-receptor (PXR), a nuclear receptor involved in the transcription of CYPs, UGTs and P-gp [2].

Fluclouxacinillin induction has been evaluated in a randomized, crossover study in which 12 healthy subjects were given fluclouxacinillin (1 g three times daily for 31 days) with a 2 mg oral dose of midazolam (as part of a cocktail) on days 10 and 28. Midazolam AUC decreased by 30% on day 10 and by 27% on day 28, thereby classifying fluclouxacinillin as a weak inducer [3]. Despite being a less potent inducer of CYP3A4, fluclouxacinillin was shown to cause clinically relevant changes in the pharmacokinetics of the following drugs:

- 38% reduction in tacrolimus (CYP3A4, P-gp substrate) [4]
- 47% reduction in posaconazole (UGT1A4 substrate) [5,6]
- 85% reduction in voriconazole (CYP2C19 > 2C9, 3A4) [7]

Dose-effect and time-effect of the fluclouxacinillin inducing effect

The voriconazole study by van Daele et al [7] indicates that fluclouxacinillin induction is dose-dependent and has been reported already for doses of 500 mg twice daily.
Clinical recommendations for coadministration of ARVs with flucloxacillin

Taken together, these data suggest that flucloxacillin is a weak inducer and has the potential to significantly reduce the exposure of some antiretroviral drugs, particularly if prescribed at higher doses (>2-3 g daily) for a prolonged course (>10-14 days).

**Induction by flucloxacillin unlikely to be clinically significant:**
- Efavirenz
- Etravirine
- Nevirapine
- Cabotegravir (oral)
- Dolutegravir
- Raltegravir
- Fostemsavir

**Interaction unlikely to be clinically relevant unless flucloxacillin is prescribed at higher doses for a prolonged course:**
- Boosted ARVs
- Bictegravir
- Doravirine
- Lenacapavir
- Maraviroc

**Use with caution**
- Cabotegravir/rilpivirine (IM)
- Rilpivirine

**References**


