Enzyme Induction by Flucloxacillin

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Flucloxacillin: a weak inducer of drug metabolism

Flucloxacillin is an antibiotic used to treat skin infections, respiratory tract infections and other infections caused by flucloxacillin-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: flucloxacillin is given up to 8 g daily in divided doses 6 to 8 hourly [1].

Clinical evidence for the flucloxacillin inducing effect

Flucloxacillin 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, flucloxacillin 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].

Flucloxacillin induction has been evaluated in a randomized, crossover study in which 12 healthy subjects were given flucloxacillin (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 flucloxacillin as a weak inducer [3]. Despite being a less potent inducer of CYP3A4, flucloxacillin 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 flucloxacillin inducing effect

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

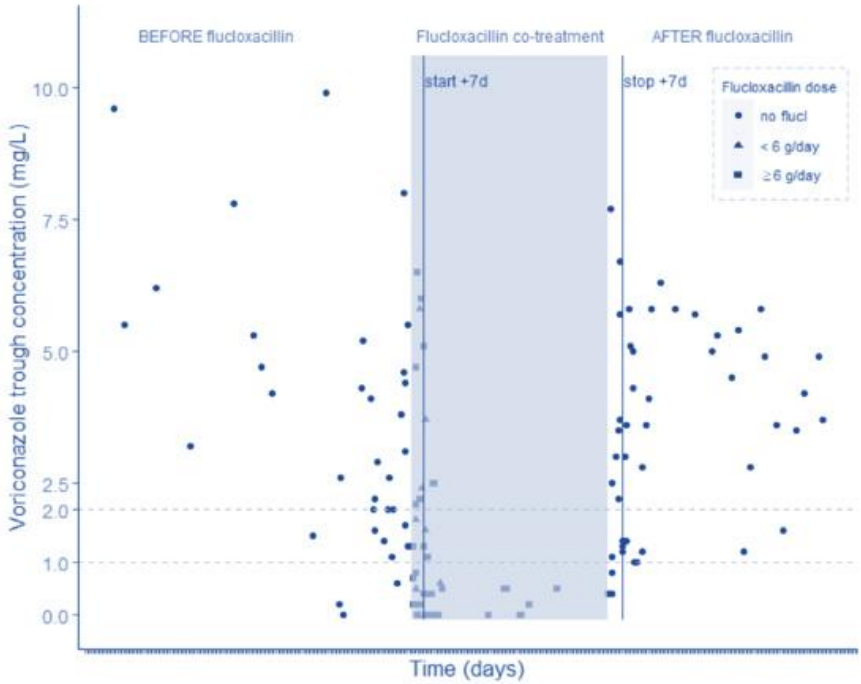

Figure 1 (from Van Daele *et al* [7]). Voriconazole concentration as a function of time before, during, and after association of flucloxacillin. The shaded area represents the time period in which flucloxacillin was administered in combination with voriconazole. White areas are the periods of time of voriconazole administration before and after flucloxacillin therapy, respectively. Each break on the x-axis represents one day and is depicted relative to the start and stop of flucloxacillin administration.

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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

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