Enzyme Induction by Flucloxacillin

Flucloxacillin: a moderate 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].

The clinical relevance of flucloxacillin induction has been highlighted with the publication of four reports showing that flucloxacillin reduced trough concentrations of the following drugs:

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

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

The voriconazole study by van Daele *et al* [6] indicates that flucloxacillin induction is dose-dependent and has been reported already for doses of 500 mg twice daily. CYP3A4 induction takes generally 2 weeks to reach maximal effect and to resolve [7]. However, the onset and resolution of induction may vary depending on the enzyme and be shorter as illustrated below for voriconazole for which a significant induction was observed 7 days after initiating flucloxacillin.

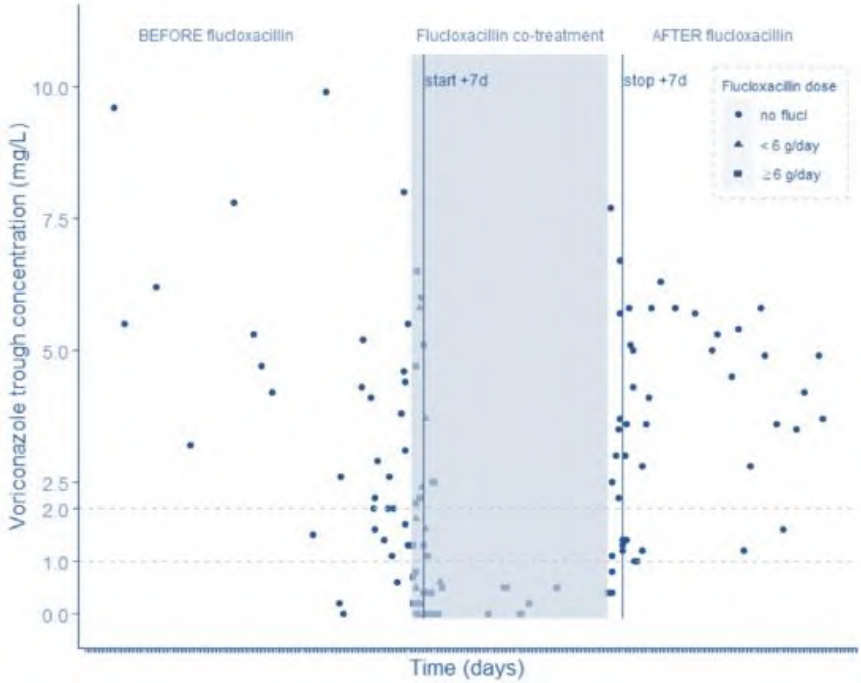

Figure 1 (from Van Daele *et al* [6]). Voriconazole concentration as a function of time before, during, and after association of flucloxacillin. The shaded area represents the time period in which flucloxacillin was administered in combination with voriconazole. White areas are the periods of time of 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.

Thus, based on these considerations, even a short course of flucloxacillin could potentially cause a clinically significant reduction in drug exposure particularly if flucloxacillin is used at high doses.

Clinical awareness of the flucloxacillin inducing effect

In their paper, Van Daele et al [6] highlight the fact that the interaction is not yet incorporated in most international drug interaction checkers, nor in product labels, which may have led to insufficient awareness of this interaction.

Clinical recommendations for coadministration of ARVs with flucloxacillin

Taken together, these data suggest that flucloxacillin is a moderate inducer and has the potential to significantly reduce the exposure of several antiretroviral drugs.

Induction by flucloxacillin unlikely to be clinically significant
(based on drug-drug interaction studies with rifabutin, another moderate inducer):

- Efavirenz
- Etravirine
- Nevirapine
- Cabotegravir (oral)
- Dolutegravir
- Raltegravir
- Fostemsavir

Use with caution

- Boosted ARVs
- Bictegravir
- Doravirine
- Maraviroc
- Rilpivirine

Avoid coadministration

- Cabotegravir/rilpivirine (IM)
- Lenacapavir

References

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