

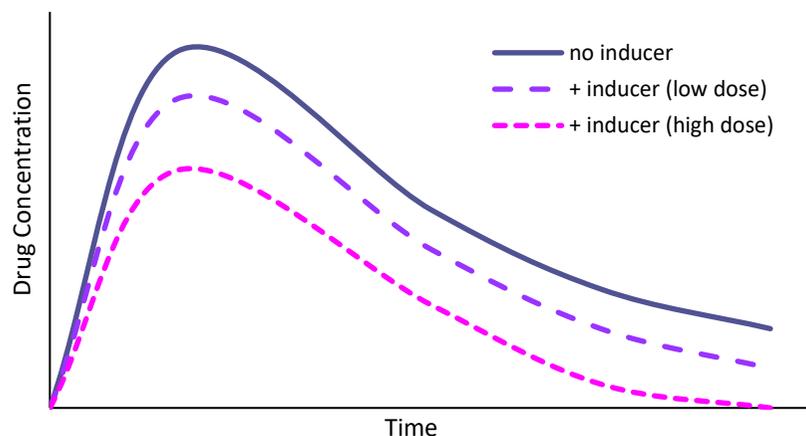
Dose Dependent Enzyme Induction

Revised December 2022.

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What is dose dependent enzyme induction?

- Enzyme induction is the process whereby a drug enhances/increases the expression of an enzyme and hence causes a change in the pharmacokinetics of another drug.
- Dose-dependent enzyme induction can be inferred when at low doses there is little or only a modest increase in expression of the enzyme whereas at higher doses expression is more markedly enhanced.
- Differential magnitude of enzyme induction will lead to differential effects on pharmacokinetics of a co-administered drug.



Why re-visit the issue of enzyme induction?

Rifampicin

There is a move to higher doses of rifampicin and the logical question arises as to the potential for increased induction.

St John's wort

Hyperforin dose varies considerably in different preparations.

Dexamethasone

A wide range of doses are used for different indications and there is the need to understand the clinical implications.

Phenytoin

Doses individualised so a range of doses used.

Carbamazepine (and related drugs)

A range of doses are used for different indications and there is the need to understand the clinical implications of dose-dependent induction. There is also the need to assess the relative inducing potential of oxcarbazepine.

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RIFAMPICIN

- There is a move to higher doses of rifampicin (RIF) [1, 2]
- The dose of RIF required to achieve maximal induction is unknown although a study suggests that 300 mg twice daily or 600 mg once daily gives a >80% decrease in midazolam exposure [3]. This approaches maximal induction.
- A study, albeit in very small numbers, suggests that increasing the dose of RIF to 900 or 1200 mg has no additional impact on clearance of propranolol [4].
- Doubling the dose of RIF to 20 mg/kg/day had only a small effect on efavirenz exposure [5].
- However, modelling suggests a non-linear increase in clearance (and therefore decrease in exposure) at higher doses of RIF [6]. In addition, single dose data suggest greater induction at a 1200 mg dose [7].

Clinical Implications

- Currently the clinical evidence suggests that higher doses of RIF will have no increased induction effect or only a relatively modest effect on drug exposure. However, we await further data [2].

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ST JOHN'S WORT

- Hyperforin is the enzyme inducing component of St John's wort (SJW) and the extent of induction by any preparation of SJW is linked to the amount/dose of hyperforin [1,2].
- Different products have very different or variable hyperforin content [2,3].
- A relatively simple way to describe SJW preparations is as low-hyperforin (≤ 1 mg/day) or high-hyperforin (> 1 mg/day) [4]

Clinical Implications

- There is a low risk of a clinically relevant pharmacokinetic interaction with low hyperforin content formulations (< 1 mg/day).

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DEXAMETHASONE

- Dexamethasone (DEX) is regarded as a moderate inducer of CYP3A4 [1]. However, there is clear evidence of dose-dependent induction [2-4].
- There was no significant effect of DEX 1.5 mg/day for 4 days on triazolam pharmacokinetics [2].
- At a dose of 8 mg twice daily for 5 days there was an increase in CYP3A activity of between 26% (erythromycin breath test) [3] and 50% (urinary ratio of hydroxy-dextromethorphan to dextromethorphan) [3].
- At a dose of 18-32 mg/day for at least 2 days there was an increase in CYP3A activity of ~55% (erythromycin breath test) [4].

Clinical Implications

- The likelihood of a clinically significant interaction is greater at higher doses of DEX.
- At doses below 8 mg/day it is very unlikely that there will be a clinically significant interaction.
- In vitro and in vivo data on the drug-drug interaction potential of DEX is summarised in a review by Jacobs *et al* [5] which also discusses the management of interactions with ARVs.
- The recommended dose used in COVID-19 patients is 6 mg/day. However, in Covid-19 patients caution is advised with a number of narrow therapeutic drugs and use of an interaction checker such as www.covid19-druginteractions.org will help guide the management of complex comorbidities.

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PHENYTOIN

- Phenytoin (DPH) is a strong inducer of CYP450 [1].
- There is evidence of dose dependent induction with DPH [2]. The clearance of antipyrine was markedly greater at a dose of 6mg/kg/day (i.e., ~400-500 mg/day) than at a dose of 2 mg/kg/day (i.e., ~200-300 mg/day) [1].

Clinical Implications

- DPH therapy should be individualised [3]. For seizures, most adults will have a maintenance dose of 200-500 mg/day. For trigeminal neuralgia the maintenance dose will be 300-500 mg/day [3].
- At the above clinical doses it is difficult to differentiate the potential extent of induction and therefore phenytoin should be regarded as a strong inducer.

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CARBAMAZEPINE

- There is clear evidence of dose-dependent induction with long term administration of carbamazepine (CBZ) [1,2]. Antipyrine clearance increased by 20% at a dose of ~400 mg (6 mg/kg/day) and by 80% at a dose of 1200 mg (18 mg/kg/day) [1]. Perampanel pharmacokinetics were related to the dose of co-administered CBZ [2].
- CBZ induction is greater than that of oxcarbazepine [3]. Perampanel mean concentration was decreased by 69% with long term CBZ (mean dose 1186 mg/day) and by 37% with oxcarbazepine (mean dose 1398 mg/day).
- There is additive induction of CBZ (400 mg/day) and efavirenz (600 mg/day) based on modelling [4].

Clinical Implications

- The magnitude of a clinically significant interaction is greater at higher doses of CBZ.
- With all formulations of CBZ, a gradually increasing dosage scheme is used and this should be adjusted to suit the needs of the individual patient [5].
- At most clinical doses induction will be near-maximal, for example:
 - For focal and secondary generalized tonic-clonic seizures the usual dose is 800-1200 mg/day in divided doses rising to a maximum of 1600-2000 mg/day if required.
 - For trigeminal neuralgia the usual dose is 200 mg 3-4 times a day, increased if necessary up to 1600 mg daily.

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OXCARBAZEPINE

- There is evidence that the induction effect of oxcarbazepine (OXCZ) is less than that of CBZ [1]. Overall, the induction of OXCZ is comparatively weak.
- Induction of perampanel by OXCZ was approximately 50% of that of CBZ at clinical doses [1].
- OXCZ at a dose of 600 mg/day had no effect on antipyrine clearance or urinary 6 β -OH cortisol excretion [2].
- However, note that with a dose of 300 mg/day increasing to 900 mg/day there was a decrease in the ethinylestradiol and levonorgestrel components of a combined oral contraceptive (48% and 37% respectively) [3].
- One small study in 4 patients suggests greater induction at higher doses of OXCZ [4].

Clinical Implications

- Although OXCZ is regarded as a weaker inducer than CBZ, caution should be exercised with drugs metabolised by CYP3A4 and UDP-glucuronyltransferases (UGTs) [5].
- There are limited data pointing to dose-dependent induction [4].

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