Dose Dependent Enzyme Induction

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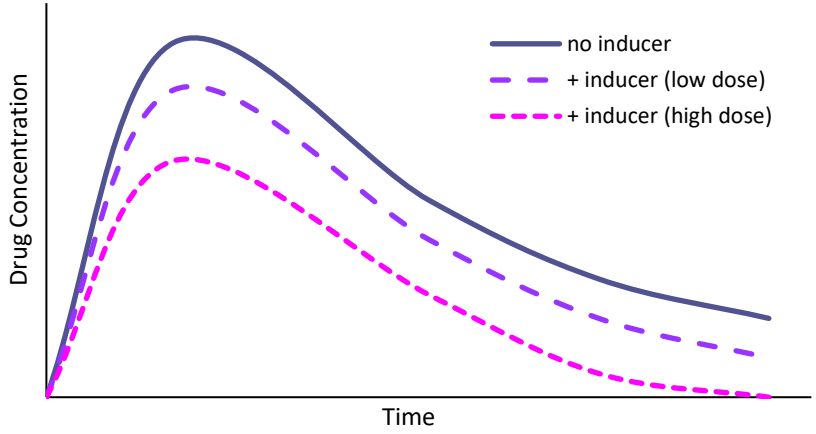
What is dose dependent enzyme induction?

- 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.

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].

References

1. Peloquin CA *et al*. Pharmacokinetic evidence from the HIRIF trial to support increased doses of rifampicin for tuberculosis. *Antimicrob Agents Chemother 2017; 61: e00038-17*.
2. Nabisere R *et al*. Pharmacokinetics, safety/tolerability and efficacy of high dose rifampicin in tuberculosis-HIV co-infected patients on efavirenz or dolutegravir-based antiretroviral therapy: study protocol for an open-label, phase II clinical trial (SAEFRIF). *Trials 2020; 21:181*.
3. Xu Y *et al*. Simulation of clinical drug-drug interactions from hepatocyte CYP3A4 induction data and its potential utility in trial designs. *Drug Metab Dispos 2011; 89: 1139-1148*.
4. Herman RJ *et al*. Induction of propranolol metabolism by rifampicin. *Br J Clin Pharmac 1983; 16: 565-569*.
5. Atwine D *et al*. Effect of high-dose rifampicin on efavirenz pharmacokinetics: drug-drug interaction randomized trial. *J Antimicrob Chemother 2020; 75: 1250-1258*.
6. Svensson RJ *et al*. A population pharmacokinetic model incorporating saturable pharmacokinetics and autoinduction for high rifampicin doses. *Clin Pharm Ther 2018; 103: 674-683*.
7. Kinvig H *et al*. High dose rifampicin for the treatment of leprosy in HIV patients taking dolutegravir. *CROI 2020, Abstract 450*.

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).

References

1. Chrubasik-Hausmann S *et al*. Understanding drug interactions with St John's wort (Hypericum perforatum L): impact of hyperforin content. *J Pharm Pharmacol 2019; 71: 129-138*.
2. Mueller SC *et al*. The extent of induction of CYP3A by St John's wort varies among products and is linked to hyperforin dose. *Eur J Clin Pharmacol 2006; 62: 29-36*.
3. Mueller SC *et al*. Effect of St John's Wort dose and preparations on the pharmacokinetics of digoxin. *Clin Pharm Ther 2004; 75: 546-557*.
4. Nicolussi S *et al*. Clinical relevance of St. John's wort drug interactions revisited. *Br J Pharmacol 2020; 177: 1212-1226*.

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.
- 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.

References

1. Dexamethasone *Summary of Product Characteristics*, Aspen, 2018.
2. Villikka K *et al*. The effect of dexamethasone on the pharmacokinetics of triazolam. *Pharmacol Toxicol 1998; 83: 135-138*.
3. McCune JS *et al*. In vivo and in vitro induction of human cytochrome P4503A4 by dexamethasone. *Clin Pharmacol Ther 2000; 68: 356-366*.
4. Watkins PB *et al*. Erythromycin breath test as an assay of glucocorticoid-inducible liver cytochromes P450. Studies in rats and patients. *J Clin Investigation 1989; 83: 688-697*.

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.

References

1. Zaccara G & Perucca E. Interactions between antiepileptic drugs and between antiepileptic drugs and other drugs. *Epileptic Disord 2014; 16: 409-432*.
2. Perucca E *et al*. A comparative study of the relative enzyme inducing properties of anticonvulsant drugs in epileptic patients. *Br J Clin Pharmacol 1984; 18: 401-410*.
3. Phenytoin *Summary of Product Characteristics*, Flynn Pharma Ltd, 2019.

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.

References

1. Perucca E *et al*. A comparative study of the relative enzyme inducing properties of anticonvulsant drugs in epileptic patients. *Br J Clin Pharmacol 1984; 18: 401-410*.
2. Yamamoto Y *et al*. Pharmacokinetics, tolerability and clinical effectiveness of perampanel in Japanese patients with epilepsy. *Seizure 2020; 83:181-186*.
3. Patsalos P *et al*. Perampanel serum concentrations in adults with epilepsy: effect of dose, age, sex and concomitant anti-epileptic drugs. *Ther Drug Monit 2016; 38: 358-363*.
4. Zhu M *et al*. Model-based approach to characterise efavirenz autoinduction and concurrent enzyme induction with carbamazepine. *Antimicrob Agents Chemother 2009; 53: 2346-2353*.
5. Tegretol (carbamazepine) *Summary of Product Characteristics*, Novartis Pharmaceuticals, 2020.

OXCARBAZEPINE

- There is evidence that the induction effect of oxcarbazepine (OXCBZ) is less than that of CBZ [1]. Overall, the induction of OXCBZ is comparatively weak.
- Induction of perampanel by OXCBZ was approximately 50% of that of CBZ at clinical doses [1].
- OXCBZ at a dose of 600 mg/day had no effect on antipyrine clearance or urinary 6β-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 OXCBZ [4].

Clinical Implications

- Although OXCBZ 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].

References

1. Patsalos P *et al*. Perampanel serum concentrations in adults with epilepsy: effect of dose, age, sex and concomitant anti-epileptic drugs. *Ther Drug Monit 2016; 38: 358-363*.
2. Larkin JG *et al*. Lack of enzyme induction of oxcarbazepine (600 mg daily) in healthy subjects. *Br J Clin Pharmacol 1991; 31: 685-691*.
3. Klosterskov Jensen P *et al*. Possible interaction between oxcarbazepine and an oral contraceptive. *Epilepsia 1992; 33: 1149-1152*.
4. Patselos P *et al*. Dose dependent enzyme induction by oxcarbazepine? *Eur J Clin Pharmacol 1990; 39: 187-188*.
5. Trileptal (oxcarbazepine) *Summary of Product Characteristics*, Novartis Pharmaceuticals, 2020.