

Pharmacokinetic Drug Interactions with Antiepileptic Drugs

Drug interactions in patients on antiepileptic drugs are important for several reasons:

- most antiepileptic drugs have a narrow therapeutic index;
- antiepileptic drugs are often chronic therapies increasing the chance of co-prescription;
- up to 20% of patients with epilepsy are managed with more than one antiepileptic drug; and
- many antiepileptic drugs affect drug metabolism.

Vulnerable patient groups include the elderly (due to reduced drug clearance, co-morbidities and concurrent treatment), women of childbearing age (especially with pregnancy or oral contraceptives) and children (as a result of continually changing physiology related to age).

Pharmacokinetic interactions involve the alteration of oral availability (absorption and first-pass metabolism), distribution or clearance of either drug, which may or may not be the antiepileptic drug. This results in altered concentrations and often changes the effectiveness for a given dose of the affected drug.

The following includes the more common clinically significant interactions. For further guidance, the CDHB 'Pink Book', CDHB Drug Information Service and ward pharmacists are useful resources.

Oral availability

Antacids have been shown to reduce the absorption of **phenytoin**, **carbamazepine**, **phenobarbitone** and **gabapentin** by a) decreasing stomach acidity (these acidic drugs become ionised in a basic environment and are less able to pass through lipid barriers) and b) by formation of insoluble complexes.

Distribution / Protein binding

Changes to protein binding of drugs in the plasma do not affect the clearance of the free drug or clinical effect for a given dose. However, interactions that alter protein-binding are important for *interpretation* of measured total drug concentrations, which usually include both the bound and free concentrations. Drugs that are highly protein-bound compete for protein-binding sites, resulting in displacement of the affected drug from their protein-drug complex. For the affected drug this typically results in reduced *total* plasma concentrations. However, *free* drug concentration is unaffected and thus clinical effect is unchanged. A prominent example is where co-administration of **valproate** with **phenytoin** results in the displacement of **phenytoin**. In this situation, a free **phenytoin** plasma concentration is a more useful guide to appropriate dosing.

Clearance

Most of the commonly used antiepileptic drugs undergo hepatic metabolism, frequently involving oxidation by the cytochrome P450 (CYP) enzymes 3A4, 2C9 and 2C19 or glucuronidation by uridine diphosphate glucuronosyltransferase (UDPGT). These drugs can therefore be affected by other drugs that alter the activity of these enzymes. The extent of the resulting effect is dependent upon the extent of:

- 1) the alteration to the enzyme(s) (inhibited or induced)
- 2) the contribution by the affected enzyme(s) to the metabolism of the affected drug.

Enzyme induction can result in reduced effect for a given dose of the affected drug*. It involves increased enzyme synthesis. Therefore, reduced drug effect may only become clinically apparent after several days or weeks.

• Antiepileptic / antiepileptic drug induction interactions

Carbamazepine, **phenytoin** and **phenobarbitone** are important enzyme inducers. **Valproate** is subject to glucuronidation and in the presence of these inducers, the plasma concentration can be reduced on average by 66%, 49%, and 76% respectively. Other affected drugs include **carbamazepine** (induced by itself as well as others), **lamotrigine** and **ethosuximide**.

• Antiepileptic / non-antiepileptic drug induction interactions

Oral contraceptives (major substrate of CYP3A4/5), **warfarin** (CYP2C9), **ciclosporin** (CYP3A4/5), some antipsychotics (e.g. **haloperidol**, **quetiapine** (both CYP3A4/5)) and some antineoplastic drugs (e.g. **vincristine** (CYP3A4/5), **paclitaxel** (CYP2C9)) are important examples of drugs affected by the antiepileptic drug inducers. **Oral contraceptives** can induce UDPGT, which can lead to a halving of plasma **lamotrigine** concentrations.

Enzyme inhibition often results in increased effect for a given dose of the affected drug* and may be clinically apparent within days if the elimination half-life of the affected drug is short.

• Antiepileptic / antiepileptic drug inhibition interactions

Valproate is an important enzyme inhibitor. Co-administration with **lamotrigine** (UDPGT) and **phenobarbitone** (CYP2C19) may increase plasma concentrations of these drugs by ~100% and 30-50%, respectively.

• Antiepileptic / non-antiepileptic drug inhibition interactions

Antiepileptic drugs rarely cause important elevations in the plasma concentrations of non-antiepileptic drugs. However, there are many significant enzyme inhibiting non-antiepileptic drugs that affect antiepileptic drugs. Some selective-serotonin reuptake inhibitors (e.g. **fluoxetine**) and macrolides (especially **erythromycin** and **clarithromycin**) are potent inhibitors of CYP3A4/5, which is important in **carbamazepine** metabolism. Many imidazole antifungals (e.g. **fluconazole**) are also potent inhibitors of CYP2C9 (**phenytoin**) and CYP3A4/5. **Omeprazole** can also increase **phenytoin** plasma concentrations by 25% by inhibiting CYP2C19.

Management

The potential for interactions may be minimised by avoiding unnecessary polytherapy and selecting drugs that are less likely to interact. Where potentially interacting drugs are co-prescribed, adverse clinical outcomes may be minimised by dose adjustment guided by monitoring of the clinical effect and relevant investigations, including plasma drug concentrations.

N.B. When withdrawing the enzyme inducer / inhibitor, it is important to remember that the loss of the interaction will result in the reversal of the concentration changes of the affected drug. The speed of onset of these reverse changes may depend on the half-life of the affected drug and the half-life of the affected enzyme.

*The opposite may be true if the affected drug has active metabolites.