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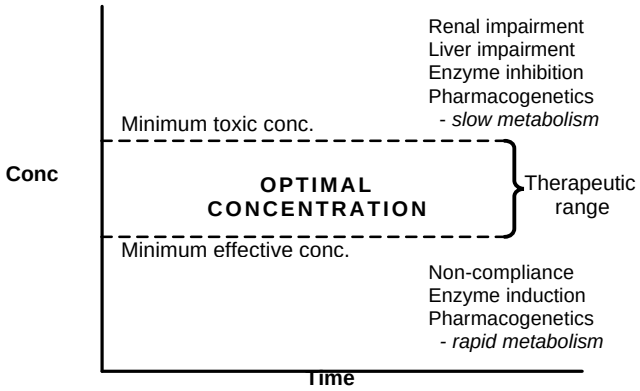
CLINICALLY IMPORTANT FEATURES OF CYTOCHROME P450 2D6 (CYP2D6)

Many factors affect plasma drug concentrations and clinical response. Elevated drug concentrations and toxicity may result from reduced elimination due to renal impairment or slow metabolism. Subtherapeutic concentrations may result from non-compliance or fast metabolism (Figure 1).

Figure 1: Factors affecting drug concentrations



CYP2D6: is involved in the metabolism of up to 25% of drugs (Table 1) including many antidepressants, antipsychotics, antiarrhythmics, β-blockers and opioids. It is an important cause of variability in drug concentrations, largely due to its polymorphic expression and involvement in drug interactions.

Polymorphism: Variations in the *CYP2D6* gene result in variable expression (polymorphism) of the enzyme protein. Individuals are classified as either 'poor' or 'extensive' ("normal") metabolisers. Poor metabolisers (PMs) do not produce functioning enzyme and are unable to metabolise drugs via this pathway. Five to 10% of Caucasian, 5% of Maori, and 1-3% of Asian/ Polynesian populations are PMs. Extensive metabolisers (EMs) comprise the rest of the population, with some individuals ('ultra-rapid' metabolisers) producing a lot of CYP2D6 and having substantial capacity to metabolise via this pathway.

Drug interactions: Many drug interactions result from inhibition (eg. by competing for the same enzyme binding site) or induction (increased enzyme protein synthesis) of cytochrome P450 (CYP450) enzymes. Unlike other CYP450 enzymes, 2D6 is not considered to be inducible (eg. by drugs such as rifampicin). However, it is subject to inhibition. Some drugs such as paroxetine inhibit CYP2D6 so strongly that up to 80% of EMs are 'converted' to PMs ie. markedly reducing ability to metabolise CYP2D6 substrates. Other strong CYP2D6 inhibitors include fluoxetine, terbinafine and thioridazine. Weaker inhibitors include tricyclic antidepressants and citalopram (see the Preferred Medicines List, 2002 p. 135).

Clinical consequences: The importance of variable CYP2D6 expression (inherited or drug induced) depends on factors such as:

- the contribution of CYP2D6 to the overall metabolism of the drug,
- the therapeutic index of the drug,
- whether the activity of the drug lies with the parent, a metabolite, or both.

In general, PMs have higher parent drug concentrations and may develop toxic concentrations with standard doses. In some cases, when the CYP2D6 metabolite is more active than the parent, reduced drug effect may occur because of reduced production of the active metabolite. Ultra-rapid metabolisers eliminate CYP2D6 substrates very quickly and may not achieve therapeutic concentrations with standard doses. Specific examples are outlined below.

Variable dependence on CYP2D6: Amitriptyline and its active metabolite, nortriptyline, are CYP2D6 substrates. However, CYP2D6 metaboliser status has minimal impact on amitriptyline concentrations but a profound effect on nortriptyline concentrations (Table 1). This difference is because amitriptyline is metabolised by several enzymes, and deficiency in one pathway still allows degradation via other routes. Nortriptyline relies heavily on CYP2D6 and PMs may have > 3-fold higher nortriptyline concentrations.

Therapeutic index: Perhexiline trough concentrations are ≈ 6-fold higher in PMs than EMs. PMs have increased risk of perhexiline toxicity, primarily neuropathy and hepatotoxicity, unless the dose is appropriately reduced.

Active metabolites: Codeine is not thought to confer analgesia in PMs as it requires CYP2D6 for conversion to its metabolite, morphine.

Table 1: Examples of 2D6 substrates

Drug	Mean - in concentrations in PMs *
Antidepressants	
- amitriptyline	see nortriptyline (active metabolite)
- desipramine	> 3-fold
- imipramine	see desipramine (active metabolite)
- nortriptyline	> 3-fold
Antipsychotics	
- haloperidol	1.7-fold (single dose)
- zuclopenthixol	1.5-fold (mean concentrations)
β-blockers	
- metoprolol	4-fold
- timolol	2- to 4-fold (single-dose)
Others:	
- codeine	low/undetectable morphine concentrations
- perhexiline	6-fold (trough concentrations)
- tropisetron	5- to 7-fold

*steady-state AUC unless specified otherwise