

## Drug Interaction Overview

### Potential Interactors

Over the counter (OTC) drugs  
Prescription drugs  
Environmental chemicals  
Food  
Herbal and nutritional supplements

### Vocabulary

*Substrate* – agent being metabolized

*Inhibitor/Inducer* – agent changing enzyme function, also called precipitant drug

*Object drug* – agent affected by interaction

*Precipitant drug* – drug causing the interaction

*Enzyme induction* – long-term administration of one drug results in the proliferation of the smooth ER resulting in increased capacity for enzyme synthesis and increasing metabolic capability.

*Enzyme inhibition* – one drug inactivates an enzyme or competes for the same binding site causing the blood levels of one or both agents to increase

Interactions can be positive or negative

Relevance of interaction depends on therapeutic margin (margin for error) of the object drug.

### Predictors for an interaction:

Object drug has a narrow therapeutic margin

The degree to which the precipitating drug interacts with the body system or enzyme

Beginning concentration of the object drug

Dose/concentration of the precipitating drug

Length of therapy

Clinical state of the patient

Presence or not of secondary metabolic pathways

Affinity of object and precipitating drug for mutual enzyme or system

Presence of a gene polymorphism

### Organs/body areas involved in metabolism

Liver - Cytochrome P450 (CYP450)

Kidneys – filters drugs from body in either changed or unchanged form

Lungs – excrete some agents or metabolites in gaseous form

Plasma – contain esterases responsible for metabolism of some agents as well as carrier proteins

GI tract – contain CYP enzymes and P-gp

Brain – contains P-gp and CYP enzymes

### Enzyme/metabolic systems

*Cytochrome P450*. Discovered in the 1970s and are found in mitochondria and both rough and smooth (main site) endoplasmic reticulum (ER). They appear as red pigments, which accumulate in liver microsomes and absorb light at a wavelength of 450nm. {Cyto (hollow vesicle, chrome (color), 450 for light wavelength. First number is the family, letter is subfamily, and 2<sup>nd</sup> number is the isozyme }

Many look alike types. Each different type is known as an isozyme and isozymes are grouped into families

Drugs can be metabolized by more than one isozyme with one generally being the primary method of metabolism and the other(s) secondary

*P-glycoprotein (P-gp) Drug Transporter*. Drug efflux transporter in cell membranes.

Drugs which affect CYP 3A4 often affect P-gp. Can be induced or inhibited and some drugs require the presence of P-gp in the GI tract, liver, and kidney for excretion.

*Glucuronosyltransferases* – Designated as the UGT superfamily of enzymes. Agents metabolized primarily by conjugation such as Lorazepam, oxazepam, or temazepam may be affected by inhibitors or inducers of UGT enzymes.

### Enzymes exhibiting polymorphisms

N-acetyltransferase

S-methyltransferase

CYP – *2C8, 2C9, 2C19* – poor metabolizers {Japanese (18%), African Americans (18%), Caucasians (3-5%)}, *2D6* – poor metabolizers {Caucasians (7-10%), African Americans (1-4%), Asians (rare)}

Dihydropyridine dehydrogenase

### Enzymes not exhibiting polymorphisms

3A4 – but amounts of enzyme may go up or down with induction

### Interaction types

Drug-Drug

Drug-Food

Drug-Disease

Pharmacokinetic – one drug alters the absorption, metabolism, distribution (includes protein and tissue binding), or excretion of another altering the concentration of the second drug at the site of action or within the body

Pharmacodynamic – involve additive, synergistic, or antagonistic effects of medications at the same receptors or within the same body systems resulting in a changed effect from that seen with the drug alone. This may be positive or negative and may not change concentration of the drugs at the site of action.

### Drug/herb interactions

Highly variable since herbal content isn't regulated. The amount of the interacting ingredient (naringin, quercetin, etc) will vary between brands and lots of each supplement

Midazolam AUC after 2 mg PO dose is considered the Phrma standard for CYP 3A4 status. Strong inhibitor  $\geq 5X$  increase in midazolam AUC, Moderate is 2-4.9X increase, Weak  $< 2 X$  increase, and none is no effect.