Metabolite vs. Parent Drug

Psychopharmacology Impacts

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Learning Objectives

1. To revisit the cytochrome P450 system with respect to kinetics and dynamics
2. To define and discuss extensive & poor metabolizers
3. To review the concept of a prodrug
4. To discuss common examples of prodrugs
5. To examine implications of metabolites in practice for practitioners and patients
ADME

Absorption

Distribution

Metabolism

Excretion
Cytochrome P450 System

A Review
Cytochrome P450 System

- The CYP isoenzyme superfamily comprises over 50 heme-containing proteins
  - Catalyze the **oxidative metabolism** of many structurally diverse drugs
  - 17 families and first 3 relate to medication metabolism, and the balance maintain homeostasis

- One of the most widely studied drug-metabolizing enzyme systems (CYP 1,2,3)

- Its name is derived from the characteristic maximum spectral absorbance at 450 nm when it is in its reduced state

- CYP exists as multiple forms or **isoenzymes**
  - Each has variable distribution in different tissues
Cytochrome P450 Enzymes

- CYP 1A2
- CYP 2B6
- CYP 2C9
- CYP 2C19
- CYP 2D6
- CYP 3A4

Involved in Drug Metabolism
Cytochrome P450 System

- What does **CYP 1A2** mean?
  - **CYP** = cytochrome P450 enzyme
  - **1** = the family of enzymes
  - **A** = the subfamily of enzymes
  - **2** = the particular gene encoding for the isoenzyme within the A subfamily
Drug-Drug Interactions

- Occur when one drug alters the effects of another drug

- **For example:**
  - Drug A causes Drug B to have ...
    - Increased or reduced effect
    - Slower or more rapid effect
    - New or increased side effects

- Many drug interactions are a result of inhibition or induction of CYP P450
Polymorphisms and the CYP P450 System:

*Extensive and Poor Metabolizers*
Polymorphisms

- **Polymorphism:**
  - Distinct population differences are apparent in the gene’s expression or activity

- Some CYP enzymes are prone to such genetic polymorphisms:
  - CYP 2D6
  - CYP 2C9
  - CYP 2C19
Different Metabolizers

• **Poor Metabolizer:**
  - Possesses two nonfunctional alleles
  - The phenotype is an autosomal recessive trait
  - More likely to have adverse effects from drugs that are substrates of the isoenzyme
  - Also will have decreased efficacy from drugs requiring CYP2D6-mediated activation

• **Extensive (Ultrarapid) Metabolizer:**
  - Result from gene duplication (up to 13 copies of CYP2D6)
  - May have therapeutic failure with drugs activated by CYP2D6 (e.g., standard antidepressant doses)
CYP 2D6

- CYP2D6 isoenzyme metabolizes 25-30% of medications, for example:
  - Dextromethorphan
  - Beta-blockers
  - Antiarrhythmics
  - Anti-depressants (e.g., fluoxetine)
  - Antipsychotics (e.g., haloperidol, risperidone)
  - Morphine derivatives

- Variability in the interindividual responses to these agents is often caused by genetic polymorphisms in CYP2D6

- Has the most variations of all genes for CYP isoenzymes
  - More than 75 allelic variants identified to date
  - Mutations result in either a reduction or complete loss of activity
• Frequency of the phenotype of poor metabolizers differs among ethnic groups
  – Less than 1% of Asians
  – 2-5% of African-Americans
  – 6-10% of Caucasians are poor metabolizers of CYP2D6
  – May be homozygous for one particular defective allele
  – Compound heterozygosity is also common
  – Proposed similar numbers are extensive metabolizers
CYP 2C9

- Examples of drugs metabolized by CYP2C9:
  - Warfarin
  - Phenytoin
  - NSAIDs

- Three allelic variants of the CYP2C9 gene have been identified that are associated with decreased enzyme activity
  - CYP2C9*2 and *3 were associated with a 5.5- and 27-fold decrease in the intrinsic clearance of S-warfarin (the active enantiomer in the racemic mixture of warfarin)
  - Mutant alleles encoding the CYP2C9 gene have a greater effect on the clinical toxicity of phenytoin
    - The CYP2C9*3 mutant allele occurs in approximately 6-9% of Caucasians and Asians
  - Since NSAIDs have relatively high therapeutic indices, these polymorphisms may have less of an impact on clinical consequences
CYP 2C19

- Exhibits genetic polymorphism
- Completely absent in 3% of Caucasians and 20% of Japanese
- Drugs commonly metabolized by CYP2C19 include:
  - PPIs
  - Diazepam
  - Imipramine
  - Amitriptyline
  - Propranolol
- Ethnic differences exist in the frequency of the poor metabolizer phenotype
  - About 3-5% of Caucasians and 12-23% of most Asian populations are poor metabolizers
- Little clinical evidence of excessive or adverse drug effects in people who are CYP2C19-deficient
CYP 3A4

- Estimated to metabolize almost 50% of drugs

- Exhibits genetic polymorphism
  - Large interindividual variability in genetic expression for CYP3A exceeding 30-fold in some populations
    - Evidence has been elusive until recently

- Such variations play a significant role in the variability of oral bioavailability and metabolism of CYP3A substrates, such as:
  - HIV protease inhibitors, benzodiazepines, calcium channel blockers, statins, antineoplastic drugs, nonsedating antihistamines, and immunosuppressants
Prodrugs
Prodrugs

• A drug that is administered in an inactive (or significantly less active) form
  – Designed to ameliorate some identified, undesirable physical or biological property
  – Purpose is usually to optimize one aspect of ADME

• Once administered, the prodrug is metabolized in vivo into an active metabolite via **metabolic biotransformation**
**Why Use Prodrugs?**

- Prodrug design may be useful in circumventing problems associated with:
  - Solubility
  - Absorption and distribution
  - Site specificity
  - Instability
  - Prolonged release
  - Toxicity
  - Poor patient acceptability
  - Formulation problems

**OR ....**

- May be discovered serendipitously!
- We are ALL different! Animal versus human models (Think Ciprofloxacin)
Conversion of Prodrugs

- Metabolism (enzyme dependant)

- Chemical Transformation
  - Hydrolysis
  - Decarboxylation
  - NOT patient dependant
Examples of Prodrugs & Their Metabolites
10% of codeine is metabolized to morphine via CYP 2D6 demethylation
- It is this 10% that is responsible for the analgesic effect of codeine

10-30% of people lack CYP 2D6 and cannot convert codeine to morphine (poor metabolizers)
- Do not experience pain relief

1-7% of Caucasians and more than 25% of Ethiopians are ultrarapid metabolizers
- Metabolize codeine too efficiently, leading to morphine intoxication
Potential removal from Hospital for Sick Children’s hospital formulary in the near future

- Oral morphine is their gold standard for pain control in children (vs. codeine) due to all the problems resulting from poor and extensive metabolizers
- Sick Kids is trying to raise awareness in the community about the switch from codeine to oral morphine
• **Terfenadine** is a prodrug that undergoes complete first-pass metabolism to an active carboxymetabolite, fexofenadine.

• Terfenadine is considered cardiotoxic
  - High plasma concentrations of terfenadine has been associated with *torsade de pointes*
  - May occur when azole antifungal medications or macrolide antibiotics are taken concomitantly
    - Terfenadine is metabolized through the CYP 3A4 system
    - Azole antifungals and macrolides are inhibitors of the CYP 3A4 system

• To counteract this problem (and other 3A4-mediated drug interactions), fexofenadines now marketed as a noncardiotoxic alternative to terfenadine
  - Terfenadine was removed from the Canadian market in 1999
Tamoxifen is a prodrug that has relatively little affinity for its target protein, the estrogen receptor.

Metabolized by CYP 2D6 and 3A4 into its active metabolites, 4-hydroxytamoxifen and N-desmethyl-4-hydroxytamoxifen (endoxifen).
- Have 30-100 times more affinity for the estrogen receptor than tamoxifen and compete with estrogen in the body for binding to this receptor.

CYP 2D6 poor metabolizers may not receive full benefit of tamoxifen due to 2D6 inactivity.
- Subsequently, the prodrug is not metabolized to the active metabolite.

Also concern if the patient is on a selective serotonin reuptake inhibitor (SSRI) such as paroxetine or fluoxetine.
- SSRIs inhibit 2D6 and can, therefore, prevent conversion of tamoxifen to its active form.
Potential value of CYP 2D6 pharmacogenomic testing in patients starting tamoxifen?
- When it works, studies show it can reduce cancer by 50%
- Test costs ~$500 Canadian

Recently in the News:

Tamoxifen does nothing for some breast-cancer patients
• **Prednisone** is a prodrug
  – Converted to **prednisolone** (active metabolite) in the liver via hydroxylation

• Primary advantage of using prednisolone in the pediatric population is that the liquid format is much more palatable than prednisone
  – **Prednisone liquid**: Very bitter taste, poor compliance
  – **Prednisolone liquid**: Lacks flavour, good compliance
Sulfasalazine is a bioprecursor prodrug used to treat inflammatory bowel disease (ulcerative colitis).

Sulfasalazine undergoes reductive cleavage (azo reduction) by anaerobic bacterial enzymes (reductases) found in the colon - Prevents small intestine systemic absorption and concentrates the drug at the desired site of action.

Two amine active metabolites result:
- 5-aminosalicylic acid (5-ASA)
- sulfapyridine
Ciclesonide is a nonhalogenated, glucocorticoid prodrug that is hydrolyzed to the pharmacologically active metabolite des-ciclesonide following administration.

The incidence of oral candidiasis, as well as other localized oropharyngeal effects, has been reported to be approximately one-half of that seen with other commonly inhaled corticosteroids (e.g., budesonide, fluticasone).

- May be due to:
  - Small particle size
  - Minimal activation and deposition in the oropharynx
**Bioprecursor prodrug**

- Strategies involving prodrugs have also been developed for slowing the release of the active metabolite.
- Haloperidol deconate has a long-chain aliphatic ester attached to it in order to slow hydrolysis.
- Particularly useful for the treatment of psychoses where patients require medication for extended periods and patient compliance is low.

**Haloperidol deconoate:**
- Injected IM as a solution in sesame oil
- Activity lasts ~ 1 month

**Haloperidol:**
- Potent orally active CNS depressant, sedative, tranquilizer
- Peak plasma levels between 2-6 hr after administration
A Newly Marketed Mental Health *Prodrug*
• **Prodrug of dextroamphetamine** *(active metabolite)*
  – Dextroamphetamine is covalently bonded to L-lysine
    • After oral ingestion and absorption through the intestines, it is converted pharmacologically to dextroamphetamine
      – This conversion is not affected by GI pH and is unlikely to be affected by alterations in normal GI transit times
  
• A non-catecholamine sympathomimetic amine with CNS stimulant activity

• Thought to block reuptake of norepinephrine and dopamine in the presynaptic neuron, as well as increase the release of these monoamines into the extraneuronal space
• **Avoid if:**
  - History of heart defects, symptomatic cardiovascular disease, stroke, moderate-severe hypertension and heart rate
  - Seizure history (lowers seizure threshold)
  - Hyperthyroidism
  - Glaucoma
  - Pre-existing psychosis, bipolar disorder (may exacerbate symptoms)

• **Potential Advantages:**
  - Because it is a prodrug, it produced a significantly lower abuse-related liking effect than an equivalent dose of dextroamphetamine
Newly Marketed Mental Health Active Metabolites
Risperidone ➔ Paliperidone

RISPERIDONE

• **Absorption**
  - **Bioavailability:** 70%  
    - Tablet (relative to solution): 94%  
    - Orally-disintegrating tablets and oral solution are bioequivalent to tablets  
  - Rapid and well absorbed; food does not affect rate or extent  
  - **Time to peak:** Within 1 hour

• **Distribution**
  - **Volume of Distribution:** 1-2 L/kg  
  - **Protein Binding:** 90%

• **Metabolism**
  - Extensively hepatic via CYP 2D6 to 9-hydroxyrisperidone [paliperidone]  
    (similar pharmacological activity as risperidone)  
  - N-dealkylation is a second minor pathway

• **Excretion**
  - **Half-life:** 8.5 hours (mean)  
  - Extensive metabolizers: 3 hours  
  - Poor metabolizers: 20 hours  
  - Urine: 70%  
  - Feces: 14%
**PALIPERIDONE**

- **Absorption**
  - **Bioavailability**: 28%
  - Paliperidone is an extended release tablet based on the OROS® osmotic delivery system
  - **Time to Peak**:
    - Extensive metabolizers: 3 hours
    - Poor metabolizers: 17 hours

- **Distribution**
  - **Volume of Distribution**: 391-487 L
  - **Protein Binding**: 74%

- **Metabolism**
  - CYP2D6 and 3A4 (limited role in elimination)
  - Minor metabolism (<10% each): dealkylation, hydroxylation, dehydrogenation, and benzisoxazole scission

- **Excretion**
  - **Half-life**: 23 hours; 24-51 hours with renal impairment (Clcr <80 mL/minute)
  - Extensive metabolizers: Risperidone: 3 hours; 9-hydroxyrisperidone: 21 hours
  - Poor metabolizers: Risperidone: 20 hours; 9-hydroxyrisperidone: 30 hours
  - **Urine**: 80%
  - **Feces**: 11%
**Clinical Pearls**

- Paliperidone has limited CYP P450 drug-drug interactions as it is the active metabolite
- Less drug interactions (except carbamazepine)
- Similar side effect profile to rispiridone
- Different kinetics and dynamics (Volume distribution) could have protective effects in avoiding discontinuation syndrome (hypothesized)
- Less potential complications with polymorphisms (especially 2D6)
- Proposed 12-20% of patients are poor or extensive metabolizers of the 2D6 system
Venlafaxine ➔ Desvenlafaxine

VENLAFAXINE

• **Absorption**
  - 92-100%
  - **Bioavailability**: 45%
  - Food has no significant effect on absorption
  - **Time to peak**: 5.5 hours

• **Distribution**
  - **Volume of Distribution**: 7.5 ± 3.7 L/kg
  - **Protein Binding**: 27%

• **Metabolism**
  - Hepatic via CYP2D6 to active metabolite, O-desmethylvenlafaxin
  - Other metabolites include N-desmethylvenlafaxine and N,O-didesmethylvenlafaxine

• **Excretion**
  - **Half-life**: 3-7 hours
  - Prolonged with cirrhosis and with dialysis
  - Urine (~87%, 5% as unchanged drug, 29% as desvenlafaxine, 26% as conjugated desvenlafaxine, 27% as minor inactive metabolites) within 48 hours
Desvenlafaxine

DESVENLAFAXINE

• Absorption
  - Bioavailability: 80%
  - Food has no significant effect on absorption
  - Time to peak: 9 hours

• Distribution
  - Volume of Distribution: 3.4 L/kg
  - Protein Binding: 30%

• Metabolism
  - Hepatic via conjugation and oxidation via CYP3A4 (minor pathway)

• Excretion
  - Half-life: 11 hours
  - Prolonged with cirrhosis, renal failure and dialysis
  - Urine (45% as unchanged drug; ~24% as metabolites)
• Clinical Pearls
  
  – Allows us to be selective and targeted in our delivery system
  – Decreases and minimizes the impact of adverse effects to the patient
  – Decreases the amount of medication that needs to be administered overall
  – Pharmacokinetics indicate better bioavailability, thus allowing lower doses to be used
  – Allows for a predictable concentration of the medication (secondary to succinate salt)
  – Less sexual adverse effects versus Venlafaxine
Pharmacogenomics

• **A brave new world…**

• Currently, preliminary dosage recommendations based on *CYP2D6* genotypes are available for antidepressants
  
  – This gives us a glimpse of how pharmacogenetics can suggest dose regimens for a small population of patients
  
  – Prospective studies are warranted to address whether genotype-based dose recommendations have a positive outcome on therapy

• Although tests for isoform expression are not widely available, it is conceivable that such testing may become standard practice in the future, given the clinical importance of isoform deficiencies

• In the future, testing may help to identify individuals at risk for drug interactions and adverse events

• *CYP2C9* genotyping may help identify high-risk patients who are candidates for lower warfarin doses, more frequent monitoring, or alternative drug treatments
Impact to Practice for Practitioners

- Because CYP2D6 isoenzyme metabolizes such a large number of drugs used in the clinical setting, practitioners have an important role in drug monitoring, including:
  - Identifying CYP2D6 substrates
  - Monitoring for drug efficacy and toxicity
  - Understanding the phenotypic and genotypic tools available

- Practitioners can explain patients' responses to medication regimens
- Identify patients at risk based on past responses
- Taking good histories may help determine polymorphisms in a proactive form
Impact to Practice for Practitioners

• We are all different!

• Our underlying premise under a bio-psycho-social model is to get the right drug to the right person at the right time for the right condition with a minimum of adverse effects…

• A side effect CAN potentially be avoided

• Now we can refine that even more for our patients!
Questions?