Training course: Pharmacotherapy in Older People

Drug metabolism in older people

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Declaration of Conflict Of Interest

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**XX I have no potential conflict of interest to report**

☐ I have the following potential conflict(s) of interest to report

<table>
<thead>
<tr>
<th>Type of affiliation / financial interest</th>
<th>Name of commercial company</th>
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<tr>
<td>Receipt of grants/research supports:</td>
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<td>Receipt of honoraria or consultation fees:</td>
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<td>Participation in a company sponsored speaker’s bureau:</td>
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<td>Spouse/partner:</td>
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<td>Other support (please specify):</td>
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Aging populations worldwide are leading to more chronic diseases and greater demand of care.

- Today, someone 65 years of age can anticipate living another 18-20 years.
- Increasing life expectancy has resulted in a progressive increase in elderly adults with chronic diseases and comorbidities (pluripathology) leading to an increased number of medications (polypharmacy).
- Individuals aged >80 years are the fastest growing group.

Health Advances analysis; OECD Health Statistics Database and CDD Health Interactive Data from NHIS, UK.
PK/PD determinants of drug action in the elderly

Delivery
- Absorption
- Distribution

Removal
- Metabolism
- Elimination

PKs

PDs

Target proteins

Other molecules with which the drug interact (off-target)

Variability in the target molecule

Changes in receptor responsiveness
- Receptor number and affinity
- Signal transduction pathways
- Cellular responses
Agenda

• The concept of drug metabolism (biotransformation)
• Phases I and II of drug metabolism
  • Enzymes and sites of metabolism
• Enzyme induction and inhibition
• Factors affecting drug metabolism
  • Role of genetics in drug metabolism
Drug metabolism

- Many drugs are lipophilic compounds and do not pass ready into the aqueous environment of the urine.
- They must first undergo a variety of enzymatic changes (i.e., biotransformed) in different tissues leading to metabolites that are readily eliminated in urine or bile.
- Also applicable to endogenous compounds (steroid hormones, cholesterol, fatty acids).
- We need to understand these changes because they explain:
  - Changes in drug efficacy and safety.
  - Drug interactions derived from the induction/inhibition of metabolic enzymes.
Hepatic function/metabolism progressively declines with advancing age

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Change</th>
<th>Consequence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metabolism</td>
<td>• ↓ liver size and mass (20-30%)</td>
<td>• ↓ bioavailability of predrugs (ACEIs)</td>
</tr>
<tr>
<td></td>
<td>• ↓ hepatic blood flow (20-40%)</td>
<td>• ↓ drug metabolism</td>
</tr>
<tr>
<td></td>
<td>• ↓ liver´s capacity (≥30%) for phase I metabolism (CYPs)</td>
<td>• ↑ exposure and t½ of highly metabolized drugs</td>
</tr>
<tr>
<td>Analgesics</td>
<td>• NSAIDs: ibuprofen, naproxen, paracetamol</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Meperidine</td>
<td></td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>• Antiarrhythmics: amiodarone, lidocaine, propafenone, quinidine</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• β-blockers: labetalol, metoprolol, propranolol</td>
<td></td>
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<tr>
<td></td>
<td>• CCBs</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Theophylline</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Warfarin</td>
<td></td>
</tr>
<tr>
<td>Psychoactive</td>
<td>• Benzodiazepines: alprazolam, chlordiazepoxide, diazepam, flurazepam, triazolam</td>
<td></td>
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<tr>
<td></td>
<td>• Phenytoin</td>
<td></td>
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<tr>
<td></td>
<td>• TCAs: Amitriptyline*, desipramine, imipramine, nortryptiline</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Trazodone</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>• Diphenhydramine</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Levodopa</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Tolbutamide</td>
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</table>

CCBs. Calcium channel blockers
**Drug metabolism (1)**

**Phase I reactions: oxidation, reduction and hydrolysis**

- Cytochromes P450: a family of enzymes containing heme-iron as a cofactor that function as monooxygenases
- Lipophilic drugs are converted to water-soluble metabolites of lesser, equal, or greater effect
- Location: hepatocyte (smooth endoplasmic reticulum) and intestinal mucosa
  - Other organs: lungs, kidneys – they are substrate specific
- Phase I reactions DECLINE in the elderly
First-pass metabolism

- Following the oral administration of a drug, a percentage of the dose can be metabolized either in the gut or in the liver before it reaches the systemic circulation.
- ↓ oral availability and activity of:
  - Dabigatran, L-dopa, lidocaine, nitroglycerin, opioids, propranolol, simvastatin, theophylline, verapamil
  - Some only I.V.
- Elderly: ↓ the first-pass effect and ↑ the oral bioavailability and Pc of some of these drugs
- ↓ the bioavailability of prodrugs (ACEIs)
Fraction of clinically used drugs metabolized by P450 isoforms and factors influencing variability

- **CYP3A4*/5 (30.2%)**
  - Induction
  - Sex (f>m)
  - Inflammation (↓)
  - Polymorphism (↓)
  - Age (↑)

- **CYP2J2 (3%)**
  - Polymorphism (↓)

- **CYP2E1 (3%)**
  - Induction (↑)
  - Inflammation (↑)
  - Various diseases (↑)
  - Sex (m>f)

- **CYP2D6 (20%)**
  - Polymorphism (↓↑)
  - Inflammation (↓)

- **CYP2C19 (6.8%)**
  - Polymorphism (↓↑)
  - Induction (↑)
  - Inflammation (↓)
  - (Sex ?)

- **CYP2B6 (7.2%)**
  - Induction (↑)
  - Polymorphism (↓↑)
  - Inflammation (↓)
  - Age (↑)
  - (Sex, f>m ?)

- **CYP2C8 (4.7%)**
  - Induction (↑)
  - Polymorphism (↓↑)
  - Inflammation (↓)
  - Age (↑)
  - (Sex ?)

- **CYP2C9 (12.8%)**
  - Induction (↑)
  - Polymorphism (↓)
  - Inflammation (↓)
  - Age (↑)
  - (Sex ?)
Phase II (conjugation) reactions

- Attach small, polar and water-soluble endogenous compounds to the drug or its phase I metabolites to form hydrophilic inactive metabolites
  - Easily excreted in urine and/or bile
  - Glucuronidation, glutathione conjugation, N-acetylation, methylation, sulfation
- Non-microsomal enzymes located in the cytoplasm, hepatocyte mitochondria, plasma
- Phase II metabolism generally preserved in the elderly

Medications undergoing Phase II metabolism are generally preferred in the elderly due to inactive metabolites (no accumulation)
Consequences of drug biotransformation

• **Active drug → inactive metabolites:** the most common fate for most drugs

• **Active drug → active metabolites:**
  - Diazepam → Oxazepam
  - Imipramine → Desipramine, Amitryptiline → Nortriptyline
  - Chemotherapy drugs

• **Inactive drug (prodrug) → biologically active metabolites:**
  - Prodrugs → hydrolysis of ester or amide bond
    - Some ACEIs, dabigatran, clopidogrel
  - Many chemotherapy drugs
  - L-dopa → Dopamine

• **A metabolite with a new action:**
  - Procainamide (Class IA) → NAPA (class III)

• **Toxic metabolites:**
  - Acetaminophen metabolites - liver failure; lidocaine/meperidine metabolites - seizures
The role of active metabolites

- **Irinotecan**
  - Metabolized by CYP3A4 and CYP3A5 to form M4 and NPC.

- **Paclitaxel**
  - Metabolized by CYP3A4 to 6-OH paclitaxel and 3'-p-OH paclitaxel.
  - metabolism includes Dihydroxy paclitaxel.

- **Etoposide**
  - Metabolized by CYP3A4 to Etoposide catechol.

- **Cyclophosphamide**
  - Metabolized by CYP3A4 and CYP2B6 to 2-Dechloroethyl cyclophosphamide.
  - Metabolized by CYP3A5 to Chloroacetaldehyde.
  - Converted to 4-Hydroxycyclophosphamide.

- **Vincristine**
  - Metabolized by CYP3A4 and CYP3A5 to Metabolite M1 (major) and Metabolite M2 (minor).
  - Metabolized by CYP2C9 to Metabolite M4 (minor).

- **Imatinib**
  - Metabolized by CYP1A2, CYP2D6, and CYP2C9 to CGP 74588, which is an inactive metabolite.
  - Excreted.
Hepatic clearance decreases with age

- It quantifies the loss of drug during its passage through the liver. It is a function of:
  - Hepatic blood flow
  - Plasma protein binding (e.g. hypoalbuminemia, displacement by other drugs)
  - Activity of liver enzymes and transporters (e.g. liver failure, specific inhibition or induction by drugs, genetic polymorphisms)

- Other factors: Nutritional state, comorbidities, other drugs
  - Hepatic diseases (cirrhosis, alcohol liver disease, jaundice, carcinoma) are more common in elderly
  - ↓ liver’s ability to recover from injury

- Drugs with high intrinsic clearance are rapidly metabolized and rate of drug loss is determined by the hepatic blood flow
  - Diltiazem, lidocaine, imipramine, metoprolol, nifedipine, propranolol, verapamil
  - Congestive HF, shock, hepatic diseases: reduce the dose up to 40%

- Drugs with low intrinsic clearance are slowly metabolized and the rate of elimination is mainly dependent on the enzyme activity in the liver
  - Carbamazepine, diazepam, phenytoin, theophylline, and warfarin
The effects of age and liver disease on the disposition and elimination of diazepam and desmethyldiazepam in adult man

Patients with cirrhosis:
$t_{1/2}$ 105.6±15.2 hr vs. 46.6±14.2 hr, P<0.001.
With acute viral hepatitis 74.5±27.5 hr, with chronic active hepatitis of 59.7±23.0 hr vs 32.7±8.9 hr (P < 0.01)

There is an increase in diazepam half-life with increasing age

<table>
<thead>
<tr>
<th></th>
<th>Young</th>
<th>Elderly</th>
<th>Very elderly</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change in mean SBP (mmHg)</td>
<td>-7.3 ± 4.2</td>
<td>-13.5 ± 5.9*</td>
<td>-15.9 ± 9.6*</td>
</tr>
<tr>
<td>Change in HR (bpm)</td>
<td>+8.0 ± 5.0</td>
<td>-1.0 ± 10.0</td>
<td>-6.0 ± 8.0*</td>
</tr>
<tr>
<td>Bioavailability (%)</td>
<td>34 ± 11</td>
<td>29 ± 16</td>
<td>---</td>
</tr>
<tr>
<td>AUC (ng/mL x h⁻¹)</td>
<td>142 ± 3</td>
<td>180 ± 52</td>
<td>372 ± 177*</td>
</tr>
<tr>
<td>t½ (h)</td>
<td>4.8 ± 1.5</td>
<td>5.8 ± 1.9</td>
<td>10.7 ± 1.8*</td>
</tr>
<tr>
<td>Total clearance (mL/min x kg)</td>
<td>15.5 ± 4.5</td>
<td>10.5 ± 3.4</td>
<td>8.0 ± 4.1*</td>
</tr>
</tbody>
</table>

Effect of age on plasma concentrations of phenytoin and propranolol

1. Genetic diversity is the rule rather than the exception with drug metabolizing enzymes
   • There is a wide inter-individual variability in drug response (efficacy/safety)
2. Due to the presence of genetic polymorphisms and differences in gene regulation/expression
   • Allelic variants with different catalytic activities from the WT form:
     • Lack of (PMs), intermediate (IMs) or enhanced catalytic ability (ultrarapid-UM, extensive-EM)
     • PM phenotype - higher risk of serious AEs due to drug accumulation in the body
     • Metabolic inhibition can convert a normal metabolizer into a poor metabolizer
   • Frequency of the polymorphisms varies with the ethnic ancestry

“If it were not for the great variability among individuals medicine might as well be a science and not an art”. Sir William Osler, 1892
<table>
<thead>
<tr>
<th>Drug-Metabolizing Enzyme</th>
<th>Frequency of Variant Poor-Metabolism Phenotype</th>
<th>Representative Drugs Metabolized</th>
<th>Effect of Polymorphism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cytochrome P-450 2D6 (CYP2D6)</td>
<td>7% in Caucasians 1% in China</td>
<td>Fluoxetine, Haloperidol, Paroxetine, Codeine</td>
<td>Enhanced drug effect, Enhanced drug effect, Enhanced drug effect, Decreased drug effect</td>
</tr>
<tr>
<td>Cytochrome P-450 2C9 (CYP2C9)</td>
<td>Approximately 3% in England (those homozygous for the *2 and *3 alleles)</td>
<td>Warfarin, Phenytoin</td>
<td>Enhanced drug effect</td>
</tr>
<tr>
<td>Cytochrome P-450 2C19 (CYP2C19)</td>
<td>2.7% among white Americans 3.3% in Sweden 20-30% in Asians</td>
<td>Omeprazole</td>
<td>Enhanced drug effect</td>
</tr>
<tr>
<td>N-Acetyltransferase 2</td>
<td>52% among white Americans 17% of Japanese</td>
<td>Isoniazid, Hydralazine, Procainamide</td>
<td>Enhanced drug effect</td>
</tr>
<tr>
<td>Uridine diphosphate–glucuronosyltransferase 1A1 (TATA-box polymorphism)</td>
<td>10.9% among whites 4% of Chinese 1% of Japanese</td>
<td>Irinotecan, Bilirubin</td>
<td>Enhanced drug effect, Gilbert’s syndrome</td>
</tr>
<tr>
<td>Thiopurine S-methyltransferase</td>
<td>Approximately 1 in 300 whites 1 in 2500 Asians</td>
<td>Mercaptopurine, Azathioprine</td>
<td>Enhanced drug effect, toxicity</td>
</tr>
<tr>
<td>Catechol O-methyltransferase</td>
<td>Approximately 25% of whites</td>
<td>Levodopa</td>
<td>Enhanced drug effect</td>
</tr>
</tbody>
</table>

Pharmacogenetics in phase II and phase I metabolism.
Consequences of Induction/inhibition

- **Enzyme induction**: ↑ the rate of hepatic metabolism
  - ↑ the first-pass effect and reduces oral bioavailability
  - ↓ the Pc, intensity/duration of drug effect
  - ↑ the effect of active metabolites
  - Dosing rates may need to be increased to maintain effective Pc

- **Enzyme inhibition**: ↓ the rate of hepatic metabolism
  - ↑ Pc of the parent drug and increases/prolongs drug effects
  - ↑ the risk of drug-induced toxicity
  - ↓ metabolite(s) levels: less effect if active metabolites (clopidogrel)

Pc: plasma concentrations
CYP3A4 modulation

CYP3A4 SUBSTRATES
- Amiodarone, dronedarone
- Most benzodiazepines
- Calcium channel blockers
- Ciclosporin, sirolimus, tacrolimus
- Ivabradine
- Lidocaine
- Macrolides: clarithromycin, erythromycin, telithromycin
- Methadone
- NOACs: apixaban, edoxaban, rivaroxaban
- SSRI: citalopram
- Statins: atorvastatin, lovastatin, simvastatin
- Ticagrelor
- VIH protease inhibitors: indinavir, nelfinavir, ritonavir, saquinavir
- Warfarin

CYP3A4 INHIBITORS
1. Weak: cimetidine
2. Moderate:
   - Amiodarone
   - Ciprofloxacin
   - Fluconazole, miconazole
   - Diltiazem, verapamil
   - Delavirdine
   - Grapefruit juice
   - VIH protease inhibitors: amprenavir, fosamprenavir
3. Strong:
   - Macrolides: clarithromycin, telithromycin, troleandomycin
   - Azoles: itraconazole, ketoconazole
   - Nefazodone
   - VIH protease inhibitors**: atazanavir, darunavir, indinavir, lopinavir, nelfinavir, ritonavir, saquinavir, tipranavir

CYP3A4 INDUCERS
1. Berbiturales
2. Carbamazepine
3. Dexamethasone
4. Phenytoin
5. Primidone
6. Rifamycins
7. St John’s wort**
# CYP2D6 modulation

## SUBSTRATES
- Antiarrhythmics: Flecainide, Lidocaine, Mexiletine
- Antidepressants: SSRIs, Trazodone, Tricyclics, Venlafaxine
- Beta blockers
- Dextromethorphan
- Haloperidol
- Omeprazole
- Phenothiazines
- Opioids: codeine****, morphine, tramadol
- Risperidone
- Tamoxifen***
- Testosterone

## INHIBITORS
- Amiodarone
- Bupropion
- Celecoxib
- Cimetidine
- Metoclopramide
- Methadone
- Paroxetine
- Quinidine
- Ritonavir
- SSRIs***: fluoxetine, fluvoxamine, sertraline

## INDUCERS
- Carbamazepine
- Dexamethasone
- Phenobarbital
- Phenytoin
- Rifampin
Clinical consequence of metabolized phenotypes on drug response

Pro-drug

Parent-drug

Active metabolite

Inactive metabolite

Single pathway with absent or severely impaired activity due to
• Genetic variants
• Interacting drugs

Absent/impaired pathway → failure of efficacy
• Clopidogrel CYP19*2
• Tamoxifen CYP2D6*4
• Codeine CYP2D6*4

Absent/impaired pathway → toxicity due to parent drug accumulation
• Warfarin and bleeding CYP2C9*3
• Terfenadine and ↑QTc CYP3A4
• Omeprazole CYP2C19

1) UM – good drug efficacy, rapid (and exaggerated) effects
2) UM – poor drug efficacy, requires higher dosage. AEs in PMs

Metabolic pathway of P2Y$_{12}$-receptor inhibitors

**CLOPIDOGREL – CYP2C19:**
- *2(*2*2): loss - ↑ risk of stent thrombosis and MACE after PCI
- *17: gain - ↑ risk of bleeding
- Omeprazol is a substrate and inhibitor of CYP2C19
Algorithm for suggested clinical actions based on CYP2C19 genotype when considering treatment with clopidogrel for ACS patients undergoing PCI

Considering antiplatelet therapy with clopidogrel for ACS/PCI

CYP2C19 genotype results

- **UM (\(^{*1/*17, *17/*17}\)**)
  - Standard dosing of clopidogrel

- **EM (\(^{*1/*1}\)**)
  - Consider alternative antiplatelet Drugs (e.g. prasugrel, ticagrelor)

- **IM (\(^{*1/*2, *1/*3, *2/*17}\)**)

- **PM (\(^{*2/*2, *2/*3, *3/*3}\)**)

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<table>
<thead>
<tr>
<th>Genotype</th>
<th>Platelet inhih.</th>
<th>Residual platelet aggreg.</th>
<th>CV risks</th>
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</thead>
<tbody>
<tr>
<td>UM (32.9%)</td>
<td>↑</td>
<td>↓</td>
<td>↓ (↑ bleeding)</td>
</tr>
<tr>
<td>EM (38.5%)</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>IM (26.1%)</td>
<td>↓</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>PM (1.7%)</td>
<td>↓↓↓</td>
<td>↑↑</td>
<td>↑↑↑</td>
</tr>
</tbody>
</table>

If the parent drug needs to be metabolized to the active compound and metabolism is inhibited, then a therapeutic failure could result:

- 80% of codeine is converted via CYP3A4 to glucuronide, eliminated by kidney
- 5-10% is metabolized into morphine by CYP2D6
- Inhibition of CYP3A4 or rapid metabolic variants of CYP2D6 during renal failure would cause opioid intoxication
  - 7% of caucasians have a non-functional CYP2D6 variant
  - <2% are ultrarapid metabolizers

Enzyme inhibition

Increasing bleeding risk with warfarin in the elderly:

- Age explains 40% of dosing variation
- Variants in VKORC1 can explain 25%
- Variants in CYP2C9 can explain 15%

- Deficiency in vitamin K-dependent clotting factors (hepatic diseases), decreased hepatic clearance (↓ hepatic blood flow and warfarin plasma protein binding)

VKORC1: Vitamin K epOxide Reductase Complex subunit 1
Drugs in which both genotype and age ratios may be of particular concern.

Affected by age

Affected by age and genotype

No particular consideration
Age-related increase in the systemic exposure to drugs

A PK ratio of 1 indicates no difference between younger and older people having received the same drug dose.

Take home messages

1. Aging is associated with pluripathology leading to polypharmacy

2. The PD/PK of CV drugs are modified due to age- and comobidities-related changes in organ function/body composition
   - Elderly people present a decrease in hepatic clearance
   - Differences in drug efficacy/safety
   - Monitor hepatic function and drug efficacy/safety

3. Genetic diversity is the rule rather than the exception with drug metabolizing enzymes

4. Evidence from RCTs in patients >75 years of age are sparse
   - Guidelines do not mention the elderly population

5. We need to better understand the pharmacology in the elderly (BEERS, STOP/START)

6. Physicians, pharmacists, nurses...... must work together to improve drug therapy in the elderly