Cardiovascular drugs: some important interaction

Prof. Dr Milica Prostran

Department of Pharmacology, Clinical Pharmacology and Toxicology School of Medicine, University of Belgrade
Belgrade, Serbia
Should be able to answer

• Define drug interactions
• Describe a mechanism of interactions
• Metabolic interactions (inducers and inhibitors)
• How to avoid or manage metabolic interactions
• High risk patients and drugs
• General strategies for the management of interactions

Magyar, 2003
Definition

Drug interaction can be defined as the modification of the effects of one drug (object drug) by the prior or concomitant administration of another drug (precipitant drug)
The clinical result of a drug–drug interaction may manifest as:

- **Antagonism** (ie. $1 + 1 < 2$)
- **Synergism** (ie. $1 + 1 > 2$)
- **Idiosyncratic** (ie. a response unexpected from the known effects of either drug)
Simple additive or antagonistic effects anticipated to occur based on known pharmacological activity are not necessarily included:

- The additive blood pressure lowering effects of combining two antihypertensive agents
- Obvious antagonistic effects of beta blockers and isoproterenol
• Predictability of drug interactions:
  o Whether the interaction occurs and produces an adverse effect or not depends on:
    ▪ The presence or absence of factors that predispose to the adverse effects of drug interactions such as diseases, organ function, dose of drugs, etc.
    ▪ Awareness on the part of the prescriber, so that appropriate monitoring can be ordered or preventive measures taken

*Horn, 2007*
Clinically documented interactions:

- Clarithromycin: ↓ statin metabolism [Predictable]:
  - Interaction occurs in most patients receiving the combination

- Clofibrate: ↑ risk of myopathy [Non predictable]:
  - Interaction occurs only in some patients receiving the combination

- Diltiazem: ↓ statin metabolism [Non established]:
  - Insufficient data available on which to base estimate of predictability
• A primary concern is the clinical relevance or significance of the interaction

• The primary factors that define clinical significance include:

  • **SIGNIFICANCE RATING**
  • The time of **ONSET** of the effects of the interaction
  • The potential **SEVERITY** of the interaction
  • The **DOCUMENTATION** that the interaction occurs clinically
SIGNIFICANCE RATING

Anticoagulants (eg. warfarin) and NSAIDs

- Significance:
  - 1, 2, 3, 4, 5
- Onset:
  - Rapid
  - Delayed
- Severity:
  - Major
  - Moderate
  - Minor
- Documentation:
  - Established
  - Probable
  - Suspected
  - Possible
  - Unlikely
SIGNIFICANCE RATING

Anticoagulants (eg. warfarin) and NSAIDs

- **Effects:**
  - Anticoagulant activity may be increased by NSAIDs, increasing risk of bleeding

- **Mechanism:**
  - Gastric irritation and decreased platelet function contribute

- **Management:**
  - Monitor patients closely and instruct them to report signs and symptoms of bleeding to health care provider

- **Note:**
  - Warfarin may be subject to many (up to 80) drug interactions
  - Two major known sites of interaction are:
    - The plasma proteins where warfarin is bound while circulating
    - The hepatic cytochrome P450 system were warfarin is broken down by CYP2C9

Tatro et al., 2004
• Direct thrombin inhibitor dabigatran etexilate:

  o Dabigatran etexilate and dabigatran are not metabolised by cytochrome P450 system and have no *in vitro* effects on human cytochrome P450 enzymes

  o Dabigatran etexilate + diclofenac:
    - The plasma exposure of both drugs remains unchanged indicating a lack of PK interactions
    - Due to the risk of haemorrhage, notably with NSAIDs with $t_{1/2} > 12$ hours, close observation for signs of bleeding is recommended
• **Transporter interactions:**

  - Dabigatran etexilate is a substrate of the efflux transporter P-glycoprotein
  - Amiodarone is an inhibitor of this transporter
  - Amiodarone + dabigatran etexilate:
    - The extent and rate of absorption of amidarone is unchanged
    - Dabigatran AUC and C\textsubscript{max} are increased by 60% and 50%, respectively
  - Mechanism of this interaction is not completely clarified
  - In view of the long \( t_{1/2} \) of amiodarone, the potential for the interaction may exist for weeks after discontinuation of amiodarone
  - Dosing of dabigatran etexilate should be reduced to 150 mg daily
• Transporter inhibitors:
  o Clarithromycin
  o Verapamil
  o Quinidine-contraindicated

• Caution should be exercised
• Transporter inducers:
  - St John’s wort (*Hypericum perforatum*)
  - Rifampicin

• May reduce the systemic exposure to dabigatran
CYTOCHROME P450
### Drugs that induce cytochrome P450 isoenzymes

<table>
<thead>
<tr>
<th>Cytochrome P450 isoenzyme</th>
<th>Inducing drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CYP1A2</strong></td>
<td>• Barbiturates</td>
</tr>
<tr>
<td></td>
<td>• Omeprazole</td>
</tr>
<tr>
<td></td>
<td>• Phenytoin</td>
</tr>
<tr>
<td></td>
<td>• Tobacco smoke</td>
</tr>
<tr>
<td><strong>CYP2D6</strong></td>
<td>• ?</td>
</tr>
<tr>
<td><strong>CYP2C9</strong></td>
<td>• Barbiturates</td>
</tr>
<tr>
<td></td>
<td>• Rifampicin (rifampin)</td>
</tr>
<tr>
<td><strong>CYP2C19</strong></td>
<td>• ?</td>
</tr>
<tr>
<td><strong>CYP3A4</strong></td>
<td>• Barbiturates</td>
</tr>
<tr>
<td></td>
<td>• Carbamazepine</td>
</tr>
<tr>
<td></td>
<td>• Dexamethasone</td>
</tr>
<tr>
<td></td>
<td>• Rifampicin</td>
</tr>
</tbody>
</table>
Enzyme induction

- Increased production of drug metabolising enzymes (primarily Phase I metabolism)
- For maximum effect 2 to 3 weeks may be required
- Some drugs (carbamazepine) may increase its own metabolism
- It is a reversible process (slower process than induction)
- Characteristics: slow onset

Decreases the therapeutic activity of the object drug
If precipitant drug discontinued, toxicity could occur

Examples: phenytoin + mexiletine

Magyar, 2003
<table>
<thead>
<tr>
<th>Cytochrome P450 isoenzyme</th>
<th>Inhibiting drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP1A2</td>
<td>• Enoxacin</td>
</tr>
<tr>
<td></td>
<td>• Cimetidine</td>
</tr>
<tr>
<td></td>
<td>• Fluvoxamine</td>
</tr>
<tr>
<td></td>
<td>• Grapefruit juice:</td>
</tr>
<tr>
<td></td>
<td>• Bioflavonoid naringenin</td>
</tr>
<tr>
<td></td>
<td>• Furanocoumarin</td>
</tr>
<tr>
<td></td>
<td>dihydrobergamottin</td>
</tr>
<tr>
<td>CYP2D6</td>
<td>• Fluoxetine</td>
</tr>
<tr>
<td></td>
<td>• Quinidine</td>
</tr>
<tr>
<td></td>
<td>• Ritonavir</td>
</tr>
<tr>
<td>CYP2C9</td>
<td>• Fluconasole</td>
</tr>
<tr>
<td></td>
<td>• Fluoxetine</td>
</tr>
</tbody>
</table>
# Drugs that inhibit cytochrome P450 izoenzymes

<table>
<thead>
<tr>
<th>Cytochrome P450 izoenzyme</th>
<th>Inhibiting drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP2C19</td>
<td>• Fluoxetine</td>
</tr>
<tr>
<td></td>
<td>• Omeprazole</td>
</tr>
<tr>
<td>CYP3A4</td>
<td>• Cimetidine</td>
</tr>
<tr>
<td></td>
<td>• Erythromycin</td>
</tr>
<tr>
<td></td>
<td>• Grapefruit juice</td>
</tr>
<tr>
<td></td>
<td>• Ketoconazole</td>
</tr>
<tr>
<td></td>
<td>• Ritonavir</td>
</tr>
</tbody>
</table>
Enzyme inhibition

- The most common mechanism of drug interaction
- Competition occurs between the precipitant and object drug on the active site of the enzyme
- Onset of interaction is rapid, occurring within hours
- Non competitive mechanisms are existing less commonly
- The enzyme inhibition is dose related
- Reversal of interaction occurs usually within 24 hours
- Increases plasma concentrations of the object drug
- The pharmacological and the adverse effects are potentiated

Examples: erythromycin + antihistamines
omeprazol + diazepam  

*Magyar, 2003*
• HMG-CoA reductase inhibitors are susceptible to CYP3A4 inhibitors/CYP3A4 inductors
  - Lovastatin
  - Simvastatin
  - Atorvastatin (to a lesser extent)

• Increased risk of additive myopathy with other drugs that can cause myopathy
### Pharmacokinetic drug interactions with NSAIDs

<table>
<thead>
<tr>
<th>Drug(s) affected by NSAIDs</th>
<th>NSAID(s) implicated</th>
<th>Effect(s)</th>
<th>Management</th>
</tr>
</thead>
</table>
| Oral anticoagulants         | Azapropazone, Oxyphenazone, Phenylbutazone | Inhibition of metabolism of S-warfarin, increasing anticoagulant effect | • Avoid NSAIDs if possible  
• Careful monitoring when unavoidable |
| Digoxin                     | All NSAIDs          | Potential reduction in renal function (particularly in very young and very old):  
• Digoxin CL ↓  
• Plasma concentration ↑  
• Toxicity ↑ | • Avoid NSAIDs if possible  
• Frequent check of serum digoxin concentrations and serum creatinine |
<table>
<thead>
<tr>
<th>Drug affected by NSAIDs</th>
<th>NSAID(s) implicated</th>
<th>Effect(s)</th>
<th>Management</th>
</tr>
</thead>
</table>
| Anticoagulants         | All NSAIDs         | • GIT mucosal damage  
                          • Inhibition of platelet aggregation  
                          • Risk of GIT bleeding | • Avoid NSAIDs if possible |
| All diuretics: loop and thiazide | All NSAIDs | • Risk of hemodynamic renal insufficiency ↑  
                          • Antihypertensive effect ↓ | • Avoid combination if possible  
                          • Adjust diuretic dose or add another agent |
NSAIDs + Aspirin or NSAIDs

- Aspirin is reported to increase, decrease or have no effect on serum indomethacin levels.
- It does not reduce serum levels of piroxicam and sudoxicam.
- Aspirin reduces serum diclofenac, fenoprofen, flurbiprofen, ibuprofen, ketoprofen, naproxen, pirprofen, tenoxicam and tolmetin levels.
Other interactions with aspirin (Fox et al., 2009):

- Concurrent warfarin and aspirin therapy increases the risk of bleeding, especially if aspirin doses are high.
- Aspirin inhibits COX-1 activity about 170 times more than COX-2:
  - Interaction with COX-2 inhibitors is unlikely.
    - NSAIDs with dominant COX-1 activity (ibuprofen, naproxen) interfere with cardioprotective activity of aspirin.
  - NSAIDs with dominant COX-2 activity (diclofenac) do not interfere with cardioprotective activity of aspirin.
• Concomitant administration of ibuprofen (400 mg/day) or 3 times per day but not rofecoxib, acetaminofen, or diclofenac competitively antagonized the irreversible platelet inhibition induced by aspirin 81 mg/day in a randomized, crossover study (Catella-Lawson et al., 2001)
CYCLOOXYGENASE INHIBITORS AND THE ANTIPLATELET EFFECTS OF ASPIRIN

FRANCESCA CATELLA-LAWSON, M.D., MUREDACH P. REILLY, M.D., SHIV C. KAPOOR, PH.D., ANDREW J. CUCCHIARA, PH.D., SUSAN DEMARCO, R.N., BARBARA TOURNIER, R.N., SACHIN N. VYAS, PH.D., AND GARRET A. FITZGERALD, M.D.
Cardiovascular Risks of Nonsteroidal Antiinflammatory Drugs in Patients After Hospitalization for Serious Coronary Heart Disease
Circ Cardiovasc Qual Outcomes 2009;2;155-163; originally published online May 5, 2009;

http://circoutcomes.ahajournals.org/cgi/content/full/2/3/155
Conclusions:

• "In patients recently hospitalized for serious coronary heart disease, naproxen had better cardiovascular safety than did diclofenac, ibuprofen, and higher doses of celecoxib and rofecoxib."
Effects of Ibuprofen on the Magnitude and Duration of Aspirin's Inhibition of Platelet Aggregation: Clinical Consequences in Stroke Prophylaxis
Francis M. Gengo, Lisa Rubin, Matthew Robson, Michelle Rainka, Michael F. Gengo, Donald E. Mager and Vernice Bates
DOI: 10.1177/0091270007310379

The online version of this article can be found at:
http://www.jclinpharm.org/cgi/content/abstract/48/1/117
Aspirin + ACE inhibitors:

- ACE inhibitors and aspirin have potentially opposing effects on renal hemodynamics:
  - Aspirin inhibits the formation of vasodilatory prostaglandins
  - ACE inhibitors promote the formation of vasodilatory prostaglandins
- When ACE inhibitors are chronically used for heart failure, postinfarct protection and high-risk prevention, they are still beneficial when aspirin is added
- Aspirin did reduce but not eliminate the ACE inhibitor’s beneficial effect on major clinical events:
  - A practical policy is to keep the aspirin dose low, especially in those with hemodynamic problems such as heart failure
The risk of aspirin-induced GI bleeding is increased by:

- Alcohol
- Corticosteroids
- NSAIDs
The efficacy of aspirin is decreased by:

- Phenobarbital
- Phenitoin
- Rifampicin
Aspirin increases the effect of:

- Oral hypoglycaemic agents
- Insulin
Aspirin may reduce the efficacy of:

- Uricosuric drugs such as sulfinpyrazone
- Probenecid
- Combination with thiazide diuretics retards the urinary excretion of uric acid, increasing the risk of gout
Facts on NSAIDs interactions

• The elderly and patients with diabetes, renal or cardiovascular disease are most at risk from drug interactions with NSAIDs
• The most important interactions of NSAIDs are pharmacodynamic
• There are also some important pharmacokinetic interactions involving NSAIDs, but:
  • NSAIDs generally have little effect on hepatic clearance of other drugs
  • Pyrazole NSAIDs: phenylbutazone and azapropazone inhibit the metabolism of warfarin, tolbutamide and phenytoin
• **COX-2 inhibitors (coxibs):**
  - Celecoxib
  - Parecoxib
  - Rofecoxib
  - Valdecoxib

• Like nonselective NSAIDs, coxibs are hepatically metabolized:
  - Rofecoxib primarily by reduction by cytosolic enzymes
  - Celecoxib by P450 enzyme system: CYP2C9

• Celecoxib inhibits CYP2D6 and may affect concentrations of CYP2D6 substrates
• The best strategy for treating pts with both arthritis and risk for cardiovascular events would be to first try acetaminophen, up to 4 g/day
• If acetaminophen is not successful, than naproxen may be prescribed
• If the patient is at increased risk for gastrointestinal event caused by aspirin or naproxen (eg. age > 60 years, history of ulcers, etc.), then a gastroprotective agent can be added (a proton pump inhibitor or misoprostol)
• NSAIDs are among the most widely used classes of drugs worldwide, available both through prescription and over the counter (OTC)
• NSAIDs are prescribed for a wide variety of indications
• They are frequently taken by patients who are taking other drugs, especially the elderly who are likely to have comorbid diseases
• Approximately 20% of patients taking NSAIDs will develop 1 or > 1 of a variety of renal function abnormalities
• Potential drug interactions are identified in more than 50% of all patients treated with NSAIDs for symptoms of arthritis alone
And something more…
<table>
<thead>
<tr>
<th>Drug</th>
<th>Herb</th>
<th>Possible effects</th>
<th>Clinical tips</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin</td>
<td>Chamomile</td>
<td>• May ↑ risk of bleeding because of coumarin or coumarin derivatives in herb</td>
<td>• Monitor pts for signs and symptoms of increased bleeding</td>
</tr>
<tr>
<td></td>
<td>Garlic</td>
<td>• Herb may ↓ platelet activation factor</td>
<td>• Monitor results of hematological and coagulation studies</td>
</tr>
<tr>
<td></td>
<td>Parsley</td>
<td>• May ↑ bleeding time in susceptible pts</td>
<td>• Advise pts to consult health care provider before using herb</td>
</tr>
<tr>
<td></td>
<td>Ginkgo biloba</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
## Some herb-drug interactions II

<table>
<thead>
<tr>
<th>Drug</th>
<th>Herb</th>
<th>Possible effects</th>
<th>Clinical tips</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atenolol</td>
<td>Ginger</td>
<td>May antagonise effect of drug</td>
<td>Monitor BP</td>
</tr>
<tr>
<td>Captopril</td>
<td>Capsaicin</td>
<td>May ↑ risk of cough</td>
<td>Discourage use</td>
</tr>
<tr>
<td></td>
<td>Ginger</td>
<td>May antagonise effect of drug</td>
<td>Monitor BP</td>
</tr>
</tbody>
</table>
## Some herb-drug interactions III

<table>
<thead>
<tr>
<th>Drug</th>
<th>Herb</th>
<th>Possible effects</th>
<th>Clinical tips</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Digoxin</strong></td>
<td>• St. John’ wort</td>
<td>• May ↓ digoxin level&lt;br&gt; • Therapeutic effect ↓</td>
<td>• Advise pts of this effect&lt;br&gt; • Monitor serum level</td>
</tr>
<tr>
<td><strong>Enalapril</strong></td>
<td>• St. John’ wort</td>
<td>• May ↑ photosensitivity adding to the risk of sunburn or skin rash</td>
<td>• Advise pts to wear sunscreen or protective clothing during sun exposure</td>
</tr>
<tr>
<td><strong>Fosinopril</strong></td>
<td>• St. John’ wort</td>
<td>• May ↑ photosensitivity adding to the risk of sunburn or skin rash</td>
<td>• Advise pts to wear sunscreen or protective clothing during sun exposure</td>
</tr>
</tbody>
</table>