Cardiovascular Toxicity of Non-Cardiovascular Drugs

By:
Amr Abdulraouf Hassan, B.Sc. Pharm., Pharm.D., BCCCP
Inpatient Pharmacy Supervisor, As-Salam International Hospital
Cardiovascular Toxicity

- **Cardiotoxicity of drugs can include a wide array of disorders; which can include:**
  - Myocardial dysfunction and Heart Failure
  - Vascular disorders;
    - Thromboembolic disease [Coronary artery disease, PVD and Stroke]
    - Arterial Hypertension
    - Pulmonary Hypertension
  - Arrhythmias
  - Valvular Disease
  - Other complications (Eg; Pericardial disease)

Cardiotoxic Drugs

- **A wide array of non-cardiovascular medication can have cardiotoxicities.**
- **Cardiotoxic medications can belong to varying classes; including:**
  - Analgesics
  - Anesthesia medication
  - Antidiabetic medication
  - Medication for BPH
  - Anti-cancer
  - Anti-depressants
  - Anti-psychotics
  - And much more......
Today’s Session, we will discuss...

- One of the most commonly used medications in the elderly (Probably with cardiovascular disease)

- One of the most commonly prescribed medications globally.

- In the United States:
  - Over 70,000,000 (70 Million) prescriptions annually
  - Over 30,000,000,000 (30 Billion) OTC medication sold annually

Today’s Session, we will discuss...

Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)
Agenda

I. Pharmacology and Classification
II. Cardiovascular Toxicities:
   – Thrombotic Complications and Myocardial dysfunction
     A. Evidence
     B. Drug interaction with Aspirin
     C. Take Home Messages

I. Pharmacology of NSAIDs

[Diagram showing the mechanism of action of NSAIDs and their effects on platelets, pain, fever, inflammation, and gastric protection.

NSAIDs = Cyclooxygenase Inhibitors

Pain, Fever, Inflammation
Gastric Prot.

Inh Plt Aggr.
VD

Platelet Aggregation]
I. Pharmacology of NSAIDs

Cyclooxygenases (COX)

COX-1

• Expressed in most tissues

• Described as a "housekeeping" enzyme, regulating normal cellular processes (such as gastric cytoprotection, vascular homeostasis, platelet aggregation, and kidney function).

COX-2

• Mainly expressed in the brain, kidney, bone, and probably in the female reproductive system, but which is undetectable in most other tissues.

• Expression is increased during states of inflammation, or experimentally in response to mitogenic stimuli.

I. Pharmacology of NSAIDs

Cyclooxygenases (COX)

COX-1

• Major (COX) in Gastric and Duodenal Mucosa (Gastric protection)

• Platelets ONLY express (COX-1) to produce Thromboxane A2 (Promoting platelet aggregation) >> Prothrombotic activity

COX-2

• Present in endothelial cells to produce PGI2.

• PGI2 restrains the effect of Thromboxane A2 (Inhibiting platelet aggregation) >> Antithrombotic activity
I. Pharmacology of NSAIDs

### COX and Platelets

**Endothelial cells**

- Platelets
  - COX-1
  - TXA$_2$
  - PGI$_2$

**Platelets**

- GP IIb/IIIa
- Fibrinogen
- ADP
- P2Y$_{1,12}$

**COX-2**

**Collagen**

**vWF**

**International Hospital**
I. Pharmacology of NSAIDs

COX and Platelets

Aspirin ↓ dose

COX-2 Inh

tNSAIDs

Non-Selective (tNSAIDs)

Gastro-Toxic
Less Thrombogenic

NSAIDs

COX-2 Inhibitors

More Thrombogenic
II. Thrombotic Complications and Myocardial Dysfunction

Evidence

Take Home Message

DDI with Aspirin

A. Evidence

2013 ESC guidelines
The Management of Stable Coronary Artery Disease

7.3 Other drugs
7.3.1 Analgesics
The use of selective cyclooxygenase-2 (COX-2) inhibitors and traditional non-selective non-steroidal anti-inflammatory drugs (NSAIDs) has been associated with an increased risk for CV events in recent clinical trials in arthritis and cancer prevention and are not recommended. In patients at increased CV risk in need of pain relief, it is therefore recommended to commence with acetaminophen or aspirin at the lowest efficacious dose, especially for short-term needs.
A. Evidence

2016 AHA Scientific Statement
Drugs That May Cause or Exacerbate Heart Failure

<table>
<thead>
<tr>
<th>Drug or Therapeutic Class</th>
<th>Association With HF</th>
<th>Magnitude of HF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Analgesics</td>
<td></td>
<td></td>
</tr>
<tr>
<td>COX, nonselective inhibitors (NSAIDs)</td>
<td>( x )</td>
<td>Major</td>
</tr>
<tr>
<td>COX, selective inhibitors (COX-2 inhibitors)</td>
<td>( x )</td>
<td>Major</td>
</tr>
</tbody>
</table>

Possible Mechanisms:
- Prostaglandin inhibition leading to sodium and water retention, increased systemic vascular resistance, and blunted response to diuretics

So...
Can’t we find a way to use NSAIDs rationally in cardiovascular patients?
A. Evidence

Let’s take A Deeper Look into the evidence behind recommendations!

- CNT Metaanalysis, Lancet, 2013
- PRECISION Double-Blinded RT, NEJM, 2016
- Retrospective Cohort, JAMA, 2009
A. Evidence

Retrospective Cohort-JAMA-2009

<table>
<thead>
<tr>
<th>Type-Journal-Year</th>
<th>Population</th>
<th>Comparators</th>
<th>End Points</th>
</tr>
</thead>
</table>
|                   | 107,092 patients surviving their first hospitalization because of HF between January 1, 1995, and December 31, 2004 and their subsequent use of NSAIDs | Rofecoxib, Celecoxib, Ibuprofen, Diclofenac, Naproxen, and other NSAIDs | • Hazard Ratios for Death  
• Hospitalization Because of HF  
• Hospitalization Because of AMI |

A. Evidence

• Conclusion:
  – Treatment with NSAIDs, both selective COX-2 inhibitors and nonselective NSAIDs, in patients with chronic HF is associated with increased mortality and cardiovascular morbidity, with a dose-dependent response.
  – Therefore, patients with HF should, if possible, avoid using any NSAIDs at any dosage for most NSAIDS and at high dosages for ibuprofen and naproxen.
A. Evidence

A Deeper Look

Table 3. Hazard Ratios for Death, and Hospitalization Because of HF or AMI

<table>
<thead>
<tr>
<th>Drug</th>
<th>Death (HR, 95% CI, P Value)</th>
<th>Hospitalization Because of HF (HR, 95% CI, P Value)</th>
<th>Hospitalization Because of AMI (HR, 95% CI, P Value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rotacorb 25 mg/d</td>
<td>1.70 (1.59-1.82, &lt;.001)</td>
<td>1.40 (1.26-1.55, &lt;.001)</td>
<td>1.00 (1.00-1.01, .01)</td>
</tr>
<tr>
<td>Rotacorb &gt;25 mg/d</td>
<td>1.42 (1.31-1.54, &lt;.001)</td>
<td>1.35 (1.30-1.40, &lt;.001)</td>
<td>.99 (1.00-1.01, .01)</td>
</tr>
<tr>
<td>Cotescib 25 mg/d</td>
<td>3.54 (3.12-4.02, &lt;.001)</td>
<td>1.06 (1.01-1.13, .01)</td>
<td>.98 (1.00-1.01, .01)</td>
</tr>
<tr>
<td>Cotescib &gt;25 mg/d</td>
<td>1.75 (1.63-1.86, &lt;.001)</td>
<td>1.24 (1.12-1.36, &lt;.001)</td>
<td>1.38 (1.38-1.40, &lt;.001)</td>
</tr>
<tr>
<td>Naproxen Any use</td>
<td>1.94 (1.98-1.99, &lt;.001)</td>
<td>1.16 (1.16-1.21, &lt;.001)</td>
<td>1.39 (1.40-1.40, &lt;.001)</td>
</tr>
<tr>
<td>Naproxen &gt;1200 mg/d</td>
<td>2.05 (2.04-2.05, &lt;.001)</td>
<td>1.18 (1.18-1.19, &lt;.001)</td>
<td>1.42 (1.42-1.42, &lt;.001)</td>
</tr>
<tr>
<td>Naproxen &gt;1200 mg/d</td>
<td>2.82 (2.84-2.80, &lt;.001)</td>
<td>1.19 (1.19-1.19, &lt;.001)</td>
<td>1.47 (1.47-1.47, &lt;.001)</td>
</tr>
<tr>
<td>Aspirin 100 mg/d</td>
<td>2.08 (2.05-2.12, .01)</td>
<td>1.20 (1.19-1.21, &lt;.001)</td>
<td>1.47 (1.47-1.47, &lt;.001)</td>
</tr>
<tr>
<td>Aspirin &gt;500 mg/d</td>
<td>2.01 (2.00-2.02, &lt;.001)</td>
<td>1.19 (1.19-1.20, &lt;.001)</td>
<td>1.48 (1.48-1.48, &lt;.001)</td>
</tr>
<tr>
<td>Other NSAID</td>
<td>1.09 (1.02-1.07, .01)</td>
<td>1.08 (1.08-1.09, &lt;.001)</td>
<td>1.32 (1.31-1.33, &lt;.001)</td>
</tr>
</tbody>
</table>

A. Evidence

Is Naproxen Safer?

- Authors DO NOT state this conclusion
- Authors recommend avoiding “high doses of naproxen and ibuprofen” in patients with heart failure

Results show uncertainty regarding Naproxen’s association with mortality or hospitalization for HF or AMI
A. Evidence

Vascular and upper gastrointestinal effects of non-steroidal anti-inflammatory drugs: meta-analyses of individual participant data from randomised trials

Type-Journal-Year  “Coxib, Traditional NSAID Trialist (CNT)”  Meta-Analysis-Lancet-2013

Population  280 Randomized trials of NSAIDs versus placebo (124,513 participants) and 474 Randomized trials of one NSAID versus another NSAID (229,296 participants)

Comparators  Any Coxib (Celecoxib, Rofecoxib, Lumiracoxib)  Individual tNSAIDs (Naproxen, Ibuprofen, Diclofenac)

Relevant End Points  • Major Vascular events (non-fatal myocardial infarction, non-fatal stroke, or death from a vascular Cause)
• Major Coronary Events
• Vascular Deaths
• Hospitalization for Heart Failure

A. Evidence

Vascular and upper gastrointestinal effects of non-steroidal anti-inflammatory drugs: meta-analyses of individual participant data from randomised trials

• **Conclusion:**
  – Major Cardiovascular events increased by Coxibs and Diclofenac (Mainly due to inc. in coronary events)
  – Major coronary events only increased by Ibuprofen
  – Vascular Deaths increased by Coxibs or Diclofenac.
  – Vascular Deaths increased by ibuprofen (But not statistically significant)
  – Heart Failure risk was doubled by ALL NSAIDS
A. Evidence

Vascular and upper gastrointestinal effects of non-steroidal anti-inflammatory drugs: meta-analyses of individual participant data from randomised trials

• **Conclusion:**
  – Naproxen did NOT increase major cardiovascular events, major coronary events or vascular deaths

The vascular risks of high-dose diclofenac, and possibly ibuprofen, are comparable to coxibs, whereas high-dose naproxen is associated with less vascular risk than other NSAIDs.

A. Evidence

Vascular and upper gastrointestinal effects of non-steroidal anti-inflammatory drugs: meta-analyses of individual participant data from randomised trials

• **However:**
  – *Is it fair to compare individual tNSAIDs with ALL Coxibs and make a conclusion to Celecoxib only; Given that Rofecoxib was withdrawn for proven cardiovascular toxicity??*  
  – *Possibly Biased results*
**A. Evidence**

### Type-Journal-Year

<table>
<thead>
<tr>
<th>“PRECISION Trial”</th>
<th>Blinded Randomized Non-inferiority Trial-NEJM-2016</th>
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### Population

24,081 patients with a Primary diagnosis (osteoarthritis or rheumatoid arthritis) randomly assigned, in a 1:1:1 ratio

### Comparators

- **Celecoxib** (100 mg twice a day)
- **Ibuprofen** (600 mg three times a day)
- **Naproxen** (375 mg twice a day)

### Relevant End Points

- **HR of Antiplatelet Trialists Collaboration (APTC) criteria** (i.e., death from cardiovascular causes, including hemorrhagic death; nonfatal myocardial infarction; or nonfatal stroke).
- **HR of Major Adverse Cardiovascular Events (MACE):** APTC plus coronary revascularization, hospitalization for unstable angina, transient ischemic attack
A. Evidence

• Conclusion:
  – At moderate doses, celecoxib was found to be non-inferior to ibuprofen or naproxen with regard to cardiovascular safety.

  *However, could the trial funding have influenced the results??* [Funded by Pfizer, the manufacturer of Celecoxib]

  *Possibly Biased Results*

A. Evidence

• To Sum things up:
  – All NSAIDs (Including COX-2 selective inhibitors) have potential for thrombotic complication, exacerbation of myocardial dysfunction or increase risk of vascular mortality
  – The risk is possibly dose related
  – COX-2 inhibitors may carry the greatest risk
  – Naproxen may carry the least risk
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<tr>
<th>B. DDI with Aspirin</th>
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- **Aspirin is the only tNSAID that binds IRREVERSIBLY on COX:**
  - Effect on Platelets’ COX-1:
    - **Short Duration (Hours)**
    - **BUT**
    - **Prolonged Antiplatelet effect (Days)**

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- **What will Happen, if another COX-1 inhibitor (tNSAIDs), competes with Aspirin to Binding with platelets COX-1 during this short duration??**
  - Can also cause a transient increase in antiplatelet activity > Increase the risk of bleeding
  - Can diminish Antiplatelet effect of Aspirin > Increase the risk of cardiovascular thrombotic events
B. DDI with Aspirin

<table>
<thead>
<tr>
<th></th>
<th>Ketorolac</th>
<th>Ibuprofen</th>
<th>Other tNSAIDs</th>
<th>Celecoxib</th>
</tr>
</thead>
<tbody>
<tr>
<td>DDI</td>
<td>Diminish Anti-Plt effect</td>
<td>Diminish Anti-Plt effect</td>
<td>Diminish Anti-Plt effect</td>
<td>Increase risk of GI bleeding</td>
</tr>
<tr>
<td></td>
<td>Increase risk of bleeding</td>
<td>Increase risk of bleeding</td>
<td>Increase risk of bleeding</td>
<td>(However, less significant with “Low doses” of Aspirin)</td>
</tr>
</tbody>
</table>

**Management**

<table>
<thead>
<tr>
<th></th>
<th>Contraindicated</th>
<th>Avoid regular frequent use of Ibuprofen with Aspirin</th>
<th>Avoid regular frequent use of tNSAIDs with Aspirin</th>
<th>Monitor closely for GI ulceration/Bleeding</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Give Ibuprofen 30-120 mins after Aspirin, or at least 8 hrs before aspirin</td>
<td>Give tNSAIDs at least 2 hrs after Aspirin</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

C. Take Home Messages

**We Should:**

1. **Council our patients on the hazards of NSAIDs and always ask for detailed medication histories**
2. **Avoid use of NSAIDs in patients with/at risk of cardiovascular disease**
3. **Avoid use of NSAIDs in patients taking Aspirin**
4. **Never combine Aspirin with Ketorolac**
5. **Consider Acetaminophen as an alternative if possible**
C. Take Home Messages

**We Should:**
6. If necessary, **Avoid regular/frequent use of NSAIDs and use them at the lowest effective doses**
7. **For CV patients who are NOT ON Aspirin, Consider Naproxen and Avoid Celecoxib**
8. **For CV patients ON Aspirin, consider Celecoxib or Naproxen**
9. **For patients taking tNSAIDs with Aspirin, consider administering the tNSAID dose 2 hours after Aspirin**
10. **Always monitor our patients for increased risk of bleeding**

Questions?
References

