Rational Use of NSAIDs

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Rational Use of Drugs – 5 R’s

“Rational use of drugs requires that patients receive medications appropriate to their clinical needs, in doses that meet their own individual requirements for an adequate period of time, and the lowest cost to them and their community.”

The **Right drug** at the **Right dose** by the **Right route** at the **Right time** for the **Right patient**.
Rational use of NSAIDs – Why?

• 73 million prescriptions per year worldwide

• 30 million people take NSAIDs daily

• Number of prescription in older population: 3-4 times more than younger population

• More than 400 formulations

• Use of various FDCs of NSAIDs
Scope of this presentation

• Risk associated with tNSAIDs

• Risk associated with selective COX-2 inhibitors

• Guidelines for use gastroprotective agents (GPA) with NSAIDs

• Comment on rationality of various FDCs of NSAIDs
  – NSAIDs + GPA
  – NSAIDs + NSAIDs
  – NSAIDs + Paracetamol
  – NSAIDs + Serratiopeptidase
Prostaglandin (PG) synthesis

Membrane Phospholipids

Arachidonic Acid

Phospholipase A2

Cyclooxygenase (COX)

Lipoxygenase (LOX)

Prostaglandins

Leukotrienes
Role of COX – 1 & COX – 2

Physiologic stimulus

COX – 1
 Constitutive

Stomach
Intestine
Endothelium

PGE$_2$
PGE$_1$
TXA$_2$
PGL$_2$

Physiologic Functions

Gastric mucosal damage

Inflammation

COX – 2
Inducible

Inflammatory sites
Macrophages, Leukocytes, Fibroblast, Endothelial cells

Inflammatory PGs

Anti-inflammatory effects

Inflammation

Physiologic Functions

NSAIDs

Inflammation

Physiologic stimulus
NSAIDs

Non-selective COX inhibitors
- Aspirin
- Ibuprofen
- Naproxen
- Indomethacin
- Piroxicam
- Mefenamic acid
- Paracetamol

Preferential COX-2 inhibitors
- Diclofenac
- Aceclofenac
- Meloxicam
- Nimesulide

Selective COX-2 inhibitors (Coxibs)
- Celecoxib
- Etoricoxib
- Lumiracoxib
- Parecoxib
NSAIDs in Essential Medicine List

- **National – 2015**
  1. Acetylsalicylic acid
  2. Diclofenac
  3. Ibuprofen
  4. Mefenamic acid
  5. Paracetamol

- **WHO – 2015**
  1. Acetylsalicylic acid
  2. Ibuprofen
  3. Paracetamol
<table>
<thead>
<tr>
<th>NSAIDs Type</th>
<th>Gastrointestinal Adverse Effects</th>
<th>Cardiovascular Adverse Effects</th>
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<tbody>
<tr>
<td>Non-selective COX – inhibitors</td>
<td>✗</td>
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<tr>
<td>Selective COX – 2 inhibitors</td>
<td>✓</td>
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NSAIDs and GI toxicity

- Dyspepsia
- Abdominal pain
- Flatulence

- Gastric ulcer
- Bleeding
- Perforation

Greater risk with non-selective NSAIDs as compared to Selective COX-2 inhibitors (Coxibs)
NSAIDs and GI toxicity

• Measures to reduce GI adverse effects

• Shall gastro protective agent be prescribed with NSAIDs?
  – If yes, when?
  – As FDC or separately?
NSAIDs and GI toxicity

- Measures to reduce GI risk of traditional NSAIDs
  - Use lowest dose of NSAIDs possible
  - Use only when needed
  - Take NSAIDs after meal
  - Use of gastro protective agents (as per guidelines for its use)
  - Use selective COX-2 inhibitors (consider Cardiovascular risk)
  - Write complete prescription

Naproxen best tolerated followed by Ibuprofen

Completeness of prescription
- Dosage form
- Drug
- Dose
- Frequency of administration
- Duration of treatment
- Special Instructions
NSAIDs and Gastro protective agents

- Conditions which warrant co-administration of a gastro protective agent with NSAIDs
  - Elderly population
  - Duration of NSAIDs therapy more than three (03) months
  - Previous history of peptic ulcer with or without haemorrhage or perforation
  - History alcoholism
  - Concomitant use of anticoagulant, low-dose aspirin or corticosteroids
  - Concomitant H. pylori infection
Selective COX – 2 inhibitors (Coxibs)

- Advantages over tNSAIDs
  - Less GI side effects, bleeding
  - Patients intolerant to conventional NSAIDs
  - OA, RA

- Are Coxibs completely safe???
Coxibs and toxicity

- Rofecoxib & Valdecoxb - Risk of myocardial infarction and stroke - Banned
Coxibs and toxicity

• Demerits of Coxibs
  – Acute myocardial infarction
  – Stroke
  – Hypertension
  – Na and water retention
  – Heart failure
  – Renal toxicity
Cardiovascular risk and NSAIDs

- COX-2 inhibitors
  - Dose-dependent
  - Duration of therapy

- tNSAIDs
  - Highest with Diclofenac
  - Lowest with Naproxen

- Ibuprofen interfere with antiplatelet action of aspirin
  - Take single dose of ibuprofen 30 min after taking aspirin
  - OR
  - Take aspirin at least 8 hours after taking ibuprofen
Algorithm for use of long-term NSAID therapy and gastro protective agents

Patient requires NSAID

- **High GI risk**
  - **High CV risk (On ASA)**
    - Avoid NSAID, if possible
    - Very high CV risk
      - Naproxen + PPI
    - Can’t avoid NSAID
      - Very high GI risk
        - COX-2 + PPI
  - Low CV risk
    - COX-2 alone or tNSAIDs + PPI
  - Low GI risk
    - Naproxen + PPI
    - Low CV risk (On ASA)
      - Naproxen + PPI
      - tNSAIDs

- **Low GI risk**
  - Low CV risk
    - tNSAIDs
NSAIDs and hepatic toxicity

- Diclofenac
- Paracetamol
- Nimesulide

**Monitoring**

- Periodic monitoring of liver enzymes
- Cessation of therapy, if the values exceed 2-3 times the upper limit of normal.

**Formulations and its combinations containing Nimesulide are banned in India for use in child < 12 years**
NSAIDs and renal toxicity

Who are at risk?

- Chronic renal insufficiency
- Congestive heart failure
- Severe hepatic disease
- Nephrotic syndrome
- Advancing age
- Diuretics
- ACE inhibitors
- Cyclosporine
- Aminoglycosides

Monitoring

- Serum creatinine at baseline and within 3 to 7 days of drug initiation

Recommendation

- Prefer acetaminophen over other NSAIDs
- Avoid combination of two NSAIDs
Acetaminophen and toxicity

- Hepatotoxicity
  - Use of dose >4 gm/day
  - Chronic alcohol intake
  - Patients with liver disease
  - Premature infants

- Renal toxicity (with long term use)
  - Increased risk with combination of NSAIDs
  - Dose-dependent
Fixed dose combinations (FDCs)

You name it, we have it
Government Bans 344 Drugs

Gazette Notification dated 10.03.2016
NSAIDs and Gastro protective agents

- Combinations available and routinely prescribed
  - Diclofenac + Pantoprazole
  - Diclofenac + Paracetamol + Pantoprazole
  - Aceclofenac + Pantoprazole
  - Aceclofenac + Rabeprazole
  - Paracetamol + Ranitidine

Justifiable???
- Pharmacokinetic incompatibility – Dosing schedule, Time of administration
- Add to cost of therapy

Recommendation
- Consider GPA only when required
- Do not use FDC, use separately
- Consider risk associated with long term use of PPI
Overuse of PPIs

• Increased cost of the treatment

• Risk associated with long term use of PPIs
  – Renal failure
  – Increased risk of fractures
  – *Clostridium difficile* infection
Fixed dose combinations

• FDC of NSAID and Paracetamol
  – Diclofenac + Paracetamol
  – Ibuprofen + Paracetamol

Justifiable ???

• Paracetamol – For Antipyretic action
• Diclofenac/Ibuprofen – For analgesic/anti-inflammatory action
Fixed dose combinations

- FDC of NSAID and NSAID
  - Diclofenac + Nimesulide
  - Ibuprofen + Diclofenac

Justifiable ???

- Risk of renal toxicity
- Risk of hepatic toxicity
- No added advantage of combination
- Increased cost of treatment
Fixed dose combinations

- FDC of NSAID and Serratiopeptidase
  - Diclofenac + Serratiopeptidase
  - Paracetamol + Serratiopeptidase

Justifiable ???

- Lack of evidence – Poor study design, ill-defined outcome variables, small sample size, short duration lack of active comparator
- Pharmacokinetic issues of Serratiopeptidase
- Increased cost of treatment
Summary

- Use NSAIDs considering risk
  - Gastrointestinal
  - Cardiovascular
  - Renal and Hepatic

- Use gastroprotective agents judiciously with NSAIDs

- DO NOT use unjustifiable FDCs of NSAIDs
Thank you...