

Slides Outline

THE INFLAMMATORY RESPONSE

- Involves a series of interactions
- Immunologically competent cells activate
- Cause vasodilation & vascular permeability
- Stimulate T cell release of cytokines. Various proinflammatory mediators (e.g., TNF, interleukin-1)
- Production of an inflammatory exudate

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graph TD
    A[INFLAMMATORY RESPONSE] --> B[IMMUNOLOGICALLY COMPETENT CELLS]
    B --> C[PROINFLAMMATORY CYTOKINES]
    C --> D[IL-1]
    C --> E[IL-6]
    C --> F[IL-17]
    D --> G[IL-1]
    E --> H[IL-6]
    F --> I[IL-17]
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- Damages cells & tissues via oxidant enzymes
- Causes vasodilation & vascular permeability
- Causes release of cytokines: active oxidant PAF
- PAF effect: oxidant release from activated inflammatory cells

Two versions of COX-1, COX-1 & COX-2

Non Steroidal Anti-inflammatory Drugs By Dr. Javald nazir

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Slides Outline

- Non-steroidal anti-inflammatory drugs
- THE INFLAMMATORY RESPONSE**
 - In acute or chronic inflammation
 - Immunologically competent cells activated
 - Outcome beneficial if infection controlled
 - Deleterious if no resolution of underlying injurious process (chronic inflammation) as in Rheumatoid arthritis
 - Mediators of ch. inflammation are different
- Diagram of COX-2 pathway
- Diagram of COX-1 and COX-2

THE INFLAMMATORY RESPONSE

- In acute or chronic inflammation.
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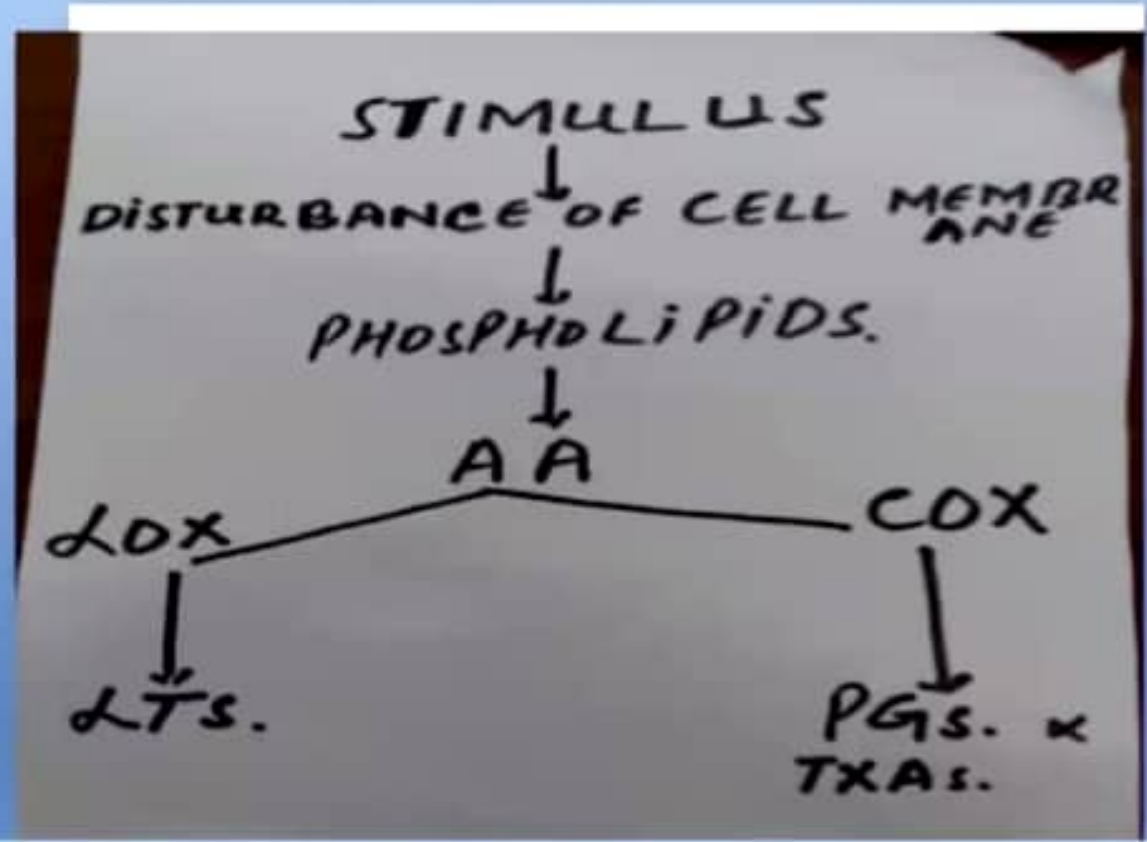
Non-Steroidal Anti-inflammatory Drugs

THE INFLAMMATORY RESPONSE

- Inflammation is a response to tissue injury.
- It is a complex process involving various cells and molecules.
- The inflammatory response is essential for healing and tissue repair.
- However, chronic inflammation can lead to various diseases.



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Non Steroidal Anti-inflammatory Drugs

THE INFLAMMATORY RESPONSE

- Involves a series of responses
- Involves the activation of various cells
- Involves the release of various mediators
- Involves the activation of various mediators
- Involves the activation of various mediators
- Involves the activation of various mediators

THE INFLAMMATORY RESPONSE

- Damaged WBC's release lysosomal enzymes
- Eicosanoids synthesized from liberated A.A
- Cyclooxygenase (COX) pathway produces PG's
- PG's affect blood vessels, nerve endings & inflammatory cells

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- Two isoforms of COX i.e. COX-1 & COX-2
- COX-1 has house keeping effects
- COX-2 inducible
- Highly selective COX-2 inhibitors developed

COX-1 has house keeping effects

- Cyclooxygenase pathway leads to prostaglandins
- They have proinflammatory effects
- All cell membranes possess it & constitutive
- Inhibits platelet aggregation & increases vascular permeability

COX-2 inducible

- Inflammation, healing
- Induced by cytokines & growth factors
- Induced by cytokines & growth factors

Highly selective COX-2 inhibitors developed

THERAPEUTIC STRATEGIES

- Two goals in treatment of inflammation
- 1. Relief of pain
- 2. Avoid of tissue-damaging effects

NSAIDs are analgesic & anti-inflammatory

- Successful in relieving inflammation
- Agents but without

- Two isoforms of COX i.e. COX-1 & COX-2
- **COX-1 has house keeping effects**
- COX-2 induced during inflammation
- **Highly selective COX-2 inhibitors developed**

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THERAPEUTIC STRATEGIES

- Two goals of treatment of inflammation
 - Relief of pain
 - Arrest of tissue damaging events
- NSAIDs are analgesic & anti-inflammatory
 - NSAIDs are cyclooxygenase inhibitors
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- NSAIDs: heterogeneous group of drugs
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THERAPEUTIC STRATEGIES

- Two goals of treatment of inflammation
- 1) Relief of pain
- 2) Arrest of tissue damaging process

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- NSAIDs are analgesics & anti-inflammatory
- Glucocorticoids are powerful anti-inflammatory agents but are toxic
- Slow acting anti-rheumatic drugs (SAARDs) or disease modifying anti-rheumatic drugs (DMARDs) slow down bone damage. More toxic than NSAIDs

- NSAIDs are analgesics & anti-inflammatory_I
- **Glucocorticoids are powerful anti-inflammatory agents but are toxic**
- Slow acting anti-rheumatic drugs (SAARDs) or disease modifying anti-rheumatic drugs (DMARDs) slow down bone damage. More toxic than NSAIDs

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THERAPEUTIC STRATEGIES

- The goals of treatment of inflammation
- 1. Relief of pain
- 2. Relief of local inflammatory process

NSAIDs are analgesic & antipyretics

- NSAIDs are powerful anti-inflammatory agents but not COX-2
- From being anti-inflammatories NSAIDs = increase resolving the inflammatory response

NSAIDs, heterogeneous group of drugs often chemically unrelated which nonetheless share some therapeutic actions & ad. effects. PROTOTYPE IS ASPIRIN, so these compounds often referred as Aspirin like drugs.

Since aspirin has a no. of ad. effects many other NSAIDs have been developed in attempts to improve upon aspirin's efficacy & dec. its toxicity.

They are non opioid analgesic antipyretics but it is their anti-inflammatory effects that make them most useful in management of disorders in which pain is related to the intensity of inflammatory process.

- Most commonly available NSAIDs are aspirin, COX-1 & 2, ibuprofen, naproxen, piroxicam & Fenoprofen (NSAIDs)
- COX-1 constitutive in nature & found in PLATELETS, KIDNEYS & STOMACH. They include aspirin's effect
- COX-2 induced in setting of inflammation. Present in various proinflammatory & anti-inflammatory agents.

Inhibition of COX-2 through blockade of pain, antipyretic, antipyretic & anti-inflammatory actions of NSAIDs but simultaneous inhibition of COX-1 results in undesirable effects esp. those related to platelet aggregation.

NSAIDS, heterogenous group of drugs, often chemically unrelated which nonetheless share some therapeutics actions & ad. effects. PROTOTYPE IS ASPIRIN, so these compounds often referred as Aspirin like drugs.

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THERAPEUTIC STRATEGIES

- 1. Two goals of treatment of inflammation
- 2. Areas of tissue damage avoided
- 3. NSAIDs are analgesic & anti-inflammatory
- 4. NSAIDs are poorly anti-inflammatory agents but effective
- 5. They acting anti-inflamm drug & NSAIDs = stressor resolving anti-inflamm drug
- 6. NSAIDs can cause side effects like renal impairment

NSAIDs: heterogenous group of drugs with chemically unrelated which nonetheless share some therapeutic actions & side effects. **PROSTAGLANDIN SYNTHASE** is aspirin, so these compounds often referred as aspirin like drugs.

Side effects include GIT, renal, hepatic, etc. NSAIDs have been developed in attempts to improve upon aspirin's efficacy & side effects.

There are two special analgesic analgesics, but it is their anti-inflammatory effect not

make them most useful in management of disorders in which pain is related to the intensity of inflammatory process.

- Most currently available NSAIDs inhibit both COX1 & 2 & thereby inhibit synthesis of PGDs & THROMBAXANES.
- COX1 constitutive in nature & found in PLATELETS, KIDNEYS & STOMACH. Has HOUSE KEEPING effect.
- COX2 induced in setting of inflammation. Present in lymphos, polymorphonuclear & other inflammatory cells.

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make them most useful in **management** of disorders in which pain is related to the intensity of inflammatory process.

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- NSAIDs are analgesic & anti-inflammatory
- Successes as pain & inflammation agents are mixed
- Even long-term use of NSAIDs is linked with cardiovascular disease. NSAIDs are also not drugs, but are like NSAIDs
- NSAIDs, heterogeneous group of drugs that chemically unrelated, but non-steroidal anti-inflammatory agents & as effect PROTOTYPE IS ASPIRIN, so these compounds often referred as Aspirin like drugs.
 - Since aspirin has anti-inflammatory effect, why the NSAIDs have been developed? Aspirin is not good aspirin's efficacy & safety.
 - They are not good analgesic, antipyretic, but it is a good anti-inflammatory effect.
- More than most useful in management of disorders in which pain is related to the intensity of inflammatory process.
 - Most commonly available NSAIDs are COX-1 & 2 selective inhibitors (PGE₂ & Thromboxane).
 - COX-1 constitutive in nature & found in PLATELETS, KIDNEYS & STOMACH. has HOUSE KEEPING effect.
 - COX-2 induced in setting of inflammation. Present in lymphoid, mononuclear & other inflammatory cells.
- Inhibition of COX-2 is thought to mediate analgesic, antipyretic & anti-inflammatory actions of NSAIDs. COX-2 selective inhibitors result in analgesic, antipyretic effect, but have no effect on platelet aggregation & thromboxane.
 - Normally, PGE₂ inhibits gastric acid secretion whereas PGE₂ & PGF_{2α} stimulate synthesis of protective mucus in both stomach & s. intestine. In presence of aspirin, these PGDs are not formed.
- Resulting in gastric acid secretion & diminished mucus protection. This may cause gastric distress, ulceration.
- COX-2 selective inhibitors are not

- Inhibition of COX2 is thought to mediate at least analgesic, antipyretics & antiinflammatory actions of NSAIDS but simultaneous inhibition of COX1 results in unwanted ad. effects esp. those related to gastric ulcers that result from dec. formation of PGDs & thromboxanes.
- Normally PGI₂ inhibits gastric acid secretion whereas PGE₂ & PGF_{2α} stimulate synthesis of protective mucus in both stomach & s. intestine. In presence of aspirin, these PGDs are not formed

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resulting in ↑ gastric acid secretion & diminished mucus protection. This may cause epigastric distress, ulceration, hemorrhage. So selective COX-2 inhibitors are effective analgesics, antipyretics, antiinflammatory agents but with fewer ad. effects. Have no effect on platelet aggregation.

- Nephrotoxicity has been observed for all these drugs which is due in part to interference with autoregulation of renal blood flow which is modulated by PGDs.

• Selectives and non-selectives also inhibit neuronal nitric oxide.

• NSAIDs are effective in the treatment of rheumatoid arthritis, osteoarthritis, ankylosing spondylitis, gout, and pain.

• Aspirin & some enzyme NSAIDs have anti-platelet effects.

• NSAIDs inhibit platelet aggregation.

NSAIDS

- **SALECYLATES**
Aspirin, salicylic acid, salicylic acid derivatives
Aspirin, salicylic acid, salicylic acid derivatives
- **Non-salicylates**
Magnesium zalcitabine salicylate
Sodium salicylate
Potassium salicylate
Diflunisal

PROPHYLACTIC ACIDS IN RHEUMATOID ARTHRITIS (RA) THERAPY

- Naproxen
- Paracetamol
- Paracetamol
- Paracetamol
- Naproxen
- Celecoxib

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resulting in ↑ gastric acid secretion & diminished mucus protection. This may cause epigastric distress, ulceration, hemorrhage. So selective COX-2 inhibitors are effective analgesics, antipyretics, antiinflammatory agents but with fewer ad. effects. Have no effect on platelet aggregation.

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- resulting in gastric acid secretion & diminished mucus production. This may cause epigastric distress, ulceration, hemorrhage. COX-2 inhibitors are effective analgesics, antipyretics, and anti-inflammatory agents but with fewer ad effects. Have no effect on platelet aggregation.
- Aspirin toxicity has been observed for all these drugs which is due to part to interference with autoregulation of renal blood flow which is mediated by COX.
- COX-2 inhibitors are used to treat rheumatoid arthritis.
- NSAIDs are effective in rheumatoid arthritis.
- Aspirin & other organic NSAIDs have anti-platelet effects.
- NSAIDs are used to treat rheumatoid arthritis & osteoarthritis.

NSAID'S

- SALICYLATES**
Acetylated salicylates: aspirin
Non acetylated salicylates
Magnesium choline salicylate
Sodium salicylate
Sallyl salicylate
Diflunisal

PROPIONIC ACID & PHENYLACETIC ACID DERIVATIVES

- Ibuprofen
- Fenoprofen
- Fluprofen
- Ketoprofen
- Naproxen
- Dexpropfen

NSAID'S

- SALICYLATES
 - Acetylated salicylate(salicylic acid derivative)
 - Acetyl salicylic acid (aspirin)
 - Non Acetylated salicylates
 - Magnesium choline salicylate
 - Sodium salicylate
 - Salicyl salicylate
 - Diflunisal

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resulting in gastric acid secretion & diminished mucus protection. This may cause epigastric distress, ulceration, hemorrhage.

COX-2 inhibitors are effective analgesic, antipyretic, anti-inflammatory agents but with fewer GI effects - have no effect on platelet aggregation.

- Aspirin toxicity has been observed for all these drugs which is due in part to interference with autoregulation of renal blood flow which is mediated by COX.

NSAIDs are similar agents with diverse mechanisms of actions.

- They are effective analgesic, antipyretic, anti-inflammatory agents.
- Aspirin has unique antiplatelet effect & platelet aggregation inhibition & also stomach irritation in part.
- Aspirin & other cyclooxygenase inhibitors have similar effects.
- Aspirin has also been shown to have anticancer effects.

NSAID'S

- SALICYLATES**
Acetylated salicylic acid ester derivatives
Aspirin salicylic acid (aspirin)
- Non acetylated salicylates**
Magnesium chloride salicylate
Sodium salicylate
Potassium salicylate
Diflunisal

PROPRIONIC ACID or PHENYLALKANOIC ACID DERIVATIVES

- Ibuprofen
- Fenoprofen
- Flurbiprofen
- Ketoprofen
- Naproxen
- Oxaprozin

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PROPRIONIC ACID or PHENYLALKANOIC ACID DERIVATIVES

- Ibuprofen
- Fenoprofen
- Flurbiprofen
- Ketoprofen
- Naproxen
- Oxaprozin

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- PROPIONIC ACID & BENZOIC ACID DERIVATIVES**
 - Ibuprofen
 - Fenoprofen
 - Flurbiprofen
 - Ketoprofen
 - Naproxen
 - Cloxacin
- FENAMATES**
 - MEFENAMIC ACID
 - MECLOFENAMIC ACID
- BENZOIC ACID DERIVATIVES**
 - Diclofenac
- INDOLE DERIVATIVES**
 - Indomethacin
 - Sulindac
- PIRROLE-2-CARBOXYLIC ACID DERIVATIVES**
 - Tolmetin
- PYRAZOLONE DERIVATIVES**
 - Phenylbutazone
- OXICAMS**
 - Piroxicam
 - Tenoxicam (RARELY USED)
- SALICYLIC ACID (ACETIC ACID DERIVATIVES)**
 - Aspirin

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FENAMATES

- MEFENAMIC ACID^I
- MECLOFENAMIC ACID

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- PROPIONIC ACID & PHENYLALKANOIC ACID DERIVATIVES
 - Ibuprofen
 - Fenoprofen
 - Flurbiprofen
 - Ketoprofen
 - Naproxen
 - Oxaprofen
- FENAMATES
 - MEFENAMIC ACID
 - MECLOFENAMIC ACID
- PHENYL ACETIC ACID DERIVATIVES
 - (Discontinued)
- INDOLE DERIVATIVE
 - Indomethacin Sulindac
- PYRROLEALKANOIC ACID DERIVATIVE
 - Tolmetin
- PYRAZOLONE DERIVATIVES
 - Phenylbutazone
- COXICAMS
 - Piroxicam
 - Tenoxicam (RARELY USED)
- HIPPURYLACETIC ACID PRODRUGS
 - Ethoracine
- ACETIC ACID DERIVATIVE
 - Ethoracine

PHENYL ACETIC ACID DERIVATIVES

Diclofenac

INDOLE DERIVATIVES

Indomethacin Sulindac

PYRROLEALKANOIC ACID DERIVATIVE: Tolmetin

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PYRAZOLONE DERIVATIVES

Phenylbutazone

OXICAMS

Piroxicam

Tenoxicam (RARELY
USED)



Slides Outline

- NAPHTHYLACETIC ACID PRODRUG**
 - Nabumetone
- ACETIC ACID DERIVATIVE**
 - Etidolac
- MISCELLANEOUS**
 - Ketorolac
- PARA AMINO PHENOL DERIVATIVES**
 - Acetaminophen

COX-2 SELECTIVE INHIBITORS

Celecoxib, Meloxicam

(Procoxib, Etodolac, Valdecoxib)

- Selective COX-2 inhibitors do not affect gastric function
- Reduction of cardiac vascular thrombotic events in patients with cardiovascular disease

NON-SELECTIVE COX INHIBITORS

Ibuprofen	Naproxen
Lidocaine	Rofecoxib
Propafenone	Toradol
Tenoxicam	Valproic acid
Acetaminophen	Acetaminophen
Acetaminophen	Acetaminophen
Acetaminophen	Acetaminophen
Acetaminophen	Acetaminophen
Acetaminophen	Acetaminophen
Acetaminophen	Acetaminophen

GENERAL COMMON PROPERTIES

- All are weak organic acids (except Nabumetone, a prodrug activated to acidic active drug)
- All will interact with many other drugs (increased toxicity)
- Most of them highly metabolized (phase I & II reactions). Only Tylenol (acetaminophen) with COX-2

NAPHTHYLACETIC ACID PRODRUG

Nabumetone

ACETIC ACID DERIVATIVE

Etidolac

MISCELLANEOUS

Ketorolac

PARA AMINO PHENOL DERIVATIVES

Acetaminophen

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NAPHTHYLACETIC ACID DERIVATIVES
Nabumetone

ACETIC ACID DERIVATIVE
Etoricoxib

MISCELLANEOUS
Ketorolac

PARA-AMINOACETIC ACID DERIVATIVES
Acetaminophen

COX 2 SELECTIVE INHIBITORS
Celecoxib Meloxicam
(Rofecoxib, Etoricoxib, Valdecoxib)

NON-SELECTIVE COX INHIBITORS

Ibuprofen	Rofecoxib
Propafenone	Valdecoxib
Acetaminophen	Etoricoxib
Acetaminophen	Etoricoxib
Acetaminophen	Etoricoxib
Acetaminophen	Etoricoxib
Acetaminophen	Etoricoxib
Acetaminophen	Etoricoxib
Acetaminophen	Etoricoxib

GENERAL COMMON PROPERTIES

- All are weak organic acids (except nabumetone, a nonacid prodrug activated to acidic active drug)
- All well absorbed, but much effect of these on bioavailability
- Most of them highly metabolized by phase I & II reactions. Others by direct glucuronidation with UGTs.

COX 2 SELECTIVE INHIBITORS

Celecoxib Meloxicam

(Rofecoxib, Etoricoxib, Valdecoxib)

Selective COX2 inhibitors do not affect platelet function.

↑ incidence of cardio vascular thrombotic events ē refocoxib & valdecoxib resulting in their **withdrawal from market.**

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NON-STEROIDAL ANTI-INFLAMMATORY DRUGS (NSAIDs)

ACETYL SALICYLIC ACID DERIVATIVES

Salicylic acid

ACETIC ACID DERIVATIVES

Ethidacetic acid

MISCELLANEOUS

Ketorolac

PARA-AMINOPHENOL DERIVATIVES

Acetaminophen

COR-2 SELECTIVE INHIBITORS

Celecoxib, Meloxicam

(Piroxicam, Etoricoxib, Valdecoxib)

Selective COX-2 inhibitors do not affect gastric function

Inhibition of gastric mucus

Thrombotic events & ulcers & nephritis resulting in their withdrawal from market

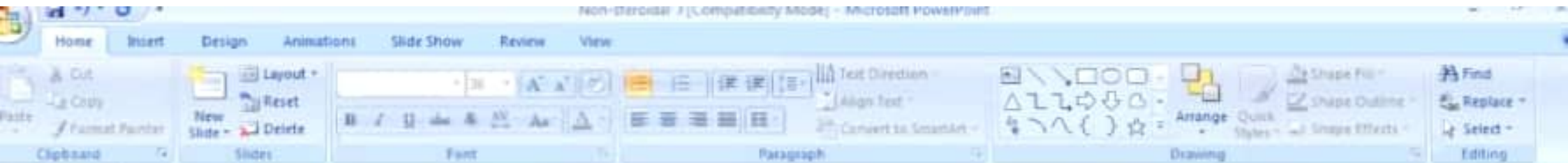
NON-SELECTIVE COX INHIBITORS

Generic Name	Brand Name
Ibuprofen	Nurofen
Naproxen	Nalgesin
Tenoxicam	Tenoxicam
Toradolol	Toradolol
Indometacin	Indometacin
Flurbiprofen	Flurbiprofen
Acemetacin	Acemetacin
Etodolac	Etodolac
Flufenamic acid	Flufenamic acid
Meclizolac	Meclizolac
Benzydolac	Benzydolac
Choline magnesium salicylate	Choline magnesium salicylate
Choline salicylate	Choline salicylate
Salicylic acid	Salicylic acid

GENERAL COMMON PROPERTIES

- All are weak organic acids(except nabumetone, a nonacid prodrug activated to acidic active drug)
- All well absorbed, not much effect of food on bioavailability.
- Most of them highly metabolized by phase 1 & 11 reactions. Others by direct glucuronidation with CYP 450.

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These questions regarding NSAIDs
 All undergo varying degree of enterohepatic circulation
 All highly protein bound upto 98% to albumin
 All appear in synovial fluid after repeated dosing. Drugs with shorter $t_{1/2}$ remain longer in joints while drugs with longer $t_{1/2}$ disappear from synovial fluid at a rate proportional to their half lives

• production of prostaglandins & PGE₂
 • interfere with Ca mediated neuronal events
 • Agents for osteoarthritis & rheumatoid arthritis
 • NSAIDs are COX inhibitors while most others are not selective NSAIDs & reversible inhibitors. Otherwise NSAIDs are COX-2 inhibitors

• Selectivity for COX-1 vs COX-2 variable & important for side effects
 • Non-selective COX2 inhibitors have side effects
 • Selective COX2 do not affect platelet function
 • Agents: Ibuprofen, Paracetamol, & Celecoxib are more effective in osteoarthritis

• COX-1 selective is equally effective as COX-2 selective with increased GI safety but may increase risk of asthma & hypertension
 • Superior & macrolide antibiotics increase renal safety & tubulonephrosis
 • Celecoxib selective for COX-2

• NSAIDs have variable sensitivity to aspirin & acetaminophen
 • Effect on platelet production from T lymphocytes & release inhibition of inflammation
 • Tissue damage at NSAIDs

- Renal excretion is most imp. route.
- All undergo varying degree of enterohepatic circulation.
- All highly protein bound upto 98% to albumin.
- All appear in synovial fluid after repeated dosing. Drugs with shorter $t_{1/2}$ remain longer in joints while drugs with longer $t_{1/2}$ disappear from synovial fluid at a rate proportional to their half lives.

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- These NSAIDs most often cause:
 - All undergo varying degrees of enterohepatic circulation
 - All highly protein bound (up to 99% to albumin)
 - All appear in urine (but after repeated dosing). Drugs with shorter $t_{1/2}$ remain longer in urine while drugs with longer $t_{1/2}$ disappear from urine faster. $t_{1/2}$ is a poor indicator of their half-life.
- ... production of superoxide & free radicals
 - Interfere with Ca mediated intracellular events
 - Aspirin, non selectively & irreversibly acetylates COX while most others are non selective NSAIDs & reversible inhibitors. Otherwise MOA similar to that of Aspirin.
- Selectivity for COX 1 vs COX 2 variable & incomplete for most NSAIDs
 - Many selective COX2 inhibitors have been synthesized
 - Selective COX2 do not affect platelet function
 - Aspirin, indomethacin, Phenoprofen, & Ibuprofen are more effective in inhibiting
- COX 11 selective are equally effective as other NSAIDs with improved GI safety but may increase the incidence of edema & hypertension
 - Aspirin & macrolides inhibit COX
 - Ibuprofen, acetaminophen & tolbutamide somewhat selective for COX2
- NSAIDs ... have sensitivity to treatment

- ↓ production of superoxide & free radicals.
- Interfere with Ca mediated intracellular events.
- Aspirin, non selectively & irreversibly acetylates COX while most others are non selective NSAIDs & reversible inhibitors. Otherwise MOA similar to that of ASPIRIN.

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NSAIDs - have sensitivity to histamine & bradykinin

- Affect lymphokine production from T lymphocytes & reverse vasodilatation of inflammation
- To varying degree, all newer NSAIDs (except COX 11 selective & non-acetylated salicylates) inhibit platelet aggregation. All are analgesic, antipyretic & anti-inflammatory
- All cause gastric irritation (newer agents less). Can cause gastric ulcers w/ bleeding

Aspirin is a non-selective & irreversible NSAID. It has been observed for all these drugs which is due in part to interference with adenosine diphosphate (ADP) binding to cyclooxygenase (COX) 1 & 2. NSAIDs are anti-inflammatory but do not stop the course of an arthritic disorder. Several NSAIDs including Aspirin appear to reduce the incidence of colon cancer when used chronically. Inactivated system.

ASPIRIN - one drug in whole world
 production. It was the first to which aspirin NSAID was compared.
 New studies of aspirin & NSAIDs which have become standard agents used in the NSAID are compared to aspirin.
 New study used to aspirin inflammation.
 Effective & safe for many years.

IBUPROFEN - VILCOXIBEN
 ACTIVE INGREDIENT is SALICYL which on hydrolysis yields SALICYLIC ACID. ACETYL SALICYLIC ACID synthesized 1853 but not used till 1859 when found to be effective in arthritis. Later was marketed.
 One of the most widely used drugs for more than a century. Over 4000 tons of Aspirin consumed every year in world.

- NSAIDs ↓ vessel sensitivity to histamine & bradykinin.
- Affect lymphokine production from T lymphocytes & reverse vasodilatation of inflammation.
- To varying degree, all newer NSAIDs (except COX 11 selective & non-acetylated salicylates) inhibit platelet aggregation. All are analgesic, antipyretic & anti-inflammatory.
- All cause gastric irritation (newer agents less). Can cause gastric ulcers with bleeding.

Click to add notes



Slides Outline

- Search for content on 2 visible & incomplete for slide NSAIDs.
- Many selective COX-2 inhibitors have side effects.
- Selective COX-2 do not affect platelet function.
- Aspirin, ibuprofen, naproxen, & celecoxib are not selective for COX-2.
- COX-1 selective are equally effective as older NSAIDs with improved safety but may increase the incidence of edema & hypertension.
- Ibuprofen & celecoxib are associated with kidney toxicity & thrombosis compared selective for COX-2.
- NSAIDs have sensitivity to tolerance & withdrawal.
- affect lymphocyte production from T lymphocytes & release histamine of inflammation.
- To varying degrees all newer NSAIDs (except COX-1 selective & non-acylated aspirin) inhibit platelet aggregation. All are analgesic, antipyretic & anti-inflammatory.
- All cause gastric irritation (ulcers, ulcers, ulcers). Can cause gastric ulcers with aspirin.
- All are hepatotoxic & hepatotoxic hepatotoxicity has been observed for all these drugs which is due in part to interference with autoregulation of renal blood flow which is modulated by PGDs.
- NSAIDs are anti-inflammatory but do not alter the course of an arthritic disorder.
- Several NSAIDs including ASPIRIN appear to reduce the incidence of colon cancer when used chronically. Mechanism unknown.
- ASPIRIN** - In long-term use without prescription it was found to inhibit gastric NSAIDs were compared.
- Not associated with liver & kidney injury.

- All are nephrotoxic & hepatotoxic. Nephrotoxicity has been observed for all these drugs which is due in part to interference with autoregulation of renal blood flow which is modulated by PGDs.
- NSAIDs are anti-inflammatory but do not alter the course of an arthritic disorder.
- Several NSAIDs including ASPIRIN appear to reduce the incidence of colon cancer when used chronically. Mechanism unknown.

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Non-steroidal [Compatibility Mode] - Microsoft PowerPoint

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ASPIRIN: Old drug available without prescription. It was the drug to which all other NSAIDS were compared.

- Now replaced by ibuprofen & naproxen which have become standard against which all other NSAIDS are compared now-a-days.
- Now rarely used as an anti-inflammatory
- Effective & has good safety records

ASPIRIN: Old drug available without prescription. It was the drug to which all other NSAIDS were compared.

Now replaced by ibuprofen & naproxen which have become standard against which all other NSAIDS are compared now-a-days.

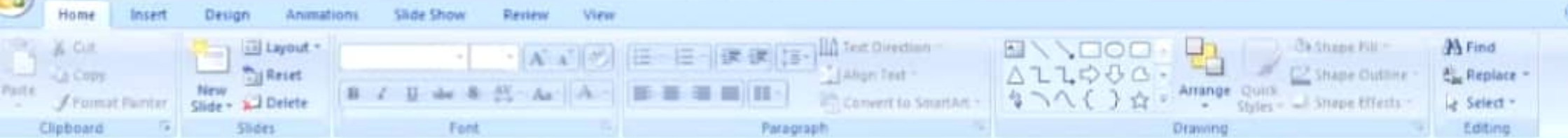
Now rarely used as an anti-inflammatory

Effective & has good safety records

SOURCE: PILLON BARK

ACTIVE INGREDIENT: SALICIN (with 20 hydroxyethyl) SALICYLIC ACID ACETYL SALICYLIC ACID (aspirin) 1000 but not used in 1999 when found to be effective in asthma & also was aspirin

One of the most widely used drugs to



Slides Outline

NSAIDs, raise sensitivity to histamine & bradykinin.
 • Affect lymphocyte production from T lymphocytes & release mobilization of interleukin.
 • To varying degrees, all newer NSAIDs (except COX-2) selective & non-acetylated salicylates, inhibit platelet aggregation. All are analgesic, antipyretic & anti-inflammatory.
 • All cause gastric irritation, however aspirin does. Can cause gastric ulcers w/ bleeding.

All are high toxicity & hepatotoxic hepatotoxicity has been observed for all these drugs which is due in part to interference with autoregulation of renal blood flow which is modulated by PGE₂.
 • NSAIDs are anti-inflammatory but do not alter the course of an arthritic disorder.
 • Several NSAIDs including ASPIRIN appear to reduce the incidence of colon cancer when used chronically. (Inactivated aspirin)

ASPIRIN One drug available without prescription. It was the first & which all other NSAIDs were compared.
 • Now replaced by coxiblen & roxiblen which have become standard agents since all other NSAIDs are compared to these.
 • Now used as anti-thrombotic (antiplatelet).
 • Effective & has good safety record.

SOURCE WILLOW BARK.
 • **ACTIVE INGREDIENT** is SALICIN which on hydrolysis yields SALICYLIC ACID. ACETYLSALICYLIC ACID synthesized in 1853 but not used till 1899 when found to be effective in arthritis & also well absorbed.
 • One of the most widely used drugs for more than a century. Over 40000 tons of Aspirin consumed every year in world.

• Discovered in 1853 by Salicylic acid. Salicylic acid is a natural salicylate & aspirin are synthetic. Effective & anti-inflammatory, all aspirin is not effective & is analgesic.

Salicylic acid is derived from

SOURCE: WILLOW BARK.

- **ACTIVE INGREDIENT** is **SALICIN** which on hydrolysis yields **SALICYLIC ACID**. **ACETYLSALICYLIC ACID** synthesized in 1853 but not used till 1899 when found to be effective in arthritis & also well absorbed.
- One of the most widely used drugs for more than a century. Over 40000 tons of Aspirin consumed every year in world.

Click to add notes



Slides Outline

- Salicylic acid is simple organic acid. Its pKa is 3
- Aspirin (ASA) has a pKa of 3.5
- sodium salicylate & aspirin are equally effective as anti-inflammatory but aspirin is more effective as an analgesic.
- PHARMACOKINETICS
- Administered orally, rapidly absorbed from stomach & upper small intestine.
- PPL of salicylate reach within 1-2 hours.
- Salicylates may damage mucosal barrier when

PHARMACODYNAMIC

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PHARMACOKINETICS:

- Administered orally, rapidly absorbed from stomach & upper small intestine.
- PPL of salicylate reach within 1-2 hours.
- Salicylates may damage mucosal barrier when

Click to add notes



Slides Outline

Aspirin (ASA) is a weak organic acid. It is a weak acid (pKa 3.5) and is mostly ionized in the blood. It is a weak acid (pKa 3.5) and is mostly ionized in the blood. It is a weak acid (pKa 3.5) and is mostly ionized in the blood.

high conc. enter mucosal cells. Aspirin rapidly hydrolyzed to acetic acid & salicylate by esterases in tissue & blood. Salicylates bound to ALBUMEN. As serum conc. ↑, a large fraction remains unbound & available to tissues. Salicylates excreted in unchanged form but most converted to water soluble conjugates & cleared rapidly by kidneys. At total body salicylate load of 600mg (analgesic & antipyretic dose), $t_{1/2}$ 3-5 hrs.

At high concentrations, salicylates can cause metabolic acidosis. Salicylates can cause metabolic acidosis. Salicylates can cause metabolic acidosis. Salicylates can cause metabolic acidosis.



PHARMACODYNAMICS

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- At total body salicylate load of 600mg (analgesic & antipyretic dose), $t_{1/2}$ **3-5 hrs.**

Click to add notes

Slides Outline

Salicylic acid is a weak organic acid. It is a...
Apply (ADA) has a pKa of 3.5
At low doses (300 mg / day) it is eliminated...
At high doses (4 g / day) it is eliminated...
PHARMACOKINETICS

Administered orally, readily absorbed from...
PPV of salicylic acid is 100%
PHARMACODYNAMICS

High doses, zero-order kinetics
Apply readily metabolized to acetylsalicylic...
Salicylic acid is converted to acetylsalicylic...
Salicylic acid is converted to salicylic acid...
At high doses, salicylic acid is converted to...
PHARMACOKINETICS

In low doses elimination is according to...
At high doses (4 g / day) $t_{1/2}$ is 12-16 hrs...
At low doses, hepatic metabolic pathways...
become saturated & zero-order kinetics...
 $t_{1/2}$ increases from 3-5 hrs (600 mg / day) to...
12-16 hrs (dosage > 3.6 g / day).
Alkalinization of urine increases rate of...
excretion of free salicylates.

- In low doses elimination is according to **1st order kinetics**.
- At high doses (4G/D) **$t_{1/2}$ inc. to 12 hrs. or more.** At this dose, hepatic metabolic pathways become saturated & **zero order kinetics prevails.**
- $t_{1/2}$ increases from 3 - 5 hrs (600 mg / day) to 12-16 hrs (dosage > 3.6 g/day).
- **Alkalinization of urine increases rate of excretion of free salicylates.**

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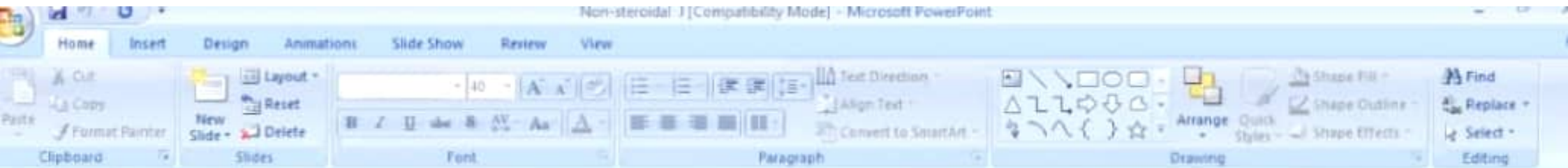
PHARMACODYNAMICS

- Anti-inflammatory activity due to PG synthesis inhibition
- Inhibition of chemokines
- Down regulation of interleukin-1 production

MOA: Aspirin non selectively & irreversibly acetylates enzyme COX (prostaglandin synthase) which catalyzes the conversion of AA to endoperoxide compounds. At appropriate doses, drug ↓ the formation of both PGS & TXA₂ but not leukotrienes. Effectiveness of aspirin is partly due to its ability to inhibit COX & partly b/o effect of its primary metabolite i.e salicylate, both to inhibit COX & also to act in other ways e.g. as an O₂ radical scavenger. Also possibly inhibition of chemotaxis, down regulation of IL 1 production, ↓ production of free radicals.

PHARMACOLOGICAL ACTIONS

1. Anti- inflammatory effect
2. **Analgesic effect**
3. Anti-pyretic effect
4. **Anti- platelet effect**
5. Uricosuric effect
6. **Respiratory action**
7. Action on kidneys



PHARMACODYNAMICS

- Anti-inflammatory activity due to PGD synthesis inhibition
- Inhibition of prostaglandin
- Down regulator of interleukin production

MOA Aspirin has weakly & low-affinity interaction with the COX/Prostaglandin synthase, which catalyses the conversion of AA to endoperoxide compounds. It acetylates aspirin, block the formation of both PGE₂ & TXA₂, but not thromboxane. Effectiveness of aspirin is partly due to its ability to inhibit COX & partly to its effect of its primary metabolite, acetylsalicylic acid, which inhibits COX & blocks both prostaglandin & α -thrombin activity. Also possibly inhibits thromboxane, down regulation of its synthesis & production of the enzyme.

PHARMACOLOGICAL ACTIONS

1. Anti-inflammatory effect
2. Analgesic effect
3. Anti-pyretic effect
4. Anti-platelet effect
5. Uricosuric effect
6. Respiratory action
7. Action on kidneys

ANTI-INFLAMMATORY EFFECTS

- Aspirin is useful in a variety of conditions including RA, osteoarthritis, musculoskeletal disorders & pericarditis. Aspirin inhibits COX activity which leads to inhibition of PGDs synthesis & modulates those effects of inflammation in which PGDs act as mediators.
- Aspirin inhibits granulocyte adherence to damaged vasculature, stabilizes lysosomes, inhibits chemotaxis of polys & macrophages to site of inflammation.
- Interferes with chemical mediators of kallikrein

ANALGESIC EFFECTS

Aspirin reduces pain through its inhibition of prostaglandin synthesis & modulation of pain receptors.

ANTI-INFLAMMATORY EFFECTS

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- Interferes with chemical mediators of kallikrein

Click to add notes

4 3 2 1 0 1 2 3 4

ANALGESIC EFFECTS: Effective in

reducing pain of mild to moderate intensity by ↓ inflammation. Pain that accompanies inflammation & tissue injury probably results from local stimulation of pain fibres & enhanced pain sensitivity (**hyperalgesia**).

Bradykinins & cytokines appear to be particularly imp. in eliciting pain of inflammation. These agents liberate PGDs(E_2 & F_2) & probably other mediators of inflammation that promote hyperalgesia.

Slides Outline

ANALGESIC EFFECT

Reducing pain often to receive information & information. Pain has a complex information & tissue-damage signals from local stimulation of pain fibers & signals pain signals to the brain.

Endorphins & opioids appear to be particularly imp. in acting pain of information. These agents block NCCs & P₂ & produce other messages of information that produce analgesia.

Aspirin acts peripherally through its effect on inflammation & probably inhibits pain stimuli at subcortical sites.

ANTIPYRETIC EFFECT

Regulation of body temp. requires a delicate balance between heat production & heat loss. Hypothalamus regulates the set point at which body temp. is maintained. In fever the set point is elevated & aspirin permits its return to normal. These drugs do not influence body temperature when it is elevated by such factors as exercise & increase in ambient temperature.

Fever may be result of infection or due to tissue damage, inflammation, malignancy, graft rejection or any other disease.

A common feature of these conditions is enhanced formation of prostaglandins in response to bacterial products which increase the release of PGE₂, which raises the hypothalamus to increase the body temperature by promoting increase in heat production or decrease in heat loss. Aspirin suppresses the response by blocking the synthesis of PGE₂.

ANTI-PLAQUE EFFECT

Aspirin effects remarkable. Single low-dose 81 mg daily aspirin is effective in reducing the risk of stroke & myocardial infarction. This is due to its ability to inhibit the synthesis of PGE₂ & cause decrease in platelet aggregation. The effect is due to its ability to block the synthesis of PGE₂.

Due to irreversible acetylation of platelet COX, aspirin's anti-platelet effect lasts for 8-10 days.

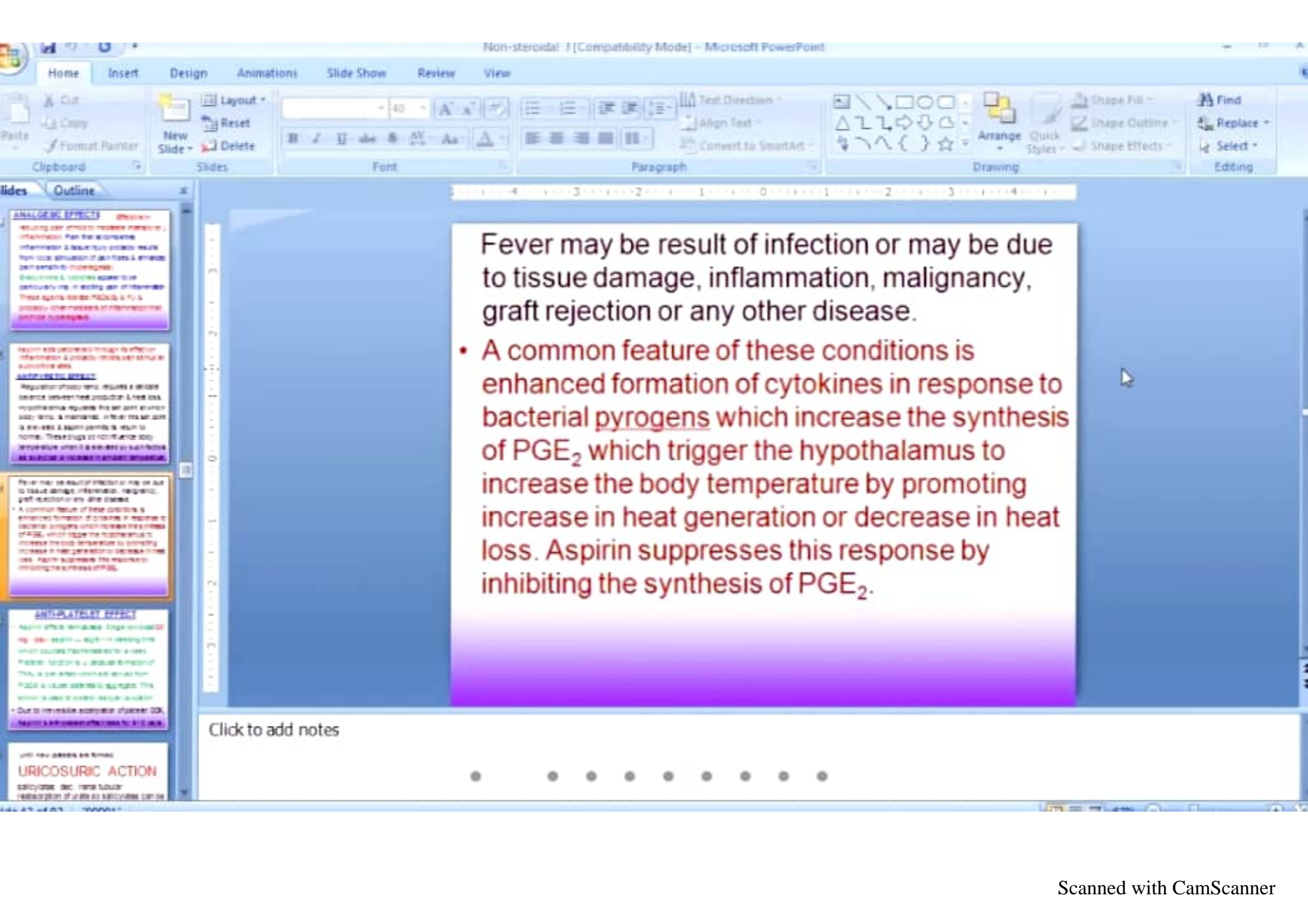
URICOSURIC ACTION

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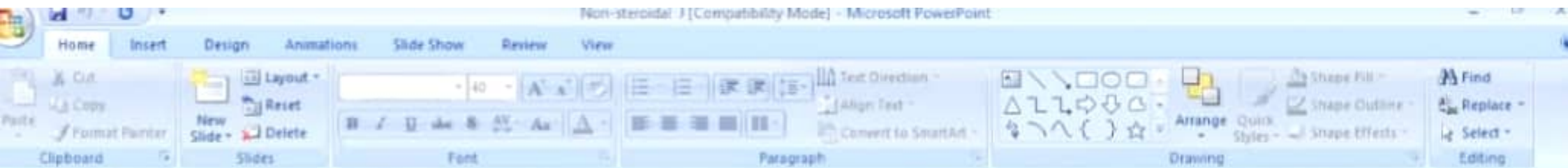
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Fever may be result of infection or may be due to tissue damage, inflammation, malignancy, graft rejection or any other disease.

- A common feature of these conditions is enhanced formation of cytokines in response to bacterial pyrogens which increase the synthesis of PGE₂ which trigger the hypothalamus to increase the body temperature by promoting increase in heat generation or decrease in heat loss. Aspirin suppresses this response by inhibiting the synthesis of PGE₂.

Click to add notes



ANTI-PLATELET EFFECT

- Aspirin affects hemostasis. Single low dose (80 mg / day) aspirin → slight ↑ in bleeding time which doubles if administered for a week. Platelet function is ↓ because formation of TXA₂ is prevented which are derived from PGDS & cause platelets to aggregate. This action is used to protect vascular occlusion.
- Due to irreversible acetylation of platelet COX, Aspirin's anti-platelet effect lasts for 8-10 days

Click to add notes

until new platelets are formed.

URICOSURIC ACTION

salicylates dec. renal tubular reabsorption of urate so salicylates can be used to deplete gouty pts. of uric acid. For this high doses are needed (5-8 gms/d) & very few pts. can tolerate this.

Uricouric action is greater in alkaline urine.

Low doses of aspirin (2gms/d or less) cause urate retention.

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Slides Outline

Respiratory effects of aspirin or NSAIDs are due to local damage, inflammation, hypercapnia, pH⁺ respiratory and others.

- A common feature of these conditions is enhanced formation of prostaglandins in response to local oxygen deficiency which increases the synthesis of PGE₂, which together with other prostaglandins increase the local temperature by primarily increasing their generation or decrease in their rate. Aspirin suppresses this response by inhibiting the synthesis of PGE₂.

ANTI-PLATELET EFFECTS

- Aspirin effect is irreversible. It irreversibly acetylates the active site of cyclooxygenase (COX) which is essential for the synthesis of PGE₂ and other prostaglandins from Arachidonic acid. This action is irreversible and is not reversible.
- Due to irreversible acetylation of platelet COX, aspirin has an anti-platelet effect which is 3-5 days.

with renal patients are formed.

URICOSURIC ACTION

Salicylates, like renal tubule reabsorption of uric acid so salicylates can be used to decrease (only) the level of uric acid. For this high doses are needed (5-8 g/day) and very few pts. can tolerate this. Uricosuric action is greater in acute uric acid. Low doses of aspirin (325mg or less) cause uric acid retention.

RESPIRATORY EFFECTS - A respiratory effect is seen in acute aspirin toxicity. Salicylates uncouple oxidative phosphorylation which leads to elevated CO₂ and hyperventilation. Higher doses work directly on respiratory center in medulla resulting in hyperventilation & respiratory alkalosis. At toxic doses, central respiratory paralysis occurs & respiratory acidosis ensues b/o continued production of CO₂.

ASPIRIN ON KIDNEYS - COX inhibitors prevent synthesis of PGE₂ & PGI₂ (PGDs responsible for maintenance of renal blood flow). This can result in retention of sodium & water & may cause edema & hyperkalemia in some pts. Interstitial nephritis can occur in some pts with all NSAIDs except aspirin.

CLINICAL USES

- NSAIDs are used for the treatment of pain of non-infectious origin e.g. rheumatoid arthritis, osteoarthritis, etc.
- Aspirin is also used for the prevention of thrombosis.

- **RESPIRATORY ACTIONS:** At therapeutic doses aspirin ↑ alveolar ventilation. Salicylates uncouple oxidative phosphorylation which leads to elevated CO₂ & ↑ respiration. Higher doses work directly on respiratory center in medulla resulting in hyperventilation & respiratory alkalosis. At toxic doses, central respiratory paralysis occurs & respiratory acidosis ensues b/o continued production of CO₂
- **ACTION ON KIDNEYS:** COX inhibitors prevent synthesis of PGE₂ & PGI₂ (PGDs responsible for maintenance of renal blood flow) so ↓ synthesis of PGDs can result in retention of sodium & water & may cause edema & hyperkalemia in some pts. Interstitial nephritis can occur in some pts with all NSAIDs except aspirin.

Click to add notes





CLINICAL USES

ANALGESIC: pain of mild to moderate intensity of non visceral origin e.g. headache, myalgias, dysmenorrhea etc.

- **ANTIPYRETIC** - very effective analgesic concentrations
- **ANTIINFLAMMATORY** - in high doses, effective in RA, Rh, fever & other inf. joints diseases
- **Transient ischemic attacks**
- Unstable angina
- Coronary artery thrombosis & M.I
- After coronary artery bypass

DOSEAGE

Aspirin analgesic is **PAIN, SUPPRESSED COLIC, ENTERIC DYSBIOTIC & ENTERIC COLIC** INHIBITORS

Analgesic is aspirin dose 100-300 mg 4-6 times daily. Large doses produce analgesic effect. Anti-inflammatory doses 3-5 gms in divided doses. Dose in RA 3-5 gms. Aspirin with anti-inflammatory effect.

Anti-inflammatory analgesic in aspirin dose in divided doses 3-5 gms 4-6 times daily. To reduce enteric colic of high dose.

ADVERSE EFFECTS

GI upset, gastric ulceration, peptic & duodenal ulcers.

GI bleeding, due to inhibition of platelet aggregation. GI bleeding is common with high dose. GI bleeding with aspirin is common. GI bleeding with aspirin is common. GI bleeding with aspirin is common.

Aspirin is a weak acid. It is absorbed in the stomach. It is absorbed in the stomach. It is absorbed in the stomach.

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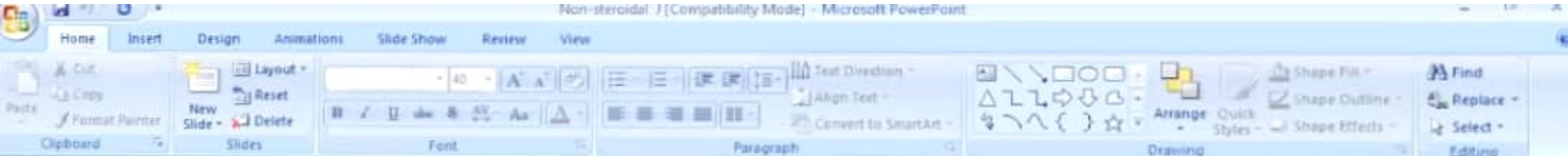
CLINICAL USES

- **ANALGESIC**: pain of mild to moderate intensity of non visceral origin e.g. headache, myalgias, dysmenorrhea. etc.
- **ANTIPYRETIC** very effective provided no contraindications.
- **ANTIINFLAMMATORY**: In high doses, effective in RA, Rh, fever & other inf. joints diseases.
- **Transient ischemic attacks**
- Unstable angina
- **Coronary artery thrombosis & M.I**
- **After coronary artery bypass**

Click to add notes



- Low dose long term use less incidence of COLON CANCER possibly related to its COX inhibiting effects.
- May be valuable in PREECLAMPSIA & ECLAMPSIA



CLINICAL USES

- ANALGESIC: used for pain to moderate levels of non-inflammatory eg. rheumatoid arthritis, osteoarthritis, etc.
- ANTI-PYRETIC: very effective against febrile temperatures
- ANTI-INFLAMMATORY: in high doses, effective in RA, but has a lower effect on steroids
- PAINKILLER: systemic effects
- Uricosuric agents
- Coronary artery vasodilator (rare)
- Anticancerous agent (rare)

ADVERSE EFFECTS

- Allergic: common, usually confined to cutaneous lesions
- Gastrointestinal: heartburn, peptic ulcer, bleeding, perforation, etc. (with NSAIDs)
- Hematologic: thrombocytopenia, leukopenia, anemia, etc.
- Hypertension: may occur with long-term use
- Renal: may lead to acute renal failure
- Hepatic: may lead to liver damage

DOSEAGE

- Analgesic or antipyretic: less than 0.6-0.65g oral/3-4 hrs. Larger doses prolong the effect.
- Anti-inflammatory: dose 3.2-4gms/d in divided doses. Blood levels 15-30mg/dl associate with Anti-inflammatory effect.
- Anti-inflammatory, analgesic or antipyretic dose in children 50-75 mg/kg/d in divided doses
- For adults starting dose 45 mg /kg/d

DOSAGE

- Aspirin available as **PLAIN, BUFFERED, SOLUBLE, EFFERVESCENT & ENTERIC COATED TABS.**
- Analgesic or antipyretic** less than 0.6-0.65g oral/3-4 hrs. Larger doses prolong the effect.
- Anti inflammatory** dose 3.2-4gms/d in divided doses. Blood levels 15-30mg/dl associate with Anti inflammatory effect.
- Anti inflammatory, analgesic or antipyretic** dose in children 50-75 mg/kg/d in divided doses
- For adults starting dose 45 mg /kg/d

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Slides Outline

CLINICAL USES

- ANALGESIC: pain of mild to moderate intensity of non-infective origin eg. rheumatic, myalgia, dysmenorrhea, etc.
- ANTIPYRETIC: febrile effects produced to counteract fever
- ANTINFLAMMATORY: in high doses, effects in RA, Ankylosing spondylitis, osteoarthritis.
- Treats rheumatoid arthritis
- Unstable angina
- Coronary artery thrombolysis (MI)
- After coronary artery bypass

DOSEAGE

- Aspirin analgesic as PAIN SUPPRESSOR: 325-650 mg, 4-6 times daily & 12-16 mg/kg/day
- Analgesic & antipyretic: less than 2.6 g/kg per 24 hrs. Larger doses prolong the effect.
- Anti-inflammatory doses: 2-4 g/day in divided doses. Blood in stool & tarry stools associated with high inflammatory effect.
- Anti-inflammatory analgesic: in children 50-75 mg/kg/d in 4-6 doses.
- For acute rheumatoid arthritis 65 mg/kg/d.

ADVERSE EFFECTS

- At usual dosage gastric upsets, peptic & duodenal ulcers
- Upper GIT bleeding due to erosive gastritis. About 1 ml. of blood loss is normal which is inc. to about 3-4 mls. with ordinary dose which further increases with inc. in dosage. After 4-6 weeks b/o mucosal adaptation, blood loss is back to normal.
- Salicylism at higher doses i.e. vomiting, vertigo, tinnitus & decreased hearing. Reversible with dec. in dosage.
- Large doses — hyperphagia due to direct stimulation of mictic.
- Toxic levels — respiratory alkalosis followed by metabolic acidosis (anion gap increased).

ADVERSE EFFECTS

- At usual dosage gastric upsets, gastric & duodenal ulcers
- Upper GIT bleeding due to erosive gastritis. About 1ml. of blood loss is normal which is inc. to about 3-4mls. with ordinary dose which further increases with inc. in dosage. After 4-6 weeks b/o mucosal adaption, blood loss is back to normal.
- Salicylism at higher doses i.e. vomiting, vertigo, tinnitus & decreased hearing. Reversible with dec. in dosage.

Click to add notes



Larger doses → hyperpnea due to direct stimulation of medulla.

Toxic levels → respiratory alkalosis followed by metabolic acidosis (salicylate accumulation)

Respiratory depression, cardio toxicity & glucose intolerance can occur at toxic doses.

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Slides Outline

Large doses — hyperuricemia due to direct stimulation of HGPRT

- Toxic levels — respiratory alkalosis followed by metabolic acidosis (anion gap accumulation)
- Respiratory depression, cardiac toxicity & possible hypotension can occur at toxic doses.

- 2 g or less increases uric acid levels & does not harm & can decrease uric acid levels
- Elevated liver enzymes, hepatitis (rare)
- Decreased renal function (dec. GFR)
- Bleeding (contraindicated in hemophilia)
- Rashes
- Asthma (aspirin sensitivity, COX inhibition → ↑ed Leukotriene synthesis)

C11 1 Hemiplegia 2 RHEEDS SWN

Swelling & blurring may progress to exudate & cause a protein-rich discharge from the eye. May inflammation, protein exudate & fatty degeneration of the eye & cornea. Swell in depth of eye & conjunctiva may damage in early stage. Do aspirin in chronic conjunctivitis or moderate eye use of ACE Inhibitor in exudates.

1. Penicillin G (highly sensitive to penicillinase and is not affected by penicillinase). Resistant to most of resistance-producing penicillinase. Action spectrum — PENICILLINASE RESISTANT.

OVERDOSAGE TOXICITY

Aspirin overdose (usually drug therapy) leads to a metabolic state of acidosis in young children. Serious reactions result when amount ingested exceeds 100-15 mg/kg. In drug, fluid or acid base status of patient.

PHYSICAL, CHEMICAL, PHYSIOLOGICAL

Acidosis, hyperventilation, tinnitus, hearing loss, hypotension, bleeding, hypothermia, respiratory distress, renal failure.

DOSE & USE (Aspirin) (See Table 1.1)

Aspirin (acetylsalicylic acid) is followed by salicylic acid, which is converted to salicylic acid.

Some drugs may have similar effects & hence, large doses of salicylic acid should be avoided. Aspirin should be avoided in patients with a history of renal or hepatic disease. Aspirin should be avoided in patients with a history of asthma.

TREATMENT (See Table 1.1)

Supportive measures (e.g., fluids, electrolyte balance, etc.)

- 2 g or less increases uric acid levels & doses > 4 g daily decrease urate levels
- **Elevated liver enzymes, hepatitis (rare)**
- Decreased renal function (dec. GFR)
- **Bleeding (contraindicated in hemophilia)**
- **Rashes**
- **Asthma (aspirin sensitivity, COX inhibition → ↑ed Leukotriene synthesis)**

Click to add notes



Navigation pane with slide thumbnails. Visible titles include: OVERDOSE TOXICITY, NOW ACETILATED SALICATES, COX-2 SELECTIVE INHIBITORS (COXIBS).

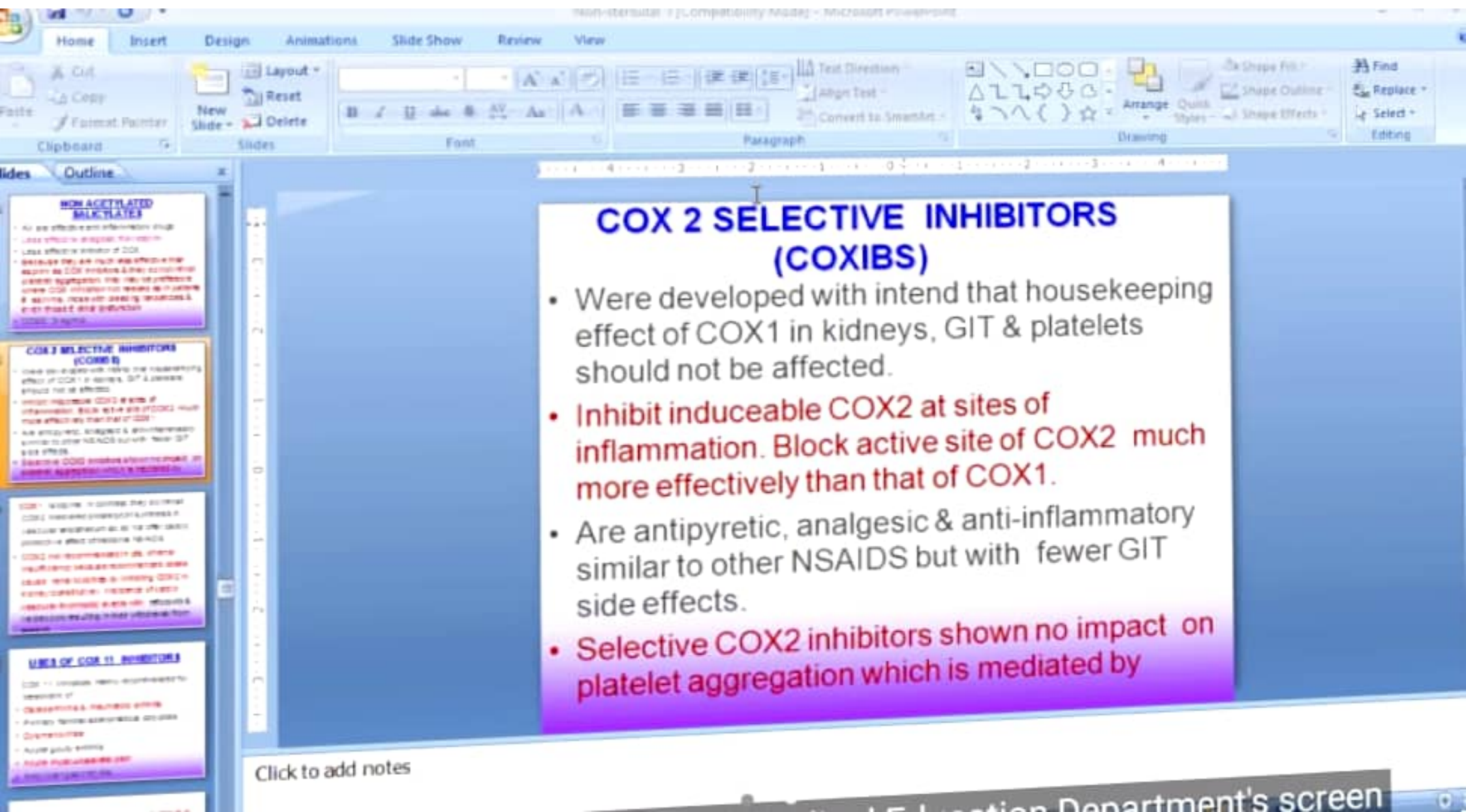
C/I: 1. Hemophilia. 2. REYE'S SYN.

Vomiting & lethargy may progress to delerium & coma in children recovering from viral inf. Also inflammatory cerebral edema & fatty degeneration of liver & kidney. Death in 20-30% of pts. & permanent brain damage in many more. **So Aspirin C/I in children during or immediately after viral inf.**

ACETAMINOPHIN recommended.

3. Previously C/I in pregnancy b/o anemia, ante & post partum hemorrhage. Also due to inc. in incidence of prolonged gestation. But now indicated in PREECLAMPSIA-ECLAMPSIA.

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COX 2 SELECTIVE INHIBITORS (COXIBS)

- Were developed with intend that housekeeping effect of COX1 in kidneys, GIT & platelets should not be affected.
- **Inhibit induceable COX2 at sites of inflammation. Block active site of COX2 much more effectively than that of COX1.**
- Are antipyretic, analgesic & anti-inflammatory similar to other NSAIDS but with fewer GIT side effects.
- **Selective COX2 inhibitors shown no impact on platelet aggregation which is mediated by**

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Slides Outline

USES OF COX 11 INHIBITORS

COX 11 inhibitors mainly recommended for treatment of

- Osteoarthritis & rheumatoid arthritis
- Primary familial adenomatous polyposis
- Dysmenorrhea
- Acute gouty arthritis
- Acute musculoskeletal pain
- Ankylosing spondylitis

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SELECTIVE COX2 INHIBITORS

1. CELECOXIB
2. MELGICAM

CELECOXIB

- 15-20 times more selective to COX 11
- On average, analgesic effect is 25% less than that of NSAIDs
- It is a sulfonamide so may cause renal dysfunction
- Inhibits by COX2, so it is a selective COX2 inhibitor

• Fewer effects & less than 4 other NSAIDs

• May cause asthma and hypertension

• Effective in osteoarthritis & rheumatoid arthritis

• Dose: 150-300mg qd

MELGICAM

- An analgesic and anti-inflammatory
- Inhibits by COX2, so it is a selective COX2 inhibitor
- Not as selective as celecoxib

Slides Outline

MELOXICAM

- 2nd generation COX-2 selective inhibitor
- 4-aminobenzoic acid derivative
- Extremely responsive to COX-2 selective inhibition
- GIT safety profile similar to other NSAIDs
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Approved in UK for use of COX-2 inhibitor for acute osteoarthritis & rheumatoid arthritis

- Acute gouty arthritis
- Risk of acute tubular necrosis
- Prurigo dermatitis

MELOXICAM

Fluorene derivative. Potent selective COX-2 inhibitor. $t_{1/2}$ 20hrs. $COX-2$ selective

- Acetaminophen analgesic/antipyretic
- In UK is approved for osteoarthritis & rheumatoid arthritis
- No inhibition of platelet aggregation
- No effect on gastric mucosal prostaglandins
- High cardiovascular safety & tolerability

MELOXICAM

- An enolcarboxamide, related to piroxicam that preferentially inhibits COX 2 at lowest therapeutic dose 7.5mg/d.
- Not as selective as celecoxib. $t_{1/2}$ 20hrs. Dose 7.5-15mg qid for rheumatic diseases & osteoarthritis.
- Less GIT symptoms than piroxicam, diclofenac & naproxen.
- While meloxicam is known to inhibit synthesis of TXA2, even at supratherapeutic doses, its blockade of TXA2 does not reach level that result in decreased platelet function in vivo.
- Other toxicities similar to other NSAID's.

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DICLOFENAC

- Non-inflammatory COX-1 inhibitor
- Inhibits prostaglandin synthesis
- Under investigation for osteoarthritis
- No effect on platelet aggregation or bleeding
- Some individuals may experience GI intolerance
- Renal toxicity in patients with renal impairment

NON-SELECTIVE COX INHIBITORS

DICLOFENAC

- Phenylacetic acid derivative
- COX non selective & adverse effects in 20%
- GI distress, GI bleeding & gastric ulceration less common than some other NSAIDs
- A preparation combining Diclofenac & misoprostol ↓ GIT ulceration but may result in diarrhea.
- $T_{1/2}$ 1.1hr. Dose 50-75mg QID.
- Diclofenac 150mg/d appears to impair renal blood flow & GFR

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DIUPROFEN

- COX-2 selective inhibitor
- No effect on platelet aggregation or bleeding
- No effect on renal function

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Outlines

INDOLINAC

- Prescription, not OTC
- OTC non-steroidal anti-inflammatory drugs (NSAIDs)
- 17% increase in liver enzyme levels in 1000 patients
- A preparation containing Diclofenac & Indometacin, 10% solution for the relief of pain
- **To Use:** Use according to the package insert
- Diclofenac (NSAID) should be used with caution in patients with a history of peptic ulcer & GI

IBUPROFEN

- Over-the-counter (OTC) NSAID
- **To Use:** Use according to the package insert
- A topical preparation (1% w/v) is available for the relief of pain
- Use with caution in patients with a history of peptic ulcer & GI
- Diclofenac and indometacin should be used with caution in patients with a history of peptic ulcer & GI

ADVERSE EFFECTS

- Headache, dizziness, lightheadedness, faintness, tinnitus, ringing in ears, nasal congestion
- Stomach pain, indigestion, heartburn, nausea, vomiting, diarrhea, constipation
- Skin rash, itching, hives, allergic reactions
- Blurred vision, changes in vision, eye pain
- Drowsiness, dizziness, lightheadedness, faintness, tinnitus, ringing in ears, nasal congestion
- Stomach pain, indigestion, heartburn, nausea, vomiting, diarrhea, constipation
- Skin rash, itching, hives, allergic reactions
- Blurred vision, changes in vision, eye pain

- Raises serum aminotransferases more commonly with this drug than with other NSAIDs.
- **A 0.1% ophthalmic preparation recommended for postoperative ophthalmic inflammation.**
- 3% topical gel effective for solar keratosis. Also available as rectal suppository form, as mouthwash & for i/m administration.

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IBUPROFEN

- Oral 2.4g ibuprofen equivalent to 4g aspirin in its anti-inflammatory effect
- In ↓ than 2.4g dose, it is analgesic but not anti-inflammatory.
- Used as topical cream for knee osteoarthritis.
- A liquid gel preparation of Ibuprofen 400 mg for post surgical dental pain.
- As safe & as effective as indomethacin in closing PDA in preterm infants both orally & i/v
- Decreases total anti-inflammatory effect of aspirin

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- Non-steroidal anti-inflammatory drugs (NSAIDs) are the most commonly prescribed class of drugs for the treatment of pain and inflammation.
- Development of NSAIDs is based on the discovery of cyclooxygenase (COX) as the key enzyme in prostaglandin synthesis.
- NSAIDs inhibit COX, leading to the inhibition of prostaglandin synthesis and subsequent reduction of pain and inflammation.

NSAID

- Non-steroidal anti-inflammatory drugs
- Non-selective COX inhibitor
- Prostaglandin synthesis inhibitor
- Used for pain, inflammation, and fever

INDOMETHACIN

- Available as oral susp. or topical preparation & ophthalmic solution
- incidence of GI bleed double that of Naproxen but other NSAID's COX-2 same
- Rarely cause allergic pneumonitis, leukocytoclastic vasculitis & platelet dysfunction

INDOMETHACIN

- Indole derivative introduced in 1963
- is a non selective COX inhibitor
- also inhibit phospholipase A₂ & C
- neutrophil migration & T & B cell proliferation
- T_{1/2} 4-5hrs & dose 50-75mg
- Probenecid ↑es indomethacin's t_{1/2} by inhibiting both renal & biliary clearance

CLINICAL USES

- musculoskeletal pain & relief of pain & inflammation
- used to reduce the risk of heart attack

INDOMETHACIN

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ADMINISTRATIVE EFFECTS
 Outline describes the following:
 - How to use the drug in the clinical setting
 - Dose, route, and frequency of administration
 - Contraindications and precautions
 - Adverse effects

ACETAMINOPHEN
 One of the most important drugs used in mild to moderate pain when an anti-inflammatory effect is not required. Phenacetin, a prodrug that is metabolized to acetaminophen, is more toxic than its active metabolite & has no rational indication.
 Acetaminophen is active metabolite of phenacetin & is responsible for its analgesic effect.

MOA - It is a weak COX-1 & COX-2 inhibitor in peripheral tissues & responsible for its weak anti-inflammatory effect.
 Acts by inhibiting PGG₂ synthesis in CNS. This explains its analgesic & antipyretic actions.

PHARMACOKINETICS - Acetaminophen is rapidly absorbed from the GI tract. It is metabolized in the liver to acetaminophen-3-glucuronide & acetaminophen-4-sulfate. It is excreted in the urine. Less than 1% is excreted unchanged. A minor metabolite is acetaminophen-5-O-glucuronide. It is not a hepatotoxic drug. It is not a carcinogen. It is not a teratogen. It is not a mutagen. It is not a reproductive toxicant. It is not a developmental toxicant. It is not a developmental neurotoxicant. It is not a developmental immunotoxicant. It is not a developmental endocrine disruptor. It is not a developmental neuroendocrine disruptor. It is not a developmental neuroimmunotoxicant. It is not a developmental neuroimmunotoxicant. It is not a developmental neuroimmunotoxicant.

TOXICITY - Acetaminophen is normally rendered harmless by conjugation with glucuronic acid. However, if the supply of glucuronic acid is limited & if the amount of acetaminophen formed is greater than the availability of glucuronic acid, the

ACETAMINOPHEN

One of most imp. drug used in mild to moderate pain when an anti-inflammatory effect is not required. **Phenacetin, a prodrug that is metabolized to acetaminophen, is more toxic than its active metabolite & has no rational indication.**

Acetaminophen is active metabolite of phenacetin & is responsible for its analgesic effect.

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Slides Outline

INDICATIONS Acetaminophen is normally rendered harmless by conjugation with SH(thiol) group of glutathione. However supply of hepatic glutathione is limited & if amount of metabolite formed is greater than the availability of glutathione, then the metabolite is available to cause cell death. This explains why the paracetamol normally a safe drug can cause hepatic necrosis in overdose i.e. 10gms or more(20 tabs).

AD: Effects In therapeutic doses, there are no significant side effects. In overdose, it causes liver damage, which can lead to liver failure and death. It also causes kidney damage and can lead to kidney failure. It is also associated with allergic reactions and skin rashes.

Caution: Avoid alcohol consumption while taking acetaminophen as it increases the risk of liver damage.

N-acetyl-p-benzoquinone is normally rendered harmless by conjugation with SH(thiol) group of glutathione. However supply of hepatic glutathione is limited & if amount of metabolite formed is greater than the availability of glutathione, then the metabolite is available to cause cell death. This explains why the **paracetamol** normally a **safe drug** can cause hepatic necrosis in **overdosage** i.e. 10gms or more(20 tabs).

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INDICATIONS: Although equivalent to aspirin as an analgesic and antipyretic agent, it differs in that it lacks anti-inflammatory properties. It does not affect uric acid levels & also lacks platelet inhibiting properties.

- Useful in mild to moderate pain such as headache, myalgia, post partum pain & other circumstances in which aspirin is an effective analgesic. Alone it is inadequate for inflammatory conditions such as RA, it may be used in combination with other anti-inflammatory drugs.
- Used as an alternative in patients allergic to

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Outline

PHARMACEUTICS Aspirin is a weak acid. Absorption starts in the stomach and continues in the small intestine. It is highly soluble in the stomach and is converted to aspirin in the small intestine. It is then converted to salicylic acid in the small intestine. Salicylic acid is the active form of aspirin. It is highly soluble in the small intestine and is converted to salicylic acid in the small intestine.

INDICATIONS Aspirin is used to relieve pain, reduce inflammation, and prevent blood clots. It is also used to prevent heart disease and stroke. It is used to relieve pain and reduce inflammation in conditions such as rheumatoid arthritis, osteoarthritis, and gout. It is also used to prevent blood clots in conditions such as heart disease and stroke.

AD. Effects In therapeutic doses, reversible mild ↑ in hepatic enzymes may occur without jaundice. With larger doses, dizziness, excitement and disorientation can be seen. In still larger doses i.e. 15gms or more, it is hepatotoxic & death may occur.

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aspirin or when salicylates are poorly tolerated.

- It is preferable to aspirin in patients with haemophilia or a H/O peptic ulcer & in whom bronchospasm is precipitated by aspirin.
- It is preferred to aspirin in children with viral infection.

AD. Effects: In therapeutic doses, reversible mild ↑ in hepatic enzymes may occur without jaundice.

With larger doses, dizziness, excitement and disorientation can be seen.

In still larger doses i.e. 15gms or more, it is hepatotoxic & death may occur.

Non-steroidal / [Compatibility Mode] - Microsoft PowerPoint

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Drawing: Drawing Tools (Line, Arrow, Rectangle, Oval, Text Box, Callout, SmartArt, Table, WordArt, Shape, Text, Image, Selection)

Editing: Find, Replace, Select

Outline

- INDICATIONS: Analgesic and antipyretic...
• Used in the treatment of pain such as headache, neuralgia, postoperative pain, rheumatoid arthritis, osteoarthritis, and menstrual pain.
• It is also used to reduce fever in children and adults.
- AD Effects: Analgesic, antipyretic, and...
• It is contraindicated in patients with peptic ulcer disease, asthma, and severe renal impairment.
• It is contraindicated in patients with a history of allergic reactions to aspirin or other NSAIDs.
- AD Effects: Analgesic, antipyretic, and...
• It is contraindicated in patients with peptic ulcer disease, asthma, and severe renal impairment.
• It is contraindicated in patients with a history of allergic reactions to aspirin or other NSAIDs.

Also may cause acute renal tubular necrosis. Doses more than 4-6gms per day not recommended.

Early symptoms of hepatic damage include nausea, vomiting, diarrhea and abdominal pain.

Therapy to hepatic damage is that apart from supportive measures, sulfhydryl groups in the form of acetylcysteine to neutralise toxic metabolite.

Cases of renal damage without hepatic damage have occured even after usual doses of acetaminophen.

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Outline

INDICATIONS: Adjuvant analgesic for relief of moderate to severe pain. It is indicated for the relief of moderate to severe pain in patients with rheumatoid arthritis, osteoarthritis, and ankylosing spondylitis. It is also indicated for the relief of moderate to severe pain in patients with acute gouty arthritis. It is also indicated for the relief of moderate to severe pain in patients with acute low back pain and acute neck pain.

ADVERSE EFFECTS: Adverse effects include dizziness, headache, nausea, vomiting, constipation, and abdominal pain. It may also cause hypotension, especially in patients with a history of hypotension. It may also cause renal impairment, especially in patients with a history of renal impairment. It may also cause liver impairment, especially in patients with a history of liver impairment.

CAUTION: Should be given very carefully in patients with any type of liver disease.

DOSE: Acute pain and fever may be effectively treated with 325-500mg QID and proportionately less for children. Recommended daily dose is up to 4gms/d. 0.5 to 1gm every 4-6hrs max. up to 4gms/d.

Hemolytic anemia and met-hemoglobinemia are very rare adverse effects.

Interstitial nephritis and papillary necrosis (serious complications of phenacetin) have not occurred nor GI bleeding.

Caution: should be given very carefully in patients with any type of liver disease.

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