Doctor 021

MSS

PHARMACOLOGY

3, V3

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Nonsteroidal Anti-inflammatory Drugs (NSAIDs) and Analgesics (pain killers)

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The editions are highlighted with yellow.

- British: paracetamol
- American: acetaminophen

*required to know both names.. they're **NOT** an example of NSAIDS.

Pain

- Universal, Complex, Subjective experience

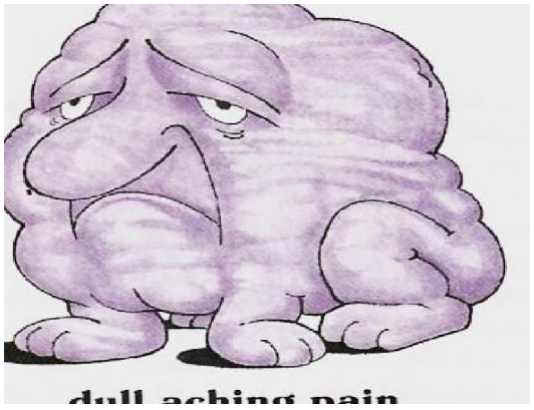
- No. 1 Reason people go to doctor and take medications to fix it.

- Generally is related to some type of tissue damage and serves as a warning signal

- *An*: not.
  Algesis: pain.
  Analgesia: not sensing pain.

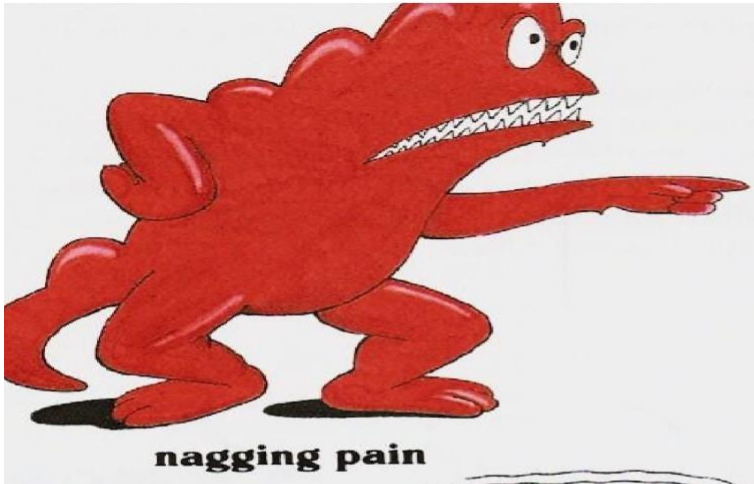
ffi

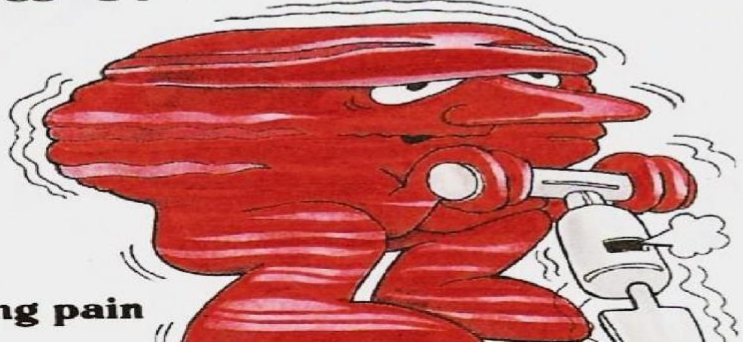
Pain types



dull aching pain

stabbing pain





Analgesics

-Pain killers

- Derived from Greek **an**- "without" & -**algia** "pain".

An **analgesic**, or **painkiller**, is any member of the group of drugs used to achieve analgesia — relief from pain .

- Act in various ways on the peripheral and central nervous systems.

Analgesics

- The non-steroidal anti-inflammatory drugs (NSAIDs): Ibuprofen, aspirin, paracetamol, diclofenac sodium.
- Paracetamol = acetaminophen
- Opioid drugs and non opioid drugs.

Comparison of Analgesics

Feature	Narcotic (Opioids) المخدرات	Nonnarcotic (nonopioid)
Efficacy	Strong	Weak
Prototype	Morphine	Aspirin
Pain Relieved	Any Type	Musculoskeletal
Site of Action	Central	Peripheral and Central
Mechanism	Specific Receptors	PG Synthesis inhibit COX
Danger	Tolerance & Dependence	G.I irritation
Anti-inflammatory	No	Yes
Antipyretic	No	Yes
Antiplatelets	No	Yes

- Why there's week and strong analgesics?

  Because each one of them is needed in different conditions, with different degree of pain.

- According to the slides and the record the doctor considered that analgesics could be subdivided into 3 groups:
  1- Paracetamol.
  2- Non-opioid drugs (NSAIDs)
  3- Opioid drugs.

- Morphine should not be taken unless needed because of its side effects, it causes tolerance and dependence.

- Other additive values from using NSAID: *anti-inflammatory*, *antipyretic*, *antiplatelets* (مميعات الدّم).

- Once there’s an encountering with an antigen (there’s an infection),

this will cause stimulation for an interaction between the

immunosystem and this antigen, this stimuli sometimes causes injury to the cell wall, this injury will result in release of phospholipids that will work up with phospholipase A 2, phospholipase A2 will convert these lipids to *arachidonic acid.*

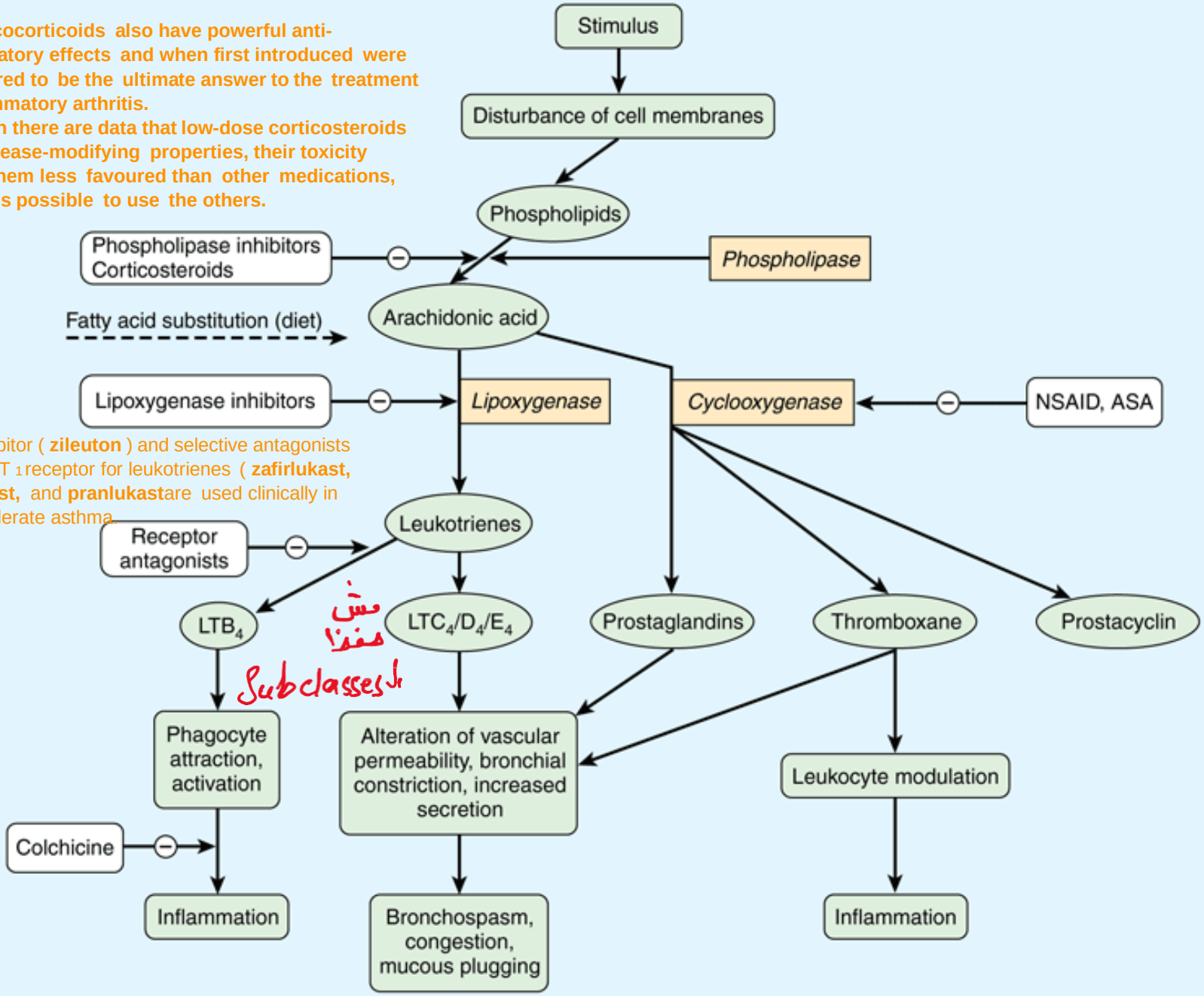
- Remember that phospholipase inhibitors are called corticosteroids.
- Morphine used for visceral pain after operations.
- Morphine given for relief strong pain not for mild pain like headaches.

Inflammatory pathways

- Cyclooxygenase (COX) pathway of arachidonate metabolism produces prostaglandins
- Effects on blood vessels, on nerve endings, and on cells involved in inflammation.
- The lipoxygenase pathway of arachidonate metabolism yields leukotrienes
- have a powerful chemotactic effect on eosinophils, neutrophils, and macrophages and promote bronchoconstriction and alterations in vascular permeability.

The glucocorticoids also have powerful anti-inflammatory effects and when first introduced were considered to be the ultimate answer to the treatment of inflammatory arthritis.
Although there are data that low-dose corticosteroids have disease-modifying properties, their toxicity makes them less favoured than other medications, when it is possible to use the others.

5-LOX inhibitor (**zileuton**) and selective antagonists of the CysLT $_1$ receptor for leukotrienes (**zafirlukast, montelukast,** and **pranlukast**are used clinically in mild to moderate asthma.



Source: Katzung BG, Masters SB, Trevor AJ: *Basic & Clinical Pharmacology*, 12th edition:

- stimulus—> producing arachidonic acid from the phospholipids by the action of phospholipase.

- One important mechanism of the action of glucocorticoids is the inhibition of phospholipase A2, so they have powerful anti-inflammatory effect.

- The treatment of the inflammatory conditions is most important in chronic inflammatory conditions so corticosteroids are used in theses cases.

- The most important side effect of corticosteroids: immunosuppression and suppression of the pituitary adrenal access in the endocrine system.

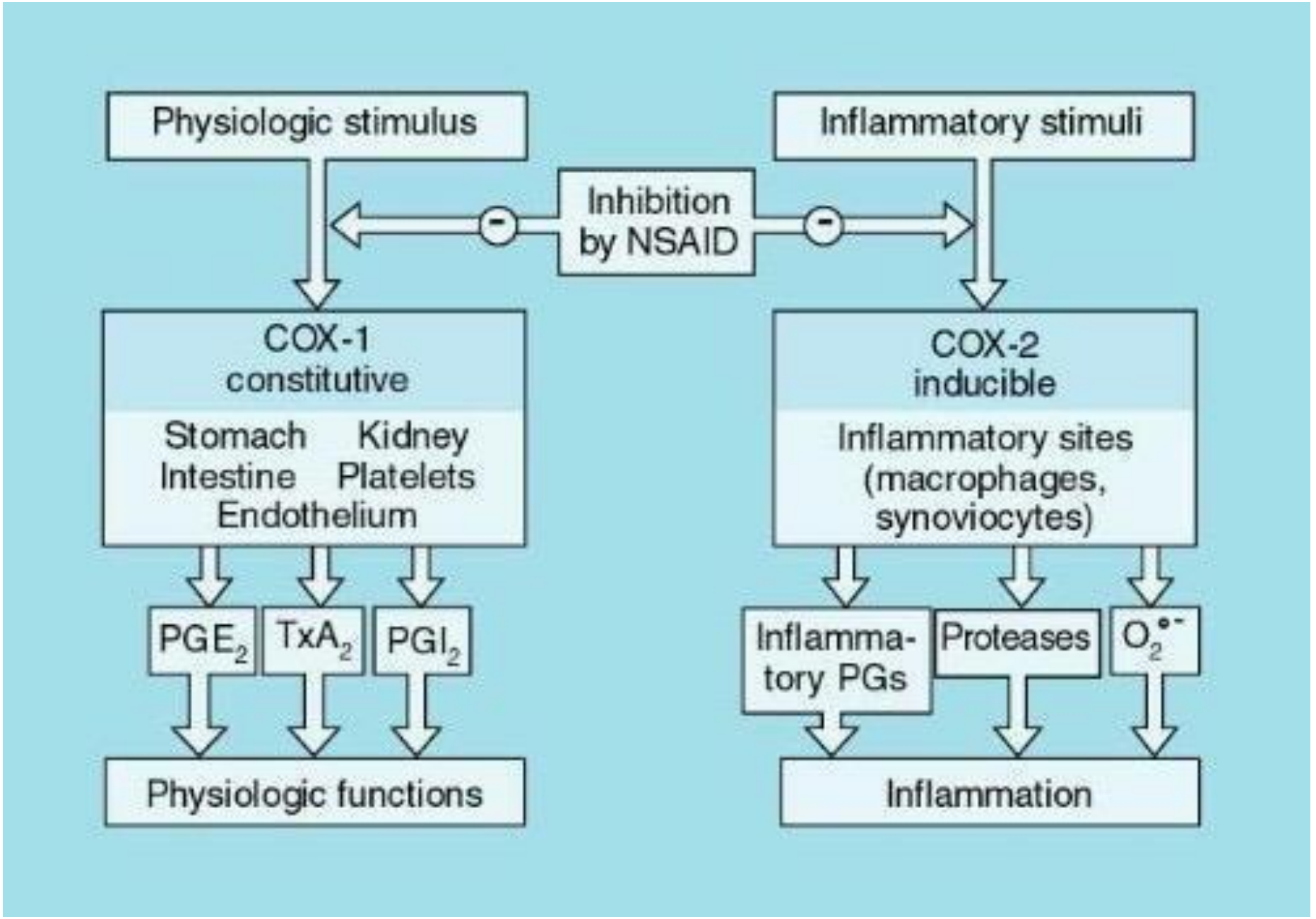
- Zileuton is a lipoxygenase inhibitor.

- Zafirlukast, montelukast and pranklukast are leukotrienes receptor antagonists.

- All these drugs that mentioned above are important for the treatment of the asthma.

- ASA: Acetylsalicylic acid.

- ASA & NSAIDs are inhibitors of cyclooxygenase.


Physiologic stimulus
Inflammatory stimuli
Inhibition by NSAID
COX-1 constitutive
Stomach Kidney
Intestine Platelets
Endothelium
COX-2 inducible
Inflammatory sites (macrophages, synoviocytes)
PGE2
TxA2
PGI2
Inflamma-tory PGs
Proteases
O2°-
Physiologic functions
Inflammation

- To treat asthma we can use:
    1. Inhaled corticosteroids.
    2. Beta agonists.
- In the bronchi —> beta 2 receptors —> upon their activation —> bronchodilation.
- Leukotriene b: fibrocyte attraction and activation which is part of the inflammatory pathway.
- Colchicine: distract macrotubules (polymers of monomers (tubulin)) —> *de* and *re* polarization of the tubules in order to make the fibrocytes move, they are very important for fibrocytes function. When becoming distracted this is an anti-inflammatory action.

Cyclo-oxygenase (COX)

- Exists in the tissue as constitutive isoform (COX-1).
- At site of inflammation, cytokines stimulates the induction of the 2nd isoform (COX-2).
- Inhibition of COX-2 is thought to be due to the anti-inflammatory actions of NSAIDs.
- Inhibition of COX-1 is responsible for their GIT toxicity.
- Most currently used NSAIDs are somewhat selective for COX-1, but selective COX-2 inhibitors are available.

Differences between COX 1 and COX 2:

COX 1:

- constitutive form: is baseline works always.
- Stomach, kidney, endothelium, intestine..etc
- Prostaglandins E2, thromboxane..

COX 2:

- is the endurable form: it becomes active with a stimulation (infection) and activation of immune cells.
- In the inflammatory sites, can be present in macrophages and synoviocytes.
- It produces inflammatory prostaglandins, proteases and

superoxide.

NSAIDs

- The NSAIDs are a group of chemically dissimilar agents that differ in the degree of their **antipyretic**, **analgesic**, and **anti-inflammatory** activities. But similar in their mechanisms (inhibit COX).

- **inhibiting** the **cyclooxygenase** enzymes that catalyze the first step in prostanoid biosynthesis.

>>>> decreased prostaglandin synthesis with both **beneficial** and **unwanted** effects.

TABLE 36-1 Prop n and :sio me other nonstl r,oidalanH--br matory drugs

Drug	Half-Ure 1[h011n,	Urtnary· Exaetlcm of Unchanged Drug	Recommend Antl-lnfl111111matorJ
Aspirin	CQ5,	<2%	U00-1500 mg tio
Salicylate,[1]	*1-rn*	2–1	S@e footnote 2
Cefecoxib	11	27%3	1 200mghid
DiclbfiE!nac	u	<1%	50-75,mg ,qid
Diflunisal	13	1 91:th	500 mg hid
Etooolac	*&5*	<:1%	200--300 mg qicl
Feoo;prof@n	*15*	30%	6.00mg qid
Rurbiprofen	.3.8	<1%	300mg t'ii1
lhuprofen	*1*	<1%	6.00mg qid
Indometfladn	4-5	]6%	50-7-0 mg liid
KetoprofiE!n	1.8	<1%	lOmgtid
Ketoro'.lac	4-10	58%	10 **mg** q'i1t
· eloxoc:am	*10*	Data not found	75-15 mgqd
Nabume.tone5	16	] %	1*CI00'-1®1:xn* mg qd6a
Napromi	14	<1%	375,mg hid
Oxaprozin	58	1-4%	1100-1800 mg qd6a
p··oxicam	57	4–1	20mgq
S.ulindac	g	7%	200mg bid
TormiE!llin	1	7%	400mg qid

Non-steroidal anti-inflammatory drugs (NSAIDs)

pain

fever

Inflammation

By inhibition of cyclo-oxygenase enzymes COX1 & COX2.

NSAIDs

3, V2

An anti-inflammatory action:

(1) decrease Vasodilator PG (PGE_2, PGI_2) leads to less vasodilatation and, indirectly, less edema.

(2) The inhibition of activity of adhesion molecule.

NSAIDs share the same functions and mechanisms of action.

(3) Accumulation of inflammatory cells is also reduced.

NSAIDs

An analgesic effect:

- Decreased prostaglandin generation means decrease sensitivty of **nociceptive** nerve endings to inflammatory mediators.

How do NSAIDs prevent the inflammation?

- Relief of **headache** is due to decreased prostaglandin-mediated vasodilatation.

The adhesion molecules are important for the chemotactic action

Analgesic action:

- Prostaglandin E2 (PGE2) is thought to **sensitize** nerve endings to the action of bradykinin, histamine, and other chemical mediators released locally by the inflammatory process.

- management of pain of low to moderate intensity arising from musculoskeletal disorders rather than that arising from the viscera.

Antipyretic Effects

- The antipyretic due primarily to the blockade of **prostaglandin** synthesis at the thermoregulatory centers in the hypothalamus and at peripheral target sites.

PGE2 makes the nerve ending more sensitive to the action of histamine and other chemical mediators.