МІНІСТЕРСТВО ОХОРОНИ ЗДОРОВ'Я УКРАЇНИ
Харківський національний медичний університет

Nonopioid analgesics

Methodical recommendation
for students of English medium

Ненаркотичні анальгетики

Методичні вказівки
для студентів з англійською мовою навчання

Затверджено
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NON-OPIOID ANALGESICS

Non-opioid analgesics are the drugs used for a decrease of intermediate and weak pain, especially resulting from inflammation. They have an analgesic, an anti-inflammatory and an antipyretic actions. They are named non-narcotic so as they do not cause sleep. Drugs with the prevalence of anti-inflammatory activity are named non-steroidal anti-inflammatory drugs (NSAIDs). Their main effects are similar and the choice between particular drugs is dictated by their pharmacokinetics and pharmacodynamics.

MAIN QUISTIONS

1. Definition of analgesics
2. Distinctions between opioid and non-opioid analgesics
3. Mechanism of non-opioid analgesics action and role of prostaglandins
4. Pharmacological effects of non-opioid analgesics and their mechanisms
5. Classification of non-opioid analgesics
6. Aspirin as prototype of non-opioid analgesics
7. Comparative pharmacokinetic and pharmacodynamic characteristics of main opioid analgesics
8. Clinical uses
9. Side effects
10. Contraindications

DISTINCTIONS BETWEEN OPIOID AND NON-OPIOID ANALGESICS

Opioid analgesics	Non-opioid analgesics
Potent analgesic effect, efficacy in the life-threatening pain	Less potent analgesic effect, but high efficacy in inflammatory pain
Prevailing central mechanism in analgesic effect	Prevailing peripheral mechanism in analgesic effect
Hypnotic effect	Absence of hypnotic effect
Drug dependence	No drug dependence
Tolerance	No tolerance
Potentiation, but lack of such effects, as antipyretic and anti-inflammatory	Antipyretic and anti-inflammatory effects in addition of analgesic
Respiratory depression	Lack of respiratory depression
Availability of universal opioid antagonists	Lack of specific antagonists, except paracetamol

MECHANISM OF NON-OPIOID ANALGESICS ACTION AND ROLE OF PROSTAGLANDINS

Non-opiods exert their analgesic effect by decreasing the production of prostaglandins.

Prostaglandins (PGs) are synthesized from cellular membrane phospholipids after activation or injury, and sensitize pain receptors especially to bradikynin. They are synthesized from arachidonic acid. Arachidonic acid is

present as a component of the phospholipids of cell membranes and other complex lipids. Free arachidonic acid is formed from tissue phospholipids by the action of phospholipase A_2 and other acyl hydrolases via a process controlled by biological active substances. There are two major pathways of arachidonic acid metabolism (Fig. 1): cyclooxygenase pathway results in PGs synthesis and lipooxygenase results in leukotrienes (LTs) synthesis. PGs generally act locally on the tissues in which they are synthesized, and they are rapidly metabolized to inactive products at their sites of action. Therefore the PGs do not circulate in the blood in significant concentrations.

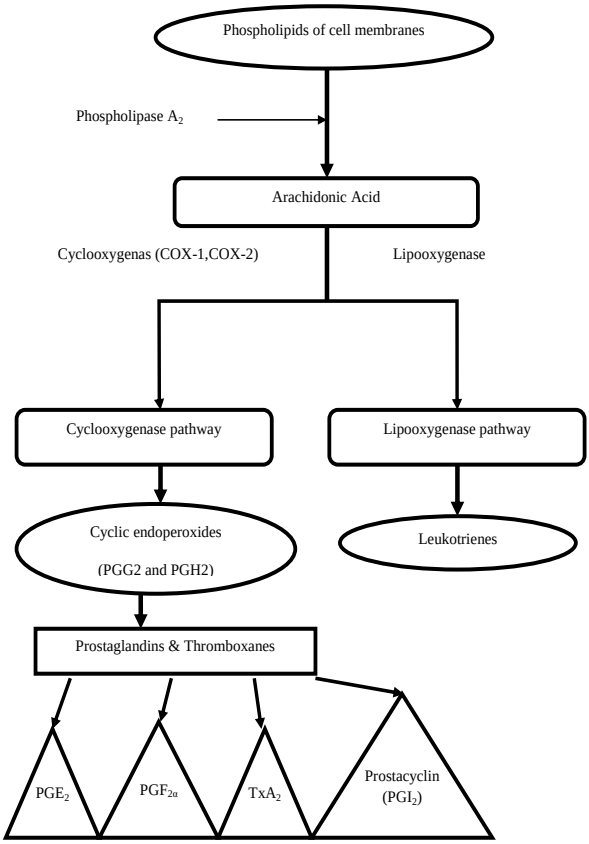

Fig. 1. Arachidonic acid metabolism

Enzyme responsible for arachidonic acid metabolism with formation of PGs is cyclooxygenase (COX). There are two isoforms: COX-1 and COX-2. Recently another type of COX – COX-3 was described; it may be implicated in fever.

Biological effects of PGs

COX-1 is a constitutive, it participates in homeostasis functions. Under the action of COX-1 in the body PGs constantly are synthesized to regulate the function of several organs and tissues. They control mucus secretion in the stomach, platelet aggregation, renal blood flow, and the contractile function of myometrium, vascular tone etc.

Physiological effects of PGs are described below. Thus PGE_2 is physiological stimulant of mucus and bicarbonate secretion that protect the lining of the stomach from erosion by gastric acid. It produces the dilation of arterioles and bronchi. Uterine muscle is contracted by low concentrations of PGE_2 but a high concentration of it causes relaxation. Along with it PGE_2 softens the cervix by increasing proteoglycan and changing the biophysical properties of collagen.

$PGF_{2\alpha}$ is physiological stimulant of mucus and bicarbonate secretion. It causes venoconstriction and constriction of bronchi. $PGF_{2\alpha}$ regulates menstruation. It is essential for the onset of parturition because $PGF_{2\alpha}$ softens the cervix, promotes it's opening, the stimulation of uterine contraction, thus promoting smooth delivery.

PGI_2 produces the dilation of arterioles and bronchi. Uterine muscle is relaxed by it. Prostacyclin (PGI_2) regulates platelet aggregation and vascular diameter. It is physiological stimulant of mucus and bicarbonate secretion.

Thromboxane A_2 (TxA_2) regulate platelet aggregation and causes the constriction of uterine muscles.

PGs regulate the renal blood flow. PG endoperoxides (G_2 and H_2) are inherently vasoconstrictor, but often produce vasodilatation or a biphasic response due to rapid conversion to other PGs, especially PGI_2 in the blood vessels.

PGE compounds inhibit the release of norepinephrine from postganglionic sympathetic nerve endings.

COX-2 is induced in the process of inflammation. The activity of COX-2 is induced in inflammation. PGs are one of important mediators of inflammation. Excessive amounts of PGs E_2 and I_2 in the inflammation cause vasodilation, increase vascular permeability, sensitize nociceptors to bradykinin, serotonin and histamine. $PGsE_2$ inhibits differentiation of B lymphocytes into plasma sells. These factors lead to the development of the major signs of inflammation. PGE_1 raises the set point of hypothalamic thermoregulatory neurons and increases the body temperature.

FARMACOLOGICAL EFFECTS OF NON-OPIOID ANALGESICS AND THEIR MECHANISMS

Mechanism of analgesic action

Analgesia is produced by affecting both the peripheral pain receptors (in the site of injury) and hypothalamus. In response to tissue injury, joint damage, or edema, active substances such as bradykinin, PGs, and histamine are released. PGs and bradykinin, in particular, stimulate peripheral nerve endings, which carry pain impulses to the CNS. Non-opioid analgesics inhibit COX

leading to decrease in the synthesis of PGs and prevent bradykinin from stimulating pain receptors. Since PGs also affect hypothalamic centers, non-opioid analgesics inhibit the recognition of pain impulses.

Mechanism of antipyretic action

The set point of the body temperature is programmed in the hypothalamic thermoregulatory center. A stable body temperature is due to the balance between heat production and heat output. Pyrogens elevate the set point of the hypothalamic temperature controller. The body responds by restricting a heat loss and elevating heat production that results in the fever.

The mechanism of the central action involves inhibition COX and blockade of PGE_2 stimulation of the CNS. In addition to the central action, these drugs increase peripheral blood flow (vasodilation) and sweating, permitting a greater loss of excess heat from the body. By such a way, they decrease the sensitivity of the hypothalamus to pyrogens, increase heat output and lower high body temperature. They do not act on body temperature in the absence of fever.

Mechanism of anti-inflammatory action

Inhibition of COX by non-opioid analgesics leads to a decrease in the synthesis of PGE_2. That results in a decrease of the permeability of blood vessels at the site of inflammation, inhibition of hyaluronidase activity, stabilization of lysosomal membranes, and a decrease in lysosomal enzymes release. All the listed events lead to a decrease in the exudation stage of inflammation. Some of most active preparations (e.g. indometacin) inhibit fibroblasts' activity and decrease the proliferation stage of inflammation. The inhibition of energy processes in the area of inflammation and the inhibition of leukocytes activity are also observed.

CLASSIFICATION OF NON-OPIOID ANALGESICS

1. Salicylates: Aspirin, Salicylic asid, Methyl salicylate, Salicylamide.
2. Propionic acid derivatives: Ibuprofen, Naproxen, Ketoprofen, Flurbiprofen.
3. Anthranilic acid derivative: Mephenamic acid.
4. Aryl-acetic acid derivatives: Diclofenac, Aceclofenac.
5. Oxicam derivatives: Piroxicam, Tenoxicam, Meloxicam
6. Pyrrolo-pyrrolc derivative: Ketorolac.
7. Indolacetic acid derivative: Indomethacin.
8. Pyramzolone derivatives: Metamizol (Dipyrone, Analginum), Propiphenazone, Oxyphenbutazone.
9. Paraaminophenol derivative: Paracetamol (Acetaminophen).
10. Benzoxazocine derivatives: Nefopam
11. Sulfonanilide derivatives: Nimesulide
12. Sulfonamide derivatives: Celecoxib

Classification of non-opioid analgesics according to the mechanism of action

1. Non-selective inhibitors of COX-1 and COX-2:

Mainly with a peripheral action

- Acetylsalicylic acid

- Metamizole
- Mefenamic acid
- Indometacin
- Diclofenac-sodium
- Ibuprofen
- Piroxicam

Mainly with a central action

- Paracetamol

2. Selective inhibitors of COX-2

- Meloxicam
- Celecoxib

SALICYLATES (ASPIRIN)

The salicylates, represented by aspirin, salicylic acid, methyl salicylate, and salicylamide, are the oldest and often used non-opioid analgesic drugs due to their analgesic, antipyretic, anti-inflammatory, and antiplatelet effects.

Aspirin is acetylsalicylic acid. It is rapidly converted in the body to salicylic acid, which is responsible for most of the actions. Other actions are the result of acetylation of certain macromolecules including COX.

Mechanism of action

Aspirin is a non-selective inhibitor of COX-1 and COX-2 in peripheral tissues and in CNS. It irreversibly acetylates and thus inactivates COX. All other non-opioid analgesics are reversible COX inhibitors.

Pharmacokinetics

After oral administration, the unionized salicylates are passively absorbed from the stomach and the small intestine (dissolution of the tablets is favoured at the higher pH of the gut). It crosses both the blood-brain barrier and the placenta. It is absorbed through intact skin (especially methyl salicylate) and binds to albumins in blood plasma.

Aspirin is hydrolyzed to salicylate and acetic acid by esterases in tissues and blood. It is converted by the liver to water-soluble conjugates that are rapidly cleared by the kidney resulting in elimination with first-order kinetics and a serum half-life of 3.5 hrs. Analgesic effect lasts for 4-6 hrs. At anti-inflammatory doses (>4g/day) aspirin has a half-life of 15 hrs or more.

Pharmacological effects

1. Analgesic, antipyretic, anti-inflammatory actions. Aspirin is a weaker analgesic than morphine type drugs: effect of 600 mg of aspirin is equivalent to 60 mg of codeine. However, it effectively relieves inflammatory, tissue injury related, connective tissue and integumental pain, but is relatively ineffective in severe visceral and ischaemic pain. The analgesic action is mainly due to prevention of PG-mediated sensitization of nerve endings. A central subcortical action such as raising threshold to pain perception also contributes, but the morphine-like actions on the mental components of pain are

not characteristic. Neither sedation, subjective effects, nor tolerance or physical dependence is produced.

Aspirin resets the hypothalamic thermostat and rapidly reduces fever by promoting heat loss (sweating, cutaneous vasodilatation), but does not decrease heat production.

Anti-inflammatory action is exerted at high doses (3–6 g/day or 100 mg/kg/day). Signs of inflammation like pain, tenderness, swelling, and vasodilatation and leucocytes infiltration are suppressed. In addition to COX inhibition neutralizing of free radicals may contribute to its anti-inflammatory action.

2. Metabolic effects. Increased the production of heat due to uncoupling of oxidative phosphorylation as a result of increased cellular metabolism particularly in skeletal muscle. Along with it increased use of glucose leads to lower blood sugar (especially in diabetic patients) and liver glycogen is depleted, however, at toxic doses hyperglycemia occurs that is associated with sympathetic stimulation. Plasma free fatty acid and cholesterol levels are reduced as well as. These are significant only at anti-inflammatory doses.

3. Respiration. The effects are dose dependent. At anti-inflammatory doses, respiration is stimulated by peripheral (increased CO_2 production) and central (increased sensitivity of respiratory centre to CO_2) actions. Higher doses work directly on the respiratory center in the medulla, resulting in hyperventilation and respiratory alkalosis that usually is adequately compensated by the kidney. Hyperventilation is prominent in salicylate poisoning. At toxic levels, respiratory depression and death is due to respiratory failure. Respiratory acidosis ensues due to continued production of CO_2.

4. CVS Aspirin has no direct effect in therapeutic doses. Larger doses increase cardiac output to meet increased peripheral O_2 demand and cause direct vasodilatation. Toxic doses depress vasomotor centre resulting in a decrease in BP.

5. GIT. Salicylates directly irritate the stomach mucosal lining. In addition, salicylates inhibit PGs synthesis. In the stomach, PGs are an integral part of the normal cytoprotective mechanisms. PGs mediate secretion of mucus and bicarbonate, which protect the lining of the stomach from erosion by gastric acid. When COX-1 is blocked, the protective environment within the stomach is altered, leading to gastric distress and ulcers. In some individuals, vomiting occurs as a result of gastrointestinal (GI) irritation and CNS stimulation (the medullary center known as the chemoreceptor trigger zone).

6. Kidney. COX inhibitors prevent the synthesis of PGE_2 and PGI_2 that are responsible for maintaining renal blood flow. Decreased synthesis of PGs can result in retention of sodium and water and may cause oedema and hyperkalaemia in some patients.

7. Urate exretion. Dose-related effect is seen: from urate retention and antagonism of all other uricosuric drug to increased urate excretion. COX inhibitors prevent the PGs synthesis such as PGE_2 and PGI_2 that are responsible for maintaining renal blood flow, particularly in the presence of circulating vasoconstrictors. Decreased synthesis of PGs can result in retention of Na^+ and water and may cause oedema and hyperkalemia in some patients. Interstitial nephritis can also occur with all NSAIDs except aspirin.

8. Blood. Low doses of aspirin irreversibly inhibit TXA_2 production in platelets via acetylation of COX. Because platelets lack nuclei, they cannot synthesize new enzyme, and the lack of TXA_2 persists for the lifetime of the platelet (7 days).

COMPARATIVE CHARACTERISTICS OF NSADS

Indomethacin. It is an indolacetic acid derivative. It is a potent anti-inflammatory drug with prompt antipyretic action. Indomethacin relieves only inflammatory related pain. It is a highly potent nonselective COX inhibitor and may also inhibit phospholipase A and C, reduce neutrophil migration, and decrease T-cell and B-cell proliferation. It inhibits exudation, as well as proliferation. Indomethacin is the most toxic drug.

Indomethacin is well absorbed orally. It is administered orally, rectally, topically. Indomethacin displays maximal concentration in 2 hrs after the oral administration. It has a half-life of 2–3 hrs. Indomethacin is 90% bound to plasma proteins, partly metabolized in the liver. Is is excreted with urine (2/3) and with bile (1/3).

Ibuprofen. The analgesic, antipyretic and anti-inflammatory efficacy is rated somewhat lower than high dose of aspirin. Inhibition of platelet aggregation is short lasting with ibuprofen. It rated as safest drug by spontaneous drug reaction.

It is well absorbed orally, highly bound to plasma proteins (90–99%), but displacement interactions are not clinically significant. All propionic acid derivatives enter brain, synovial fluid and cross placenta. They are metabolized in liver by hydroxylation and glucoronide conjugation and inactive metabolites are excreted in urine as well as in bile.

Acetaminophen (paracetamol). It is the deethylated active metabolite of phenacetin. Paracetamol is a good and promptly acting antipyretic. Acetaminophen produces adequate analgesia that is beneficial in the relief of a minor pain. Paracetamol has negligible anti-inflammatory action. It is a poor inhibitor of PG synthesis in peripheral tissues, but more active on COX in the brain. It exerts slow and prolonged analgesic and antipyretic effects. It reduces elevated body temperature by a direct action on the heat regulation centers in the hypothalamus, postulated to occur through the COX-3 receptors, that is mainly found in the brain. In contrast to aspirin, paracetamol does not stimulate respiration and does not affect acid-base balance, does not increase cellular metabolism. causes damage of liver and kidney if used for a long time and at high dose.

Acetaminophen does not affect platelet function or clotting factors and is not uricosuric.

Paracetamol is well absorbed orally, only about ¼ th is protein bound at plasma and it is uniformly distributed in the body. Metabolism occurs mainly by conjugation with glucuronic acid and sulphate and conjugates are excreted rapidly in urine. Effects after an oral dose last for 3–5 hrs.

Naproxen. Naproxen is a naphthylpropionic acid derivative. It is a nonselective COX inhibitor and is particularly potent in inhibiting leucocyte migration.

Naproxen is effective in the usual rheumatologic pathology and is available in a slow-release formulation, as an oral suspension, a topical preparation and an ophthalmic solution are also available.

Diclofenac-sodium. Diclofenac is a phenylacetic acid derivative that is nonselective as a COX inhibitor. It reduces neutrophil chemotaxis and superoxide production at the inflammatory site. Diclofenac has similar analgesic, anti-inflammation and antipyretic effect to naproxen. It is administered orally, IM, topically (gel, ointment). It displays maximal concentration in plasma in 1–2 hrs after the oral administration and binds to proteins in blood plasma (96% of preparation). An ophthalmic preparation is also available. Diclofenac accumulates in synovial fluid, and the primary route of excretion for the drug and its metabolites is the kidney and partly excreted with bile.

Piroxicam. Piroxicam, an oxicam, is a nonselective COX inhibitor that at high concentrations also inhibits polymorphonuclear leukocyte migration, decreases oxygen radical production, and inhibits lymphocyte function. Piroxicam is taken orally once a day. It has a half-life of 40–45 hrs, thus is permitted once-daily administration, the parent drug as well as its metabolites are renally excreted in the urine (in the form of glucuronides). Piroxicam has a strong durative anti-inflammatory action.

Mefenamic acid. Mefenamic acid is fenamate. An analgesic, antipyretic and weaker anti-inflammatory drug, which inhibits COX as well as antagonises certain actions of PGs. It has structural similarity to salicylates. Mephenamic acid exerts peripheral as well as central analgesic action. Anti-inflammation and analgesia exceed those of aspirin; apyrexia is equal to that of aspirin. Mefenamic acid is the inductor of interferon.

Oral absorption is slow but almost complete. It is highly bound to plasma proteins - displacement interactions can occur. Mefenamic acid partly metabolized and excreted in urine as well as bile.

It has fewer side effects in comparison with salicylates. Diarrhoea is the most important dose-related side effect and associated with the inflammation of the bowel.

Metamizole (Analginum). Metamizole is a pyrazole derivative. This derivative of amidopyrine is a potent and promptly acting analgesic, antipyretic but poor anti-inflammatory, and not uricosuric drug.

It can be given orally, IM as well as IV, but gastric irritation, pain at injection site occurs. The time of onset of action 20 min after the IM injection and acts during 3–4 hrs is potentiated by antihistamines.

It is indicated in intermediate somatic pains (headache, toothache, myalgia, neuralgia, and arthralgia), visceral pans, and control of intermediate postoperative pain, and fever.

THERAPEUTIC USES OF NSADS

1. Gout, rheumatic fever, osteoarthritis, rheumatoid arthritis, and ankylosing spondylitis. Diclofenac, Piroxicam are approved for a long-term use in the treatment of rheumatoid arthritis, osteoarthritis, and ankylosing spondilitis.

2. Headache, arthralgia, toothache, neuralgia and myalgia (Indomethacin, Ibuprofen, Mefenamic acid, and Metamizole). Acetaminophen is effective against headache because it inhibits PGs synthetase within the CNS but it is not a drug of choice in the treatment of pain associated with muscle and inflammation, especially arthritis.

3. Trauma of joints and soft tissues, thrombophlebitis, tendovaginitis, myositis (Indomethacin typically in the form of ointment and Ibuprofen is indicated orally).

4. Dysmenorrhoea. Ibuprofen suppresses uterine $PGF_{2\alpha}$ even more than PGE_2. Mefenamic acid is quite effective in dysmenorrhoea. Metamizole controls dysmenorrhoea.

5. Misclosure of ductus artriosus (Salysilates, Indomethacin).

6. Prevention of rethrombosis, myocardial infarction, or stroke and thrombophlebitis due to antiplatelet agent effect salysilates are used).

7. Pain associated with uveitis and postoperative ophthalmic procedures, in Hodgkin's disease fever (Indomethacin).

8. Prevention of colorectal cancer.

SIDE EFFECTS OF NSADS

1. Gastric ulceration, erosions, and esophagitis (resulting decreased prostacyclin (PGI_2) and PGs (PGE_2 and $PGF_{2\alpha}$) synthesis in the gastric wall, as well as from the irritation of the gastric mucosa). It is a common side effects all of non-selective inhibitors of COX.

2. A decrease in renal blood flow, the retention of sodium and water. It is a common side effects all of non-opioid analgesics. Indometacine causes renal papillary necrosis. Paracetamol causes damage of liver and kidney if used for a long time and at high dose.

3. Rised transamines, hepatic failure (rarer).

4. Reye's syndrome (fatal, fulminating hepatitis with cerebral oedema) occurs in children and adolescents (usually aged 4–12 years) during the salicylates treatment of fever caused by a virus (influenza, measles, chicken pox).

5. Hypocoagulation, bleeding (a common side effects all of non-selective inhibitors of COX).

6. Thrombocytopenia (Indomethacin, Diclofenac).

7. Methaemoglobinaemia (Acetaminophen).

8. Inhibition of hematopoiesis such as agranulocytosis (Piroxicam, Metamizole), haemolytic anaemia (Mefenamic acid), leukopenia, and aplastic anemia (Indometacin).

9. Hypersensitivity and idiosyncrasy (resulting from acetylation of albumins by aspirin)

10. Spasm of bronchi, "aspirin asthma" (resulting from the inhibition of PG synthesis and overproduction of leukotrienes).

11. Skin rash.

12. Allergic pneumonitis, vasculitis, and pseudoporphyria are caused Naproxen.

13. Disturbances in normal development of pregnancy, prolonged labor, bleeding tendency in the mother and infant, a premature closure of ductus arteriosus.

14. Toxic action on CNS such as headache, dizziness, dormancy, depression, mental confusion (Indomethacin, Ibuprofen, Piroxicam, Mefenamic acid). Indomethacin rarely causes psychosis with hallucinations.

CONTRAINDICATIONS OF NSADS

1. Ulcerative disease of the stomach and duodenum.
2. Ulcerative colitis.
3. Bleeding.
4. Bronchial asthma.
5. Disturbances of haemopoesis such as anaemia and inhibited haemopoiesis.
6. Hepatic and renal impairment.
7. Pregnancy.
8. Lactation.
9. G-6-PD deficient individuals (haemolysis can occur)
10. Epilepsy, Parkinson's disease, psychic disorders (Indomethacin).

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Навчальне видання

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