General and Particular Structural Characteristics of Acetylsalicylic Acid - Aspirine

Chemical properties

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Anti-inflammatory-analgesic medication is known to have a wide spread, its indications going beyond the area of rheumatology, aimed at various fields, cardiology, nephrology, hematology,neurology, etc. Many years of aspirin has constituted the health expectation of millions of patients. Most nonsteroidal anti-inflammatory analgesics (ASNS) are acidic compounds derived mainly from carboxylic acids and enolic acids. The non-acidic compounds are numerically reduced and relatively unrelated. The main effects of non-steroidal anti-inflammatory analgesics arise following antipyretic action, analgesic action and anti-immflamatory in varying proportions to each structural group. Each drug has the specificity of single actions, the global way of explaining the clinical effects remains little known. Anti-inflammatory (anti-termic) in acute rheumatism or other inflammatory joint disorders, anti-platelet antiaggregant, aspirin prevents aggregation of blood platelets (which have a role in stopping bleeding).This is why it is used to prevent thrombosis (clotting of blood in the arteries or veins) with an impOliant role in preventing myocardial infarction. The study includes 126 patients who often used aspirin. Interaction of aspirin with other drugs mainly occurs in the plasma albumin, platelets, liver, kidney and gastrointestinal tract. Considered a common drug, often used by patients without the physician's indication, some of them under maintenance medication (corticosteroid, anticoagulants, antiplatelet, antidiabetics, cytostatics), aspirin may cause important complications.

Keywords: anti-inflammatory, analgesic, non-steroidal, platelet antiaggregant, acetylsalicylic acid

Administration to humans of antiimmflamatory - analgetic nesteroidian drugs generally follows a phalmacokinetic and pharmacodynamic pathway dictated by general and particular structural features.

The active serum concentration of the compound is the result of pharmacokinetic processes of absorption, distribution, metabolism and excretion. The intensity and characteristics of the drugreceptor interaction, as well as the physiological and pathological modulating factors of this interaction, ultimately define the pharmacodynamics of the compound [1-7].

Among the modifying factors, we also mention the influence on receptor functionality, disease related changes in the target organ or organs, development of long-term tolerance to compounds,drug associations that can generate pharmacodynamic or pharmacokinetic interactions, [8,9]conelation with biorhythms.

A great influence on the pharmaco-therapeutic effects has the acid-base balance and the consequences of the ionization of drugs in the blood and tissues, in their turn ionized media.

In this way the diffusion, the hematic and cell membrane transversion, depends on the polarity of the ionizable drugs. Non-ionizable substances diffuse more easily through lipoprotein cell membranes, preferentially absorb into the gastrointestinal tract and resorb to the renal tubules [gastro].

In drug associations, similar ionized compounds (e.g., anions) may compete for plasma transport albumin and for renal elimination [10-17]

The pharmacokinetics and pharmacodynamics of the drug may be modified; such hyposerinemic states in which, due to the *free* fraction of salicylates, fenibutazone, diphenylhydantoin, can become toxic in *normal* doses.

Things get complicated when a drug shifts the other from the transport protein, as is the case with corticosteroid-aspirin [18-23].

The metabolism of drugs is mostly done in the liver. Any drug is metabolized, in a first phase, in a constant dose per unit dose of time. The active-blood-dose relationship is not so linear and low doses can produce important effects, as demonstrated for aspirin, heparin and diphenyl-hydantoin.[8]

Hepatic function inhibitors can produce toxic effects on allopurinol, azathioprine. In tum, allopurinol sometimes inhibits hepatic metabolism, such as the hypoglycemic action of sulfonylurea derivatives, to increase dangerously.

By inhibiting competitively the oxidation of drugs such as ethylmorphine and hexabarbital, hydrocortisone makes their toxicity increase.

Drug interaction occurs due to the in-effect of medicinal products on liver microsomal enzymes,resulting in faster metabolism of the associated substances. This is the case for short-chain barbiturates, glutetimide and fenbulasone. The management of anti-inflammatory drugs is based on a half-life strategy (1/2)[23-34]

Acetylsalicylic acid - Aspirine

The year 1897 is considered the year of birth of aspirin. In 1897, a German chemist, Felix

Hoffmann, who worked for the well-known company Friedrich Bayer et Co., discovered acetylsalicylic acid, aspirin, which has become the most famous medicine. But history of aspirin stalis over 3500 years ago. With 1500

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years, i.e. Egyptians used the infusion of dry myrrh leaves for rheumatic pain.

Salicylates are used for therapeutic purposes for two millennia, at first as salicin, a herb shell extract. In 1763 Reverend Edward Stone, who was part of the Royal Society of London, has initiated the first clinical study on the effects of willow bark powder on patients suffering from colds, then fever considered one of the symptoms of malaria.

The active extract of the bark, called the salicin, after the Latin name for the White Shallot (Salix alba), was isolated in its crystalline form in 1828 by the French pharmacist Henri Leroux and the Italian chemist Raffaele Piria who managed to separate this acid in its pure form.During the Tsin Dynasty (2000 years ago), a yeast (Kombucha) was discovered, being considered the mysterious remedy of eternal life with miraculous effects on the body, including anti-inflammatory effects especially at the digestive level [35]. Natural remedies such as hot pepper, black pepper, lavender,curcumina, but also synthetic, such as ibuprofen, are known for their anti-inflammatory, analgesic and anti-rheumatic effect along with acetylsalicylic acid [36-40].

Salicylic acid is very acidic when it is in a saturated aqueous solution, having a *p*H of 2.4, hence the name of salicylic acid.

In 1839 it was observed that salicylic acid causes digestive problems, stomach irritation or diarrhea. In 1897, a researcher from Friedrich Bayer, Germany, replaced one of the hydroxyl functional groups of salicylic acid with an acetyl group that significantly reduced the negative effects. This was the first synthesis drug and the beginning of the pharmaceutical industry.

The name *aspirin* was launched in 1899 by Bayer, consists of the letter *A* from acetyl, of the name Spiraea ulmaria, which was in tum a source of salicin, and the suffix *in* was given to all medicines made during the same period as aspirin.

Who discovered acetylsalicylic acid is a rather controversial issue. Officially, the inventor of aspirin was Felix Hoffmann. Arthur Eichengriin said in 1949 that he planned and directed the synthesis of aspirin, while Hoffmann's role was merely the initial synthesis of the drug, using the Eichengriin process.

Structure and physico-chemical properties

Salicylic acid has the molecular formula C7H603, the molar mass: 138, 121 g / mol; melting point: 158.6 0 C, density: 1.443 g / cm3, boiling point 211 DEG C.

Salicylic acid (Latin, salix, meaning willow) is an aromatic hydroxyacid, precursor of acetylsalicylic acid. Colorless, crystalline high in organic synthesis, but which may also be a hormone in some plants.

Chemical properties

-Salicylic acid has the formula C6H4 (OH) COOH, wherein the hydroxyl-OH group is substituted in the ortho position on the aromatic ring to the carboxyl-COOH group. Thus, 2hydroxybenzoic acid can also be referred to. It is hardly soluble in water (2 g / L at 20 0 C).

Aspirin (acetylsalicylic acid) can be prepared by the acylation reaction of the phenolic group of salicylic acid with acetyl radicals (acetic anhydride or acetyl chloride) or by the Kolbe-Schmitt reaction (fig.1).

Aspirin or acetylsalicylic acid is a non-steroidal anti-inflammatory drug in the salicylate family, generally used as a minor analgesic, antipyretic or anti-inflammatory.

Salicylic acid can be biosynthesized using an amino acid precursor called phenylalanine.

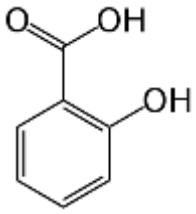
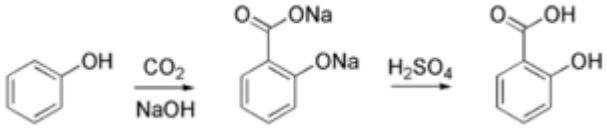


Fig.1 Salicylic Acid

White willow

Sodium salicylate can be commercially available by treating sodium phenoxide with high pressure and high temperature (100 atm and 390 K) carbon dioxide, known as the Kolbe-Schmitt process. Salicylic acid is obtained of this salt by treatment with sulfuric acid:



Salicylic acid can also be prepared by hydrolysis of acetylsalicylic acid (aspirin) or by reaction between methyl salicylate and a base or a strong acid.

Salicylic acid is used to relieve pain and reduce fever. Thus, it can be said to have bactericidal,antipyretic and antiseptic propeliies, but can also be used as a food preservative.

Acetic salicylic acid is insoluble in water (solubilization increases for sodium salts in weak alkane solutions); ionization constant has a value of 3.5 (does not ionize in gastric acid, but in the medium of the body it partially ionizes, ensuring good diffusion); water solubility increases for sodium salt in effervescent form.

Absorption of the compound occurs in the stomach, facilitated by lack of ionization in the environment acid, but also in the intestine, this time in ionizing fonn. Aspirin hydrolyses spontaneously as acetate. After absorption it is metabolized exclusively in salicylate by disacetylation due to acetyl protease acceptors (prostaglandin synthesis, hemoglobin and albumin) as well as by predominantly hepatic enzymatic hydrolysis. Within 10-20 min after ingestion of aspirin, the dominant form in plasma occurs rapidly in the synovial fluid (20 min). The half-life (Tl / 2) is 15min; therefore the blood level depends on the rate of absorption.

The remaining alicydine behaves differently in pharmacokinetics (Tl /2 = 2 h).

The aspirin parțially binds to plasma albumin; salicylate is 50-80% bound and rapidly diffuses into the synovial fluid and the cerebrospinal fluid, crossing the placenta as quickly. 60-70% of the serum level of the drug is concentrated in the synovial fluid. In advanced rheumatoid arthritis, due to hypo-semm, the risk of overdosing by increasing the free fraction of aspirin increases.

During the third trimester of pregnancy, all inhibitors of prostaglandin synthesis may have the following effects: on the fetus: cardiopulmonary toxicity with (premature ventricular arrest and pulmonary hypertension); kidney dysfunction, which may develop into renal impairment with oligo-hydramnios, on the mother and newborn: at the end of pregnancy, possible prolongation of bleeding time and anti-aggregation effect that may occur even at very low doses; inhibition of uterine contractions leading to postponement or prolongation of labor [45-49].

Exclusively metabolised in the liver, aspirin possesses three major metabolites resulting from conjugation:

- a glycine conjugate: salicyluric acid,

- two glycuronic conjugates: on the hydroxyphenol group and on the carboxyl group.

-glicino-conjugation is done at a fixed metabolic rate determined individually genetically, doseindependent.

The fourth metabolite that retains attention is gentisic acid produced by oxidation, which has prostaglandin synthesis inhibition properties.

Extention of metabolism depends on the size of the dose administered. Primary plasma concentration of metabolites does not exceed 7% of the total salicylate concentration.

Metabolites are renal excreted independently of urinary *p*H with variations in nonnal range.

High *p*H changes greatly affect clearance of salicylates, as well as the use of soluble gastric antiacids or insoluble (the rate of excretion increased), exercise, the pulmonar functional state.

In the conditions of an alkaline urine, approximately 35% of the acetylsalicylic acid dose is eliminated unchanged by the urine, while at a normal *p*H the elimination decreases to less than 25%.

Long-telm administration, aspirin shows minor variations when used at 4 h (fluctuations of 1mg / deciliter) but significant at 8 h (2.5 mg / deciliter) with a marked variation in the individual.

Unfortunately, there are no pharmacological studies performed in the long-term use of aspirinanalgesic doses.

Acetylsalicylic acid in medium doses has analgesic and antipyretic action, attributable to cyclooxygenase inhibition, with diminished prostaglandin synthesis. The analgesic action is exerted in the central nervous system, less at the peripheral nicotreceptors.

The antipyretic action is exerted at the level of the hypothalamus and consists in normalizing the function of the center of thelmoregulation, affected by the pyrogens.

The high doses of acetylsalicylic acid (3-4g per day) inflammatory. At low doses, acetylsalicylic acid has long-acting platelet antiaggregant action. The inhibition of platelet function is due to the irreversible inactivation of cyclooxygenase by acetylation, with the consequent blocking of thromboxane synthesis A2.

The anti-inflammatory effect is not fully clarified, but the mechanism inhibiting the production of prostaglandins, especially PgE2, of some lymphokines, reducing the migration of neutrophils and monocytes by directly affecting the surface of the granulocytes (Mac Gregor, 1974). The explanations of the anti-inflammatory action of aspirin have been reviewed.Aspirin can inhibit phosphodiesterase but only at very high doses [50-57] The release of naturalglucocorticoids from their binding to plasma albumin does not explain the therapeutic antiinflammatory effect due to the very low rate of circulating cortisol.

Clinical use of aspirin is justified by the presence of fever (articular accute rheumatism, rheumatoid poliarthritis, rheumatoid juvenile arihritis, abarticular rheumatism) and inflammation (inflammatory rheumatism, pleurisy, collagen pericarditis, nephropathy, serum sickness, cutaneous nodular rash). For antiplatelet purposes aspirin is used practically for prevention of atherosclerotic thrombosis [58-60]. The first signs of overdose are: hyperpnea, tinnitus, acupuncture, vel1igo, heartburn.

The aspirin formulations aimed at digestive tolerance are: sodium salt, the effervescent form.

Experimental part

Materials and Methods

The study comprises 126 patients from rheumatic diseases who have consumed aspirin, and include: 21cazuri (16.66%) with rheumatic fever, per os, the loading dose was 5-7 g / day; 63 cases (50.00%) with rheumatoid arthritis; acetylsalicylic acid is considered to be the drug of choice in the treatment of acute pus occurring during the usual PR form, is administered as a maximum dose within 2-4 g / 24h; 42 cases (33.33%) with ankylosing spondylitis, chronic progressive inflammatory disease affecting sacroiliac joints, dianheal joints of the spine and adjacent soft tissues, patients also exhibiting extraarticular manifestations: gastrointestinal, pulmonary, renal, cardiovascular disorder.

Acetylsalicylic acid administered on a short-term basis, relieves lumbar pain and function, 4 to 6g / 24h-average doses are administered, then reduced as appropriate to 1-2g / 24h.

Results and discussions

Adverse effects are numerous, some severe but controllable.

Aspirin allergy is more common in allergology clinics and has two clinical pictures: bronchospasm and urticaria or angioedema.

Tinnitus and hearing loss occur especially in cases of overdose action on the inner ear and cessation within 24-48 h of drug discontinuation, requiring replacement by another antiinflammatory.

More frequent and severe are the side effects of aspirin on the gastrointestinal tract, appear in most patients and manifest as epigastric discomfort, nausea. They occur either as a direct irritant action, either due to psychological attention often made by a physician, or to the action of salicylate on the central nervous system.

Micro-bleeding occurs in 70% of aspirin users, directly proportional to the dose, constantly in all fOlliS of aspirin. The standard potentiates this effect of aspirin.

Micro-bleeding occurs equally in healthy volunteers and in hyperemia, petechiae, submucosal haemorrhages to bloody obvious ulcers.

The mechanism of micro-bleeding is complex, complicates the antiplatelet effect with the penetration of undiluted aspirin microparticles into the mucosa requiring the presence of hydrochloric acid (aclorhiders do not bleed to aspirin). The effervescent and buffered forms seem to produce less micro-bleeding.

Over time, iron deficiency anemia can occur Acupressure ulceration is a clinical reality, although it exaggerates due to the reserve of major digestive bleeding; after the ingestion of aspirin has gastric site and occurs in three situations: ill urinate, patients with ulcerogenic risk, genetic charge, old ulcero-duodenal [61-68]

Aspirin produces gastric ulcer both to stimulate gastric acid secretion Davenport theory-updated by researches on reducing the electrical potential of the mucosa and by altering the quality of secreted gastric mucus. Gastric ulceration bleeds slightly due to the addition of aspirin effect on coagulation (on platelets) and prothrombin production.

Haemolytic tumors in carriers of intracellular enzyme genetic defects occur rarely at very high doses, especially in cases of pyruvate kinase deficiency [69-74] Exceptionally, without cardiac involvement (hemo-dynamic) being explained by the modification of the intrapulmonary lymph flow to blood concentrations above

400 mg /100 mL. Simple hyperpneumonia has a central mechanism.

Cardiac conduction disorders occur in cases of salicylate intoxication. Hepatitis conditioned by aspirin is mainly present in collagenesis, where there is already a degree of parenchymal reticulocytocytosis in which the use of anti-inflammatory drugs is chronic. Renal changes in aspirin may occur by adding to different degrees of drug effects. Recent studies have shown that non-steroidal anti-inflammatory drugs (NSAIDs) have prophylactic potential in some cancers.

Aspirin is the first non-steroidal anti-inflammatory with this potential. As all fOlms of cancer, colon cancer affects haemostasis. In vitro, aspirin-NO inhibits cellular proliferation, induces apoptosis and produces a cell cycle blockage.

Conclusions

In clinical conditions, small doses of acetylsalicylic acid significant benefits in coronary artery disease, controlled trials in patients with unstable angina have demonstrated a reduction in myocardial infarction and mortality.

Good results have also been obtained under conditions of use in coronary surgery. Also, low doses of acetylsalicylic acid have been shown to be useful in patients with ischemic stroke. Considered a commonly used drug commonly used by patients without aspirin, some of themunder maintenance medication, aspirin causes important clinical complications. Interaction of aspirin with other drugs occurs especially in the plasma albumin, platelets, liver,kidney, and gastrointestinal tract.

The delay risk of surgical wound healing in patients treated with aspirin can be conected with high doses of vitamin A and E. In the future, it is possible to formulate acetylsalicylic acid in the form encapsulated to reduce side effects, and to obtain retarded pharmaceutical forms [75-77]

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