Non-Steroidal Anti-Inflammatory Drugs in Musculoskeletal Disorders

Essay

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By

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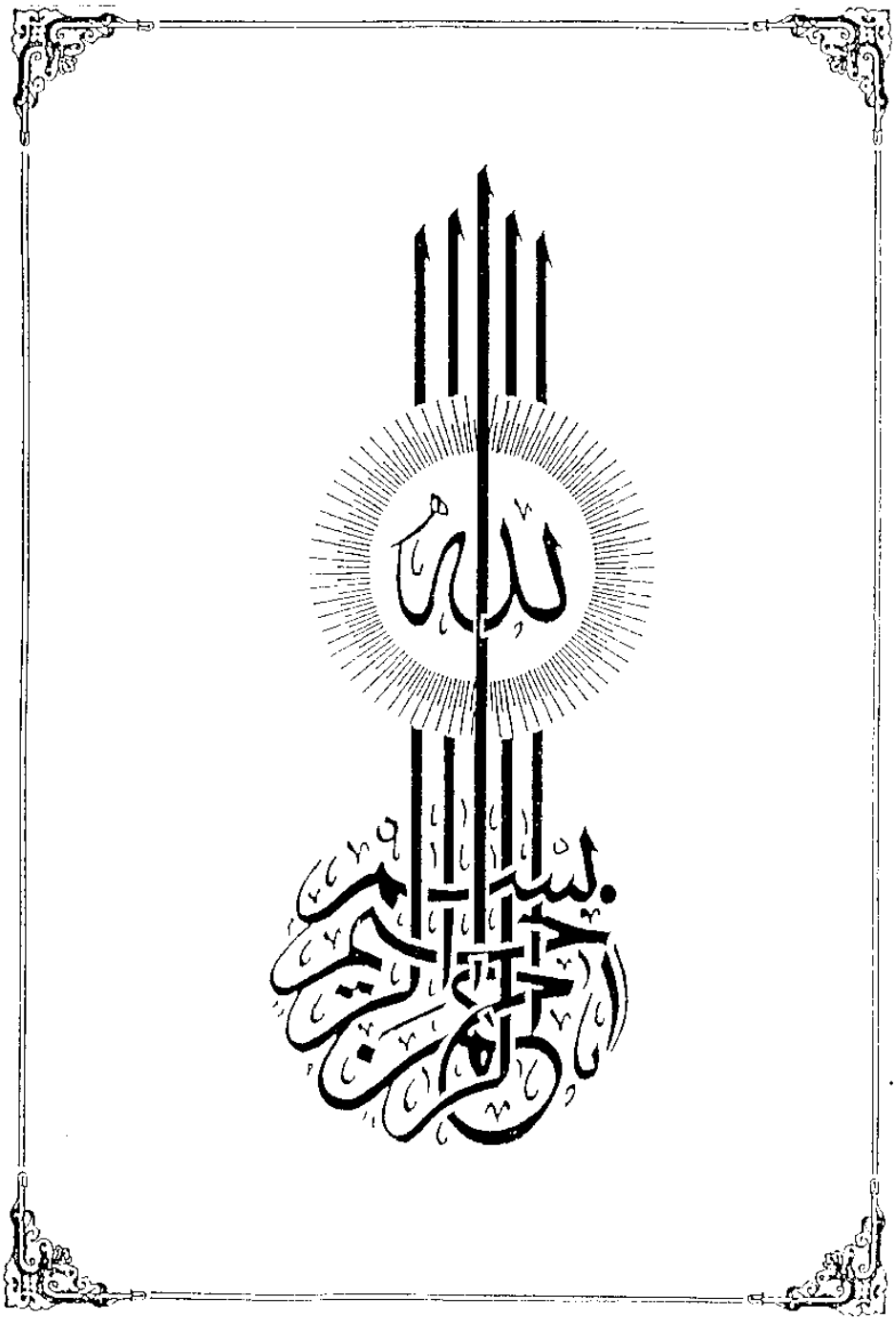
بسم الله الرحمن الرحيم

رب اشرح لى صدرى * ويسر لى

امرى * واحلل عقدة من لسانى *

يفقهوا قولى *

صدق الله العظيم



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CHAPTER 1.

Introduction.

Musculoskeletal system is a locomotor system and the system which forms the axial and appendicular skeleton of the body, and so preserves the posture of the skeleton. Its joints and muscles help to perform different actions depending upon the smooth surface of the articular cartilage which gets the movement smooth, distributes the load applied to the joint and forms a bearing surface for its free movement, also the cartilage components make the joint relatively resistant to compressive, tensile and shearing forces (shock absorbing properties).

The synovial fluid acts as a joint lubricant, as well as being the lowest coefficient of friction known for any surface contact, also the actions of muscles and muscles antagonist of each joint get the movement under well, also ligaments which help in stability of the joint. So by all structures of the musculoskeletal system, the person can perform different actions in all directions, can do fine and hard movements and can carry heavy weights as joint and all system can tolerate these actions.

Any musculoskeletal disorder that affects any component of this system may lead to diffiuelt in performing daily activity. Pain and stiffness are the main complaint due to inflammation.

To overcome this complaint of inflammation, we should reduce the inflammation and kill the intensity of pain. We use drugs known as anti-inflammatory drugs. These drugs depend upon inhibition of biosynthesis of certain chemical mediator which is released during

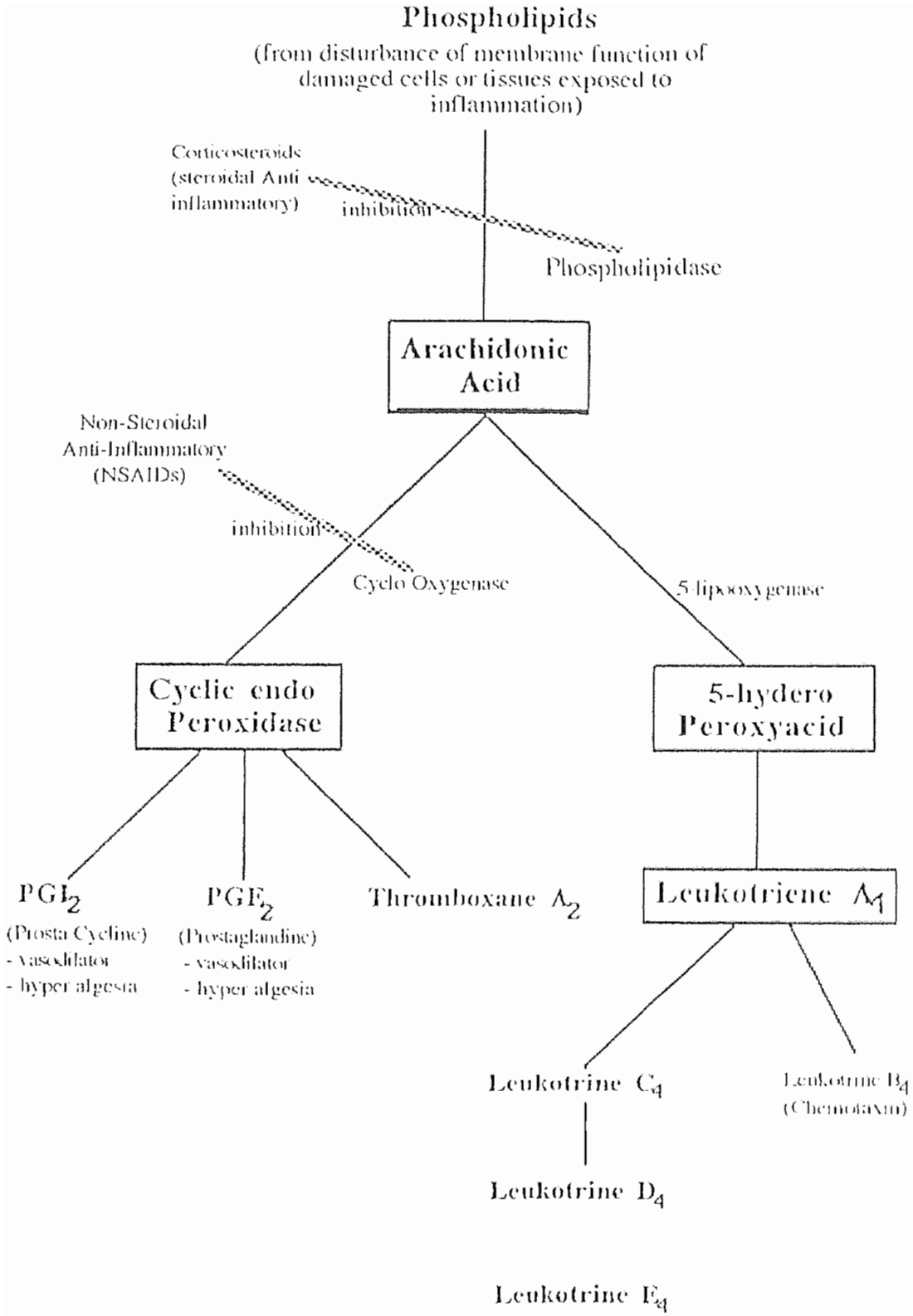
the damage of cells or in initiation of inflammatory process. This chemical mediator helps in progression of inflammation and increases the intensity of pain. So inhibition of it will help in treating the disorders associated with inflammation and pain. This chemical mediator is prostaglandin which first proposed as inflammatory mediator as it was shown to produce the fine diagnostic signs of inflammation. There is evidence that prostaglandins are not stored within the cells but are formed upon physiological demand probably to act close to the site of synthesis. Most processes which disturb memberane function activate the hydrolysis of Arachidonic acid from Phospholipids.

There are two types of anti-inflammatory drugs which inhibit the synthesis of prostglandin:

1. Steroidal anti-inflammatory drugs which act by inhibition of phospholipidase enzyme which transforms phospholipid into arachidonic acid and so consequently arachidonic acid is not transformed into prosatglandin.

2. Non-steroidal anti-inflammatory drugs "NSAIDs" which act by inhibition of transformation of arachidonic acid into prostaglandin through inhibition of cyclo oxygenase enzyme. Non-steroidal anti-inflammatory drugs are the first line of treatment of musculoskeletal system disorders associated with stiffness and pain specially rheumatic one. In this group of drug about over than 30 million of people took an aspirin or an NSAID each day, and that shows its importance as a group of drug widely used in the world.

The NSAIDs are chemically unrelated but have the same pharmacological actions as anti-prostaglandin (anti-inflammatory). It has many classifications according to their chemical groups, therapeutic effect on articular cartilage, and also according to their potency in their anti-inflammatory effects. They all shared in most modes of actions, but there are only some of them that have specific action on musculoskeletal system as indomethacine which have prophylactic action against heterotropic ossification mainly in acetabular fracture.


Phospholipids
(from disturbance of membrane function of damaged cells or tissues exposed to inflammation)
Corticosteroids (steroidal Anti inflammatory)
inhibition
Phospholipidase
Arachidonic Acid
Non-Steroidal Anti-Inflammatory (NSAIDs)
inhibition
Cyclo Oxygenase
5-lipooxygenase
Cyclic endo Peroxidase
5-hydero Peroxyacid
PGI2
(Prosta Cycline)
- vasodilator
- hyper algesia
PGE2
(Prostaglandine)
- vasodilator
- hyper algesia
Thromboxane A2
Leukotriene A4
Leukotrine C4
Leukotrine B4
(Chemotaxin)
Leukotrine D4
Leukotrine E4

CHAPTER 2.

Non-Steroidal Anti-Inflammatory Drugs.

The non-steroidal anti-inflammatory drugs (NSAIDs) have attracted a lot of adverse publicity over the last few years. Principally, this has been due to the significant adverse reactions seen with a few of these agents which have subsequently been withdrawn from the market. Despite this, the NSAIDs continue to be the major pharmacological agents for pain relief in museuloskeletal disorders. NSAIDs are the main agent of treatment for many artheritic conditions and in order to gain maximum benefit with minimum risk, certain principles must be followed when prescribing them.

The NSAIDs are a heterogenous group of compounds, often chemically unrelated, which nevertheless share certain therapeutic actions and side effects. The prototype is aspirin, hence these compounds are often referred to as aspirin like drugs. The theraputic activity appears to depend to a large extent upon the inhibition of defined biochemical pathway responsible for the biosynthesis of the prostaglandins and related chemical mediators (Peter.M. Brooks 1990).

History.

Despite the introduction of many new drugs.Aspirin (Acetyl salicylic acid) is the most widely prescribed analgesic and anti-inflammtory agent and is the standard for comparison and evaluation of other NSAIDs. In England, in mid eighteenth century, Reverend Edmund stone described in a letter an account of the success of the bark of the willow in the cure of

fever. The active ingredient in the willow bark was a bitter glycoside called salicin, first isolated in a pure form in 1989 by leroux. Sodium salicylate was first used for the treatment of rheumatic fever in 1875 from hydrolysis of salicin and conversion of salicylic acid. The discovery of its urocosuric effects and of its utility in the treatment of the gout soon followed. After demonstration of its anti-inflammatory effects, this compound was introduced into medicine in 1899 by Desert under the name of aspirin (Roderick. J. Flower. et al 1985).

Classification Of Non-steroidal Anti-inflammatory Drugs.

I. Antipyretic Analgesic Except Aniline Derivatives.

A. Acidic group

1. Carboxylic acids

a. Salicylates derivatives
Acetyl salicylic acid (Aspirin)

b. Acetic acids

i. Phenyl acetic acids
Declfenac sodium (voltaren)

ii. Carbo and hetero cyclic acetic acids
(Indole deivatives)
Indomethacin (Indocid)

c. Fenemates derivatives
Mefenamic acid (Ponstan)
Mechlofenmic acid (Melomen)

d. Propionic acids derivatives
Ibuprofen (Brufen)
Ketoprofen (Profenid)
Naproxen (Naproxen)
Flurbiprofen (Froben)
Pirprofen (Rengasil)
Tiaprofenic acid (Surgam)

2. Enolic acids

a. Pyrazolones derivatives

Phenylbutazone (Butazolidine)
Oxyphenyl butazone (Tanderil)
Azapropazone (Prexane 300), Rheumox)

b. Oxicams derivatives

Piroxicam (Feldene)
Tenoxicam (Tilcotil)

B. Non acidic Group

Proquazone (Biarison)

II. Gold therapy (Gold salt).

Sodium Aurothiomalate (Myocrisine)
Aurothioglucose (Solganol)

III. D.Penicillamine.

Distamine

IV. Anti malarial drugs.

Chloroquine (Chloroquine)
(Hydroxychloroquine)

V. Cholchicine.

VI. Immunosupressive drugs.

Azathioprine (Imuran)
Cyclophosphamide

VII. Immuno-stimulant drugs.

Levamisole

VIII. Cytotoxic drugs.

Methotrexate

General properties of non-steroidal anti-inflammatory drugs.

In 1971, Van and associates and Smith and Willis demonstrated that low concentration of aspirin and indomethacin inhibited the enzymatic production of prostaglandins. There was, at that time, some evidence that prostaglandins participated in the pathogenesis of inflammation and fever, and this reinforced the hypothesis that inhibition of the biosynthesis of prostaglandins could explain a considerable number of the clinical actions of the drugs (Roderick, j. Flower 1985).

Subsequently, the following major points have been established:

1. Prostaglandins are always released when cells are damaged and have been detected in increased concentrations in inflammatory exudates

2. All available evidence indicates that cells do not store prostglandins, and their release thus depends on biosynthesis de novo.

3. All non steroidal anti-inflammatory drugs inhibit the biosynthesis and the release of prostaglandins in all cells tested.

4. With the exception of the anti-inflammatory glucocorticoids, other classes of drugs generally do not affect the biosynthesis of prostaglandins.

Shared Therapeutic Activities and Side Effects of NSAIDs:

As analgesic, these drugs are usually effective only against pain of low to moderate intensity, particularly that associated with inflammation.They have much lower effects than the opioids. However, they do not cause dependence and are mainly free of the unwanted effects of the opioids on the central nervous system.

NSAIDs do not change the perception of sensory modalities other than pain. The type of pain is important;chronic post operative pain or pain arising from inflammation is particularly well controlled by NSAIDs.

As anti-inflammatory, the class of drugs finds its chief clinical application as anti-inflammatory agents in the treatment of musculoskeletal disorders such as rheumatoid artheritis,osteoartheritis and ankylosing spondylitis. In general, NSAIDs provide only symptomatic relief from the pain and inflammation associated with the disease and do not arrest the progression of pathological injury to the tissue.

Unwanted Effects:

1. The most common unwanted effect is apropensity to induce gasteric or intestinal ulceration that can sometimes be accompanied by secondary anaemia from the resultant blood losss.

2. Disturbance in platlets function and the prolongation of gestation or spontanous labour (due to prevention of formation of thromboxane, a potant aggregating agent).

3. NSAIDs have little effect on renal function in normal human subjects. However, they decrease renal blood flow and the rate of glomerular filtration in patients with congestive heart failure or hepatic cirrhosis with ascitis or in those who are hypovolemic for any reason . Similar effects occur in patients with chronic renal disease.

4. NSAIDs promote the retention of salt and water by reducing the prostaglandin induced inhibition of both the reabsorption of chloride and the action of antidiuretic hormone. This may cause edema.

Pharmacokinetics Of Non steroidal Anti-inflammatory Drugs:

Pharmacokinetics of nonsteroidal anti-inflammatory drugs discuss the relationship between dose administration and plasma concentration. Concentration of the drugs in plasma are observed if the active drug is measured close to the site of actions. However, it has been shown that the synovial prostaglandins concentrations in NSAIDs administration in rheumatic diseases remain suppressed long after a NSAIDs becomes undetectable.

The NSAIDs can be divided broadly into those with *short half life* and those with *long half life*. It is imporant to remember that studies on synovial fluid kinetics and site of actions studies demonstrate that these concentrations are more sustained and show less variability than plasma concentrations.

Practically, this means that many of the short half life NSAIDs can be reasonably effective in terms of reducing pain and stiffness in a twice daily dose. Long half life NSAIDs take more time to reach steady state in plasma and synovial fluid or site of actions, and they might remain in the body for a longer time once administration ceased. Recently, *slow release preparations* of some of the short half life NSAIDs have been produced in an attempt to reduce frequency of dosing (Peter, M. Brooks, 1990).

Clearance :

Clearance of some NSAIDs might be affected by renal disease and age. This is important because many patients taking this medication are elderly and have underlying renal disease and so reduction of this drug may reduce the toxic effect in these cases which come from its accumulative effect in the vital organs as kidney and liver.

Half lives of some NSAIDs:

Drug	Mean Plasma Half Life
Aspirin	0.25
Diclofenac	1.1
Flurbiprofen	3.8
Indomethacin	4.8
Tiabrofenic acid	3
Ketoprofen	1.8
Azapropazone	15
Naproxen	14
Phenylbutazone	68
Piroxicam	57
Tenoxicam	60

Adapted from Day RO,Graham GG,Williams KM.
Pharmacokinetics of NSAIDs Baillieres clin.Rheumatol 1988;2:363-93

Routes Of Administrations:

There is more than one way for administration, each one have its benifits. From these routes the *oral route* which is the common one and can be used mostly if the drugs are needed for prolonged peroid as in chronic cases. *Rectal route* in the form of suppository which have the same indications of use as oral one. *Parentral route* of administration which may be I.M. or I.V. The I.M. usage is more common than I.V. as some of the NSAIDs have irritant bases (disolvents) which are sever irritant in I.V. pathway. I.V. and I.M. pathway have the same indications of usage in induction of pain release in rheumatic or musculoskeletal disorders and may be mentained by oral or rectal route. Also, in cases of sever trauma need rapid onset of analgesic anti-inflammatory drugs as in cases of sprain, fracture or in postoperative cases in traumatic or orthopeadic operations, we use I.V. or I.M. route.

Another route of administration *Percutaneous route* of administration which is a new method for administration of the drugs (NSAIDs) which have the advantages of effective anti-inflammatory concentrations in local tissue beneath the site of application, without exposing distant tissues to significant drug levels. Percutaneous administration should therefore enhance the efficacy of local therapy, which minimizing the risk of systemic side effects (Walter Riess 1987).

Topical NSAIDs therapy was found to produce local tissue concentrations in underlying muscle and synovium that compared with those resulting from oral therapy at conventional dosage.

Many large joints are separated from overlying skin by thick layers of connective tissue which may prevent access of therapeutic concentration of percutaneously applied drugs to the target area. However, several physiological phenomena involve neurovascular interaction between deep structure and overlying skin. Interactions of this kind could enable a drug applied topically to exert deep effects on underlying tissues (Hermann Handwerker 1987).