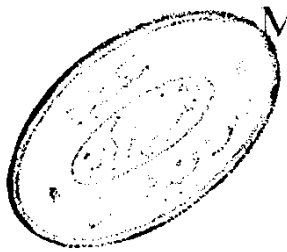
GASTRODUODENAL PROTECTION AGAINST NSAID

THESIS

Submitted for partial fulfillment of
Master Degree in Internal Medicine



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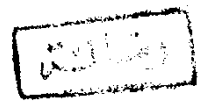

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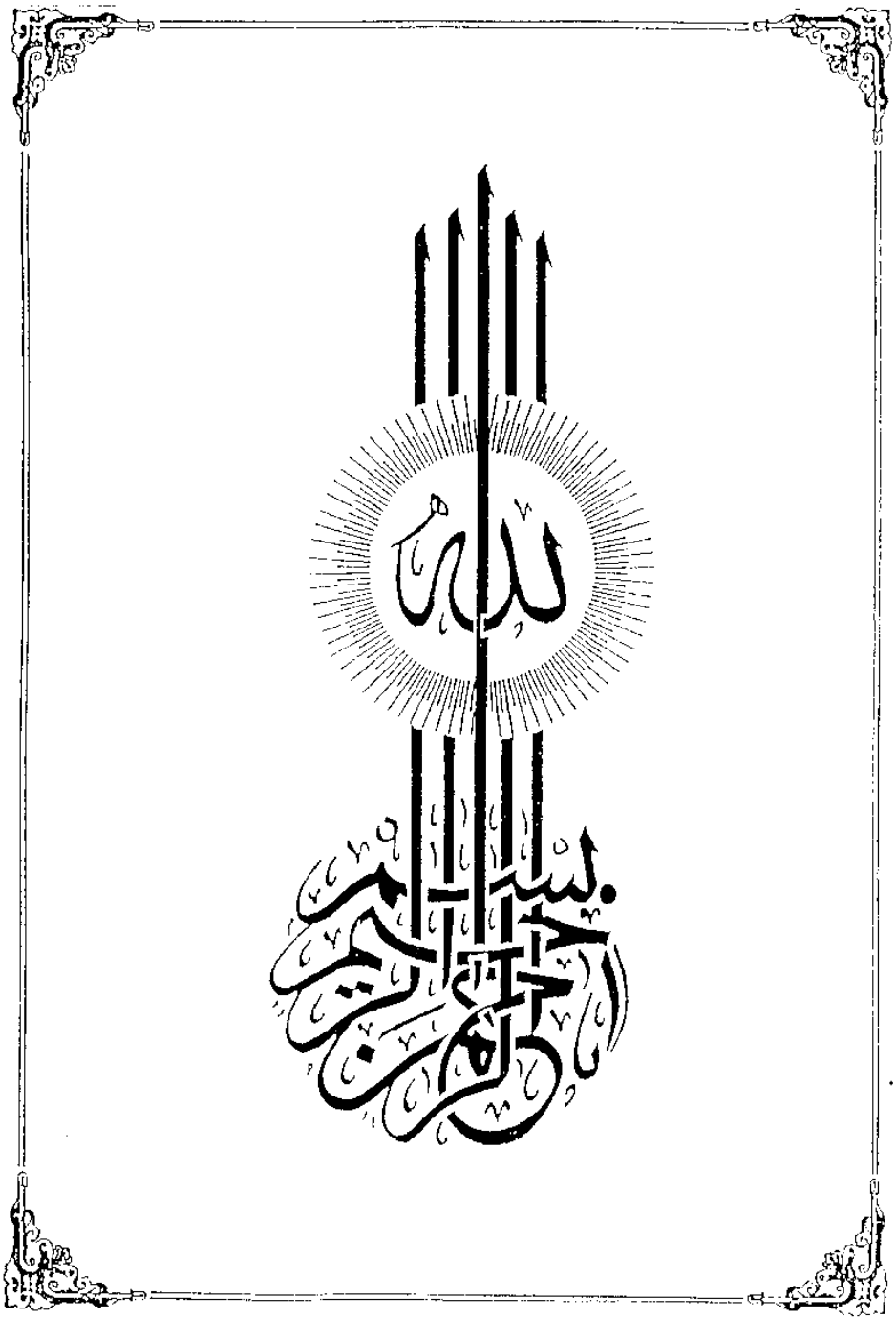
To My Parents

to whom everything is due



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Introduction and Aim of the Work

INTRODUCTION

Although, the non steroidal anti-inflammatory drugs are among the most widely used drugs in medicine, side effects are common and may be serious. The most common side effects of non steroidal anti-inflammatory drugs are those of the upper gastrointestinal tract. The association between non steroidal anti-inflammatory drug therapy and damage to the gastroduodenal mucosa is well established (*Roth*, 1987). Non steroidal anti-inflammatory drugs may cause erosive gastritis, peptic ulceration and gastrointestinal bleeding (*Dwight*, 1983).

The effect of non steroidal anti-inflammatory drugs on the gastroduodenal mucosa appears to be multifactorial as:

1) Disruption of the gastric mucosal barrier.
2) Reduction of the pH gradient across the mucosal surface.
3) Inhibition of the mucus and bicarbonate secretion.
4) Reduction in the mucosal blood flow.
5) Inhibition of the synthesis of protective gastrointestinal prostaglandins.

On the other hand, different drugs acting on ulcer healing are again acting through different mechanisms as stimulation of endogenous prostaglandins (sucralfate), inhibition of acid secretion (cimetidine-pirenzepine) or buffering the already present acid (antacid).

The aim of the thesis is:

To assess the best antiulcer therapy to be given in combination with non steroidal anti-inflammatory drugs to minimize gastroduodenal mucosal damage.

Review of Literature

I. ANTI-RHEUMATIC DRUGS

Dudley in 1978, classified the non steroidal anti-inflammatory drugs as follows:

I. Acidic agents:

a. Aryl carboxylic acids:

i. Salicylic acid: aspirin, diflunised

ii. Anthranitic acids: flufenamic acid (Arlef), mefenamic acid (Ponstan), meclofenamic acid

b. Aryl and hetero aryl alkalonic acids:

i. Aryl-acetic acids: alcolofenac (Zumaril), (Neaston) diclofenac (Voltaren).

ii. Aryl-propionic acids: Ibuprofen (Brufen), (Martin), ketoprofen (Profenid), (Oradis), fenoprofen (Fenopron), (Nalfon), Naproxen (Naprosyn), (Proxen), flurbiprofen (Froben), benoxaprofen (Opero), indoprofen, pirprofen.

iii. Hetero-aryl acetic acids: tolmetin (Tolectin), fenclozic acid.

iv. Indole and indene acetic acids: indomethacin (Indocid), sulindac (Clinoril), acemetacin (Rantudil), (Fendosal).

c. The pyrazoles:

Phenylbutazone (Butazolidin), (Butazone), oxyphenbutazone (Tandril), (Tandacot), azopropazone (Apazone), (Prolixan), (Rheumax), feprazone (Methrazone).

II. Non-acidic agents:

a. Proquazone (Biarison).

b. Diftalone.

There are many recently introduced NSAIDs such as: zomiperoc sodium (Zomax) which is chemically related to tolmetin, fentiazac (Donorest) and piroxicam (Feldene) which is an oxicam derivative (*Dudley*, 1978).

Another Classification of Drugs used in Treatment of Rheumatism

Non steroidal anti-rheumatic drugs are also classified according to their pharmacological action into:

I. Drugs with analgesic, but negligible anti-inflammatory action:

Aniline derivative: paracetamol is the only member of this group now used.

II. Drugs with analgesic and mild to moderate anti-inflammatory action:

1. Propionic acid derivatives:

Ibuprofen (Brufen)

Ketoprofen

Fenoprofen

Fenbrufen

Naproxen (Naprosyn)

Flurbiprofen (Froben)

2. Fenamic acid derivatives:

Mefenamic acid (Ponstan).

III. Drugs with analgesic and marked anti-inflammatory action:

1. Salicylic acid derivatives:

Aspirin

Sodium salicylate.

Benorylate (Benoral).

Diflunisal (Dolobid).

Aloxiprin (Palapin).

Salsalate (Disalcid).

2. Pyrazolone derivatives:

Azapropazone.

Phenylbutazone.

3. Acetic acid derivatives:

Diclofenac (Voltaren).

Fendofenac.

Indomethacin.

Sulindac (Clinoril).

Tolmetin.

4. Oxicam derivatives:

Piroxicam (Feldene).

(*Laurence and Bennett*, 1987).

Mechanism of Action of NSAIDs

During the first two decades in which non steroidal anti-inflammatory drugs were in use, explanation of their mechanism of action tended to reflect current scientific beliefs. In the late 1960s, medical students were taught that NSAIDs "uncoupled oxidation from phosphorylation". This explanation was succeeded by the concept that NSAIDs somehow work through the cyclic AMP system, perhaps by inhibition of phosphodiesterase.

This situation changed in 1971 when *Vane* showed that all NSAIDs tested were potent inhibitors of prostaglandin production (*James*, 1984).

The work of *Vane and colleagues* in the early 1970s led to the hypothesis that the major therapeutic as well as toxic effects of NSAIDs may be accounted for by their ability to inhibit prostaglandin synthesis. They inhibit prostaglandin synthesis by acting on cyclooxygenase enzyme; therefore, the synthesis of prostaglandin is inhibited non selectively, presumably, the anti-inflammatory effect of these drugs are related to inhibition of prostaglandin E_2 and prostacyclin synthesis. Although limited experimental data are available, the non steroidal anti-inflammatory drugs have no known major effects on leukotriene pathway (*Dwight*, 1983).

Recent research has focused on the possibility that some agents may exert their anti-inflammatory effects by inhibiting leukotriene rather than prostaglandin synthesis (*George*, 1983).