COMPARISON OF THE TOXICITY OF INDOMETHACIN AND A NEWER ANTI-RHEUMATIC DRUG "DICLOFENAC SODIUM" ON THE STOMACH

THESIS
SUBMITTED IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE MASTER DEGREE IN GENERAL MEDICINE

BY
WAEL YOUSSEF SIDKY
M.B., B. CH.

FACULTY OF MEDICINE
AIN SHAMS UNIVERSITY

1982

مقارنه للتأثير السمى لعقار الاندوميثازين وعقار جديد لعلاج الروماتيزم "دايكلوفيناك صوديوم" على المعدة

COMPARISON OF THE TOXICITY OF INDOMETHACIN AND A NEWER ANTI-RHEUMATIC DRUG "DICLOFENAC SODIUM" ON THE STOMACH

BY
WAEL YOUSSEF SIDKY
M.B., B. CH

MASTER DEGREE THESIS IN GENERAL MEDICINE

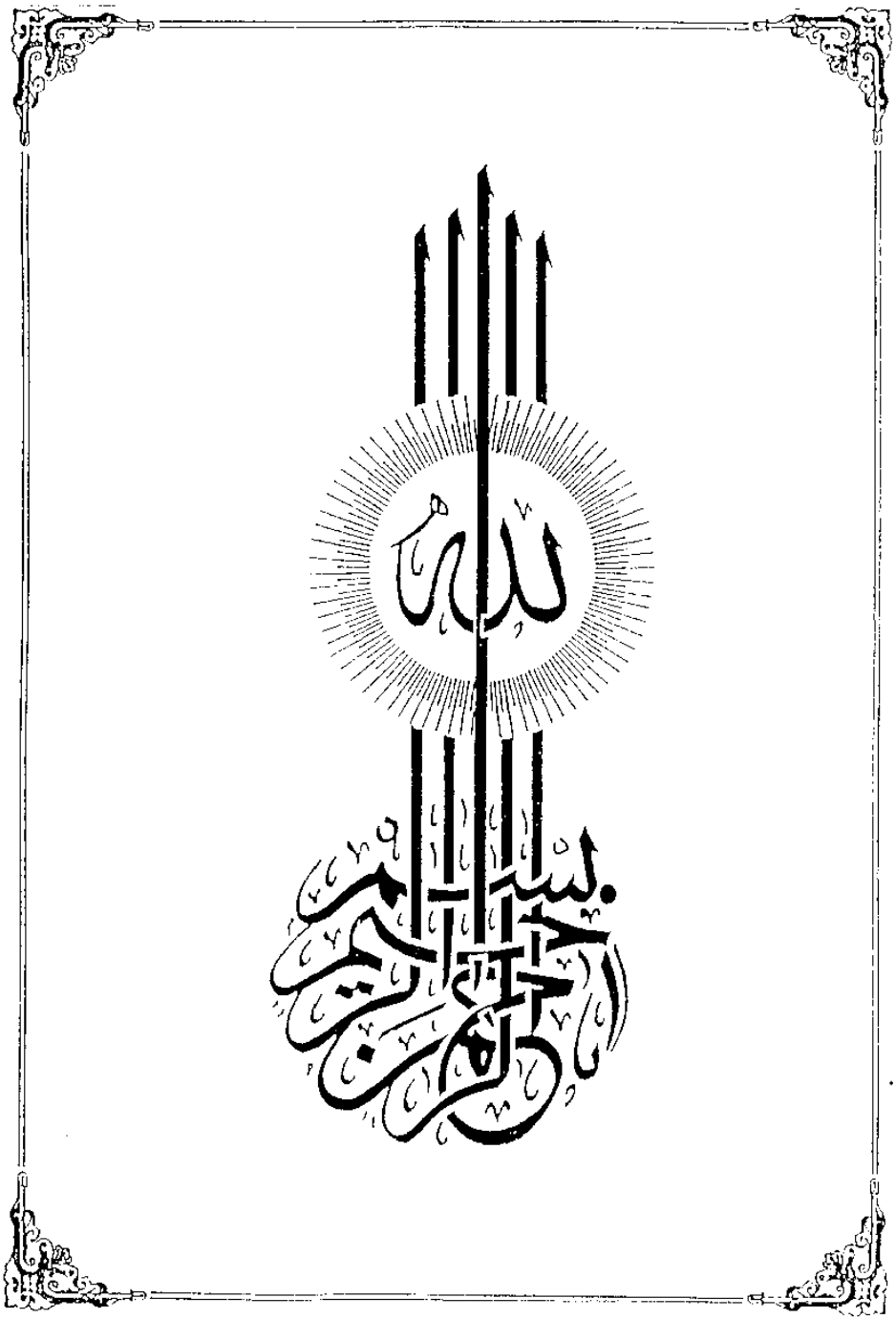
SUPERVISED BY
PROF. DR. SOHEIR SHEIR
PROF. IN GENERAL MEDICINE DEPARTMENT
FACULTY OF MEDICINE
AIN SHAMS UNIVERSITY

PROF. DR. ADLY FARID GHALY,
PROF. IN PATHOLOGY DEPARTMENT
FACULTY OF MEDICINE
AIN SHAMS UNIVERSITY

PROF. DR. SAWSAN HAMZA
PROF. IN CLINICAL PATHOLOGY DEPT.
FACULTY OF MEDICINE
AIN SHAMS UNIVERSITY HOSPITAL

DR. MOHAMED RAMADAN
LECTURER IN GENERAL MEDICINE DEPT.
FACULTY OF MEDICINE
AIN SHAMS UNIVERSITY

DR. LAILA ABO EL MAGD
LECTURER IN CLINICAL PATHOLOGY DEPT.
FACULTY OF MEDICINE
AIN SHAMS UNIVERSITY



ACKNOWLEDGEMENTS

I would like to express my profound gratitude to Professor Dr. **SOHEIR SHEIR**, General Medicine Department, Ain Shams University for her generous help and unlimited cooperation and who gave so much time and effort.

It is a pleasure to acknowledge Professor Dr. **ADLY FARID GHALY**, Pathology Department, Ain Shams University, for his kind cooperation.

I wish to thank Professor Dr. **SAWSAN HAMZA**, Clinical Pathology Department, Ain Shams University, for her fruitful assistance.

I am particularly grateful to Dr. **MOHAMED RAMADAN BADAR**, Lecturer in General Medicine Department, Ain Shams University for his valuable guidance. His enthusiasm and scientific assistance made possible the achievement of this work.

I would like to stress my utmost thanks to Dr. **LAILA ABO EL MAGD**, Lecturer in Clinical Pathology Department, Ain Shams University, for her sincere help.

***

CONTENTS

*

INTRODUCTION

Rheumatic diseases are among the most common, the most medically severe, the most socially disabling and financially crippling of all the chronic diseases in man.

Rheumatic diseases are usually characterised by pain, and are frequently associated with swelling, stiffness and tissue dammage - in short, inflammation. Inflammation, as seen in these cases, is a disordered mechanism in which the physiological protective and reparative functions overshort and becomes damaging.

In recent times, many agents that relieve pain, check inflammation have been offered. Although these drugs have been carefully screened for efficacy and for unwanted characteristics, many have proved somewhat unpredictable and all carry a potential for damage to tissue. The concern about unwanted side-effects with the drugs is as important as the wish for efficious medication.

The available anti-rheumatic drugs can be classified in five general groups according to Hart (1980):

1. Analgesic agents without anti-inflammatory action.
2. Non corticosteroidal anti-inflammatory drugs (NSAIDs).

3. The corticosteroids.
4. Long term anti-rheumatic agents.
5. Metabolic correctors.

The non corticosteroidal anti-inflammatory drugs are the most commonly used group of drugs in treatment of rheumatic diseases. They have anti-inflammatory, analgesic and anti-pyretic activity. Their site of action in the affected tissues peripherally rather than (as is usually the case with the simple analgesics) centrally in the central nervous system. Their action is complex but in most an inhibition of prostaglandin (PG) synthesis plays a major role (Hart, 1980).

Disturbances of the gastrointestinal tract are well known side-effects of many NSAIDs, and these side effects frequently limit their usefullness. These gastrointestinal side-effects are more severe in arthritic patients and animals than in normal persons (Dipasqual and Welaj, 1973; Shriver et al., 1977).

Many NSAIDs produce ulceration and sometimes perforation of the gastrointestinal tract in the experimental animals (Cuthbert, 1973). These ulcers may penetrate deep into muscle layers and are in fact the cause of death after either single or repeated doses of the drugs

(Stone et al., 1974). The stomach is the target organ for many NSAIDs's toxic effect(Stone et al., 1974).

One explanation for the gastrointestinal toxicity of NSAIDs may be related to their ability to inhibit prostaglandin (PG) synthetase. Continual synthesis of PGshas been postulated to be necessary for the maintenance of the gastric mucosa (Shriver et al., 1975).

Indomethacin (indocid) was the product of a laboratory search for drugs, and was introduced in 1963 for the treatment of rheumatoid arthritis and related disorders (Goodman and Gilman, 1980). It is one of the most effective NSAIDs. It causes gastrointestinal symptoms rather more frequently than most of the other NSAIDs but, if tolerated, is among the the most effective (Hart, 1980). Reports of the Committee of Safety of Medicines have shown that indomethacin has a peak for gastrointestinal adverse reactions taking a primary place in the fatal reactions (Cuthbert, 1974).

Diclofenac sodium (voltaren) is a recent non steroidal anti-inflammatory drug. Its efficacy and tolerability have been widely investigated. The studies carried out with dicolfenac sodium demonstrated that this new

drug is at least as potent as currently available substances (Trang, 1976).

During the course of chronic rheumatic diseases, anti-inflammatory drugs have in most cases to be given for long periods of time. When a new agent is introduced, it is essential to ensure that it is well tolerated and safe in both short-term and long-term use. So, the objective of this thesis is to compare between disclofenac sodium as a recent NSAID and an older well established NSAID - indomethacin, in their gastrointestinal effect, specially on the stomach. Through this comparison, the mechanism by which NSAIDs affect the gastro-intestinal tract will be studied, specially in their relation to prostaglandins.

*

CLASSIFICATION OF DRUGS USED IN TREATMENT OF RHEUMATISM

They may be classified as:

1. **Drugs with analgesic but negligible anti-inflammatory actions:**

   Aniline derivatives - Paracetamol is the principal member of this group now used; phenacetin is obsolescent.

2. **Drugs with analgesic and mild to moderate anti-inflammatory actions**

   A) Propionic acid derivatives which include ibuprofen KETOPROFEN, FENOPROFEN, NAPROXEN, FLUBIPROFEN.

   B) Anthranilic acid derivatives which include mefenamic acid, flufenamic acid.

   C) Arylacetic acid derivative which include fenclofenac, diclofenac.

3. **Drugs with analgesic and marked anti-inflammatory actions**

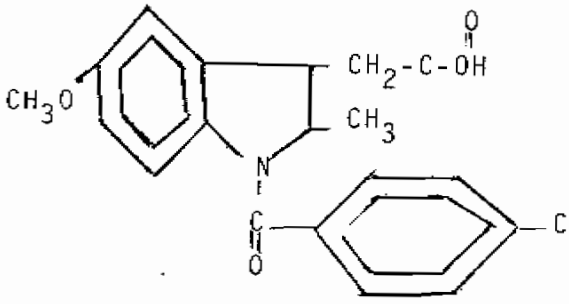
   A) Salicylic acid derivatives which include aspirin, sodium salicylate, benorylate, diflunisal, aloxiprin, salsalate.

   B) Pyrazolone derivatives which include phenylbutazone.

C) Indol derivatives which include indomethacin, sulindac. (Laurance and Bennette, 1980).

CHEMISTRY OF INDOMETHACIN

Indomethacin is 1- (P-chlorobenzoyl) - 5 - methoxy - 2-methylindole - 3-acetic acid. (C_{19} H_{16} Cl NO_4 = 357.8) (Wade and Rynolds, 1977).



(Goodman and Gilman, 198

A pale yellow to brownish yellow, odourless or almost odourless, crystalline powder with a faintly astringent taste. There are two forms, one melting at about 155°c and the other at about 162°c, and the mixture melts between 155°c and 162°c. Practically insoluble in water, soluble in alcohol, and in acetone. It is soluble in alkaline solutions but with decomposition (Wade and Rynolds, 1977).

DICLOFENAC SODIUM

Chemistry:

The active substance contained in disclofenac sodium was synthesised and developed in the Geigy Research laboratories in Basle, Switzerland.

Diclofenac sodium is the sodium salt of o-aminophenylacetic acid, the chemical designation of which is N-phenyl aminophenyl acetic acid.

Its emperical formula is: $C_{14}\ H_{10}\ Cl_{12}\ Na$ (Krupp et al., 1975).

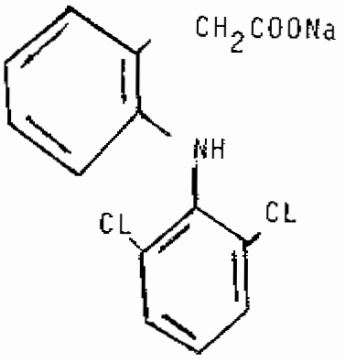


Fig. 1 Chemical structure of the active substance contained in diclofenac sodium.

Diclofenac differs from indomethacin in that it does not contain a heterocyclic ring (Krupp et al, 1975).

PHARMACOKINETICS OF INDOMETHACIN

The pharmacokinetics of indomethacin was studied by giving radio-active indomethacin (Duggan et al., 1972).

Absorption:

The drug is rapidly absorbed from the gut. The rectal absorption of indomethacin is good. It is more rapid than the oral route but with lower peak plasma level (Goodman and Gilman, 1980).

Metabolism:

It is mostly excreted as hepatic metabolite (Lancester, 1980). About half of a single dose of indomethacin is o-demethylated and about 10% is conjugated with glucuronic acid by the hepatic microsomal enzymes. A portion is also N-deacetylated by a non microsomal system in the kidney (Goodman and Gilman, 1980).

Indomethacin is not an enzyme inducer and repeated daily administration of 75 mg for 8 days did not enhance the metabolism or influence the kinetics (Stein et al, 1977).

Plasma Concentration:

Peak plasma concentrations were achieved between ½ to 2 hours (Wade and Reynolds, 1977). In the plasma, over

90% of a dose is bound to albumin (Lancester, 1980). Its plasma half life is 2-4 hours (Lancester, 1980).

Excretion

Conjugated indomethacin appears in the urine in the first hour, and a small amount, 10 to 20% of the free unchanged drug appear in the second hour (Wade and Reynolds, 1977).

Indomethacin is also excreted in the bile and undergoes an enterohepatic circulation. Part of a dose being excreted unchanged in the faeces (Lancester, 1980).

*

PHARMACOKINETICS OF DICLOFENAC

Using radioactively labelled preparations and gas chromatographic techniques, the kinetics and metabolism of diclofenac were studied in mouse, rat, dog, monkey and man (Riess et al., 1975).

Absorption

Diclofenac is rapidly absorbed from an orally administered aqoues solution. Following oral administration of enteric-coated tablets the onset of absorption is delayed owing to the longer time taken by the tablets to reach, and to release their active substance in the duodenum. Absorption of diclofenac from suppositories commences immediatly after administration. The active substance is totally absorbed from all the dosage forms so far investigated (Riess et al., 1975).

Metabolism:

In the rat, dog, rhesus monkey and man, diclofenac is metabolised chiefly by aromatic hydroxylation and by direct conjugation in the liver (Riess et al., 1975).

Plasma concentration

Maximum plasma concentrations being attained within 10 - 20 minutes (Riess et al., 1975). Diclofenac is