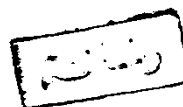


NON STEROIDAL ANTIINFLAMMATORY DRUGS AND LOWER GASTROINTESTINAL TRACT

THESIS

Submitted for partial fulfillment of the
Master Degree in
Internal Medicine

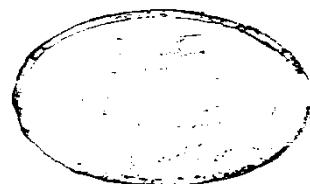
Presented by
Ali Saad Ali
M. B., B.Ch. (1990)



616. 3 3
A. 3

Supervised by:
Prof. Dr. Mohammed Abdel-Fattah Taha
*Professor of Internal Medicine
Faculty of Medicine
Ain Shams University*

Dr. Ahmed Shawky El-Sawaby
*Ass. Professor of Internal Medicine
Faculty of Medicine
Ain Shams University*



Dr. Salwa Ibrahim El-Haddad
*Ass. Professor of Pathology
Faculty of Medicine
Ain Shams University*

**FACULTY OF MEDICINE
AIN SHAMS UNIVERSITY
1995**

Handwritten signature and date: 1995/5/13

Handwritten signature

1995/5/13

بسم الله الرحمن الرحيم
الحمد لله الذي هدانا لهذا وما كنا
لنهدى لولا أن هدانا الله "
صدق الله العظيم



TO MY PARENTS..

*Who offered too much
and took nothing.*

Acknowledgment

First and foremost , thanks are all to GOD for blessing this study until it has reached its end as a little part of his generous help throughout my life.

I find no words by which I can express my extreme thankfulness , appreciation and profound gratitude to my professor Dr. Mohammed Abdel-Fattah Taha, professor of internal medicine, Ain Shams Faculty of Medicine, for his valuable instructions and remarks, fatherly guidance and support and supply of recent literature.

My deepest appreciation goes to Dr. Ahmed Shawky El-Sawaby, assistant professor of internal medicine, Ain Shams Faculty of Medicine, for his meticulous revision, great support and guidance, without which this work would not have been completed.

My sincere thanks go to Dr. Salwa Ibrahiem El-haddad, assistant professor of pathology, Ain Shams Faculty of Medicine, for her guidance and cooperation as regards the histopathological studies in this work.

Last but not least, my love and appreciation go to my wife and children for thier continuous support throughout this work.

List of Abbreviations

ANA	= Antinuclear antibody.
ATP	= Adenosine triphosphate.
Ca²⁺	= Calcium
cm	= Centimeter.
GD	= Gastro duodenal.
GI	= Gastrointestinal.
GIT	= Gastrointestinal tract.
gm	= Gram.
H⁺	= Hydrogen ions.
H₂ O₂	= Hydrogen peroxide.
Hx & E	= Haematoxylin and eosin.
H-pylori	= Hilocobacter pylori
J. R. A.	= Juvenile rheumatoid arthritis.
mg	= Milligram.
mm	= Millimeter.
No.	= Number.
N. S.	= Non significant relationship.
NSAIDs	= Non steroidal antiinflammatory drugs.
P.	= Probability.
P G_s	= Prostaglandins.
PGI₂	= Prostacyclin.
Pt.	= Patient.
S L E	= Systemic lupus erythematosus.
S. D.	= Standard deviation.
TxA₂	= Thromboxanes.

Contents

	Subject	Page
1.	<i>Introduction and aim of the work.</i>	1
2.	<i>Review of Literature.</i>	3
	.. NSAIDs.	3
	.. General mechanism of action.	4
	.. Adverse effects of NSAIDs on upper GIT.	9
	.. General adverse effects of NSAIDs.	12
	.. Basis for clinical differentiation among NSAIDs.	18
	.. NSAIDs induced colonic and small bowel diaphragm Like disease.	23
	.. Stercoral perforation of the colon and complicated diverticular disease associated with the use of NSAIDs.	28
	.. Gastro-colic fistula secondary to aspirin abuse.	31
	.. NSAIDs - induced lower GIT bleeding	35
	.. Anorectal stenosis with NSAIDs.	38
	.. NSAIDs as a possible cause of collagenous colitis	40
	.. NSAID-Induced enteropathy.	44
	.. NSAID-Induced intestinal protein loss and ileal dysfunction.	52
	.. NSAIDs Effect on colonic polyps.	53
3.	<i>Materials and Methods.</i>	57
4.	<i>Results.</i>	61
5.	<i>Discussion.</i>	85
6.	<i>Summary and conclusion.</i>	97
7.	<i>Recommendations.</i>	100
8.	<i>References.</i>	102
9.	<i>Appendix.</i>	
10.	<i>Arabic summary.</i>	

List of tables

	Table	Page
1.	Classification of some NSAIDs.	6
2.	Adverse effects of NSAIDs.	8
3.	Summary of the adverse effects of NSAIDs on the small bowel	21
4.	Summary of the adverse effects of ingested NSAIDs on the large intestine.	22
5.	Clinical presentation of gastrocolic fistula secondary to unoperated gastric and duodenal ulcers.	33
6.	Effect of sulindac or piroxicam on polyp size.	56
7.	Mean age of patients' groups.	61
8.	Relation between sex of patients and incidence of lower GIT complications.	62
9.	Effect of type of NSAIDs on lower GIT.	63
10.	Effect of duration of therapy with NSAIDs on lower GIT.	64
11.	Sigmoidoscopic results.	64
12.	Clinical data of patients.	66
13.	Histopathological parameters.	68
14.	Occult blood results.	69
15.	Relation between sigmoidoscopic results and occult blood.	69
16.	Relation between histopathological changes and occult blood.	70
17.	Relation between histopathological changes and sigmoidoscopic findings.	71
18.	Relation between histopathological changes and type of NSAIDs.	72
19.	Relation between sigmoidoscopic findings and the type of NSAIDs.	73
20.	Relation between sex of patients and sigmoidoscopic results.	74
21.	Relation between sex of patients and histopathological changes	75
22.	Relation between the sigmoidoscopic findings and the individual histopathological parameters.	76

List of Figures

Serial number	Figure	Subject	Page
1.	Arachidonic acid metabolism.	Review of literature.	5
2.	Mechanism of NSAID-induced damage to the intestine.	Review of literature.	46
3.	Acute nonspecific colitis.	Results.	77
4.	High power of the previous slide.	Results.	78
5.	Ulcerative colitis.	Results.	79
6.	High power of the previous slide.	Results.	80
7.	Solitary rectal ulcer.	Results.	81
8.	High power of the previous slide.	Results.	82
9.	Chronic nonspecific colitis with excessive fibrosis.	Results.	83
10.	The same previous slide stained with masson trichrome.	Results.	84

Introduction and Aim of the Work

It is not widely appreciated that Non-steroidal Anti-inflammatory drugs (NSAIDs) may cause damage distal to the duodenum and most of studies concentrate on the complications of (NSAIDs) on the upper Gastrointestinal tract (GIT) and hazards of peptic ulceration and haematemesis on chronic use of these drugs (*Lanas et al., 1992*).

The adverse effects of (NSAIDs) on the lower GIT were not thoroughly studied. **The aim of this work** is to study the possible complications of (NSAIDs) on the lower GIT and how can the adverse effects of these drugs represent a range of pathologies that may be asymptomatic but some of them are life threatening (*Bjarnason et al., 1993*). These pathologies include:

.. Ano-rectal lesions in patients taking suppositories containing (NSAIDs) in the form of erosions or ulcer in the rectum and stenosis of the anal verge (*Gizzi et al., 1993*). Also ano-rectal stenosis could occur in patients with prolonged use of suppositories containing paracetamol and acetylsalicylic acid (*Gossum et al., 1993*).

.. Stercoral perforation of the colon in patients taking (NSAIDs) for long duration especially in constipated patients as constipation is thought to be the most significant contributing factor in the development of stercoral perforation (*Hollingworth and Willimas, 1991*).

.. Increased risk of lower gastrointestinal bleeding. (*Holt et al., 1993*).

.. NSAID-induced colonic and small bowel diaphragm disease. (*Pucius et al., 1993*)

***REVIEW OF
LITERATURE***

"Non Steroidal Anti-inflammatory Drugs "

"Aspirin-Like Drugs"

These drugs are antipyretic, analgesic and anti-inflammatory, however there are differences in their individual activity as well as in the individual response to these drugs. Their prototype is Aspirin, hence these compounds are referred to as aspirin-like drugs. Aspirin is almost certainly the most widely used drug in the world. It is used both therapeutically (to reduce pain, inflammation, and fever) and prophylactically (to prevent thrombotic events). (*Lee et al.,1994*). These non steroidal antiinflammatory drugs (NSAIDs) reduce the signs and symptoms of established inflammation but do not in themselves eliminate the underlying causes of the inflammation. They have no effect on the course of the basic disease process and do not protect against tissue or joint injury; thus damage to joints continues to occur during the administration of such a drug to patients with chronic inflammatory arthritis. (*Clements and Paulus,1993*).

General Mechanism of Action :

Currently favored mechanism of action of NSAIDs include inhibition of cyclo-oxygenase. Essentially all cells in the body have the capacity to synthesize prostaglandins (Figure 1). In response to inflammatory stimuli arachidonic acid is cleaved from membrane phospholipids by specific phospholipases. Arachidonic acid is oxidized and cyclized by the enzyme cyclo-oxygenase to form cyclic endoperoxide prostaglandin G_2 ($PG\ G_2$), which is converted to $PG\ H_2$ by peroxidation with concomitant production of unstable toxic oxygen radicals. $PG\ H_2$ is then converted to the stable prostaglandins E_2 and $F_{2\alpha}$, thromboxane, or prostacyclin by appropriate enzymes as indicated in (Figure 1). Elevated levels of prostaglandins have been demonstrated in synovial effusions from untreated patients with inflammatory arthritis. (*Clements and Paulus, 1993*).

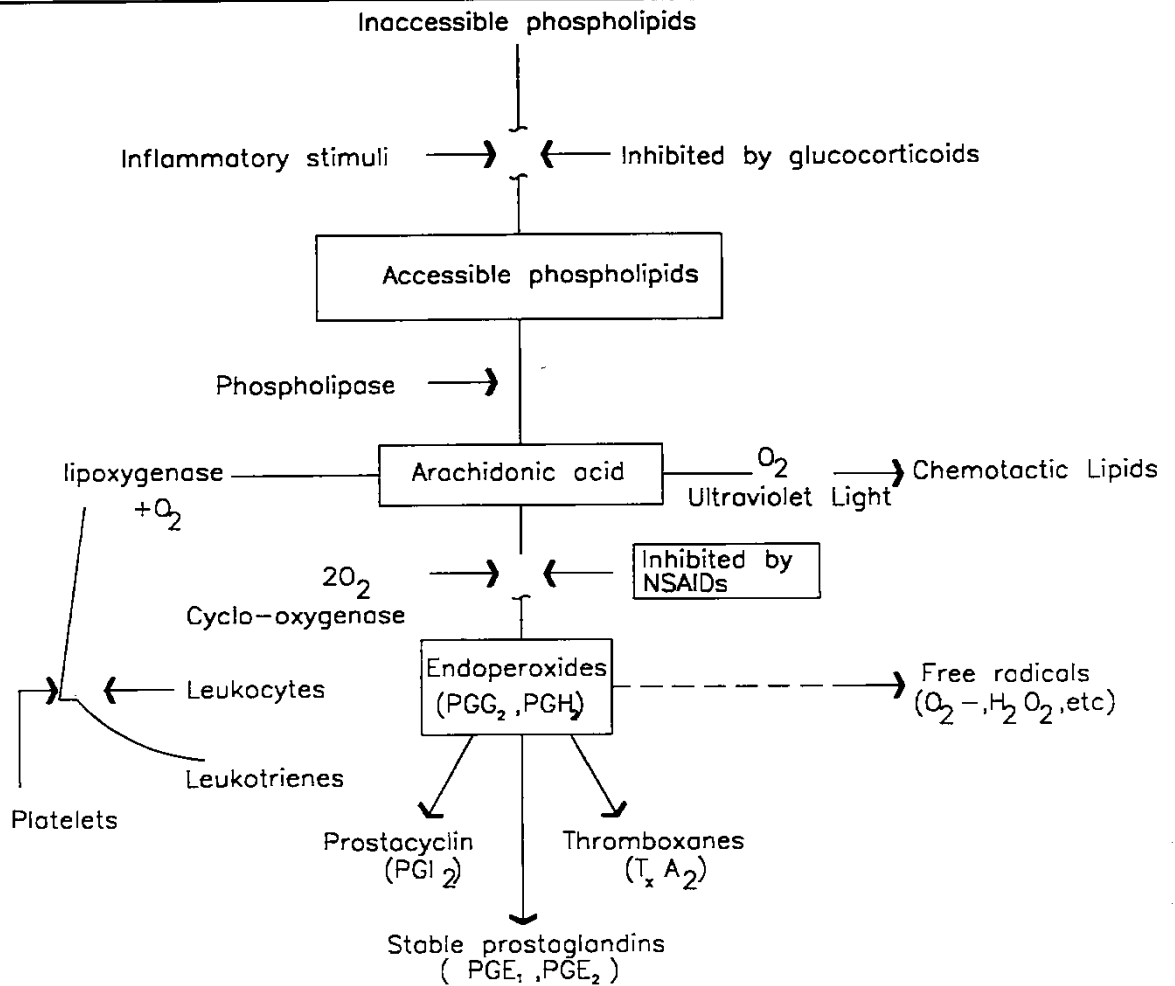


FIGURE (1), Arachidonic acid metabolism
(Furst and paulus ,1993)