HISTOLOGICAL STUDY OF THE EFFECT OF DICLOFENAC SODIUM ON THE FUNDIC MUCOSA OF ADULT ALBINO RAT

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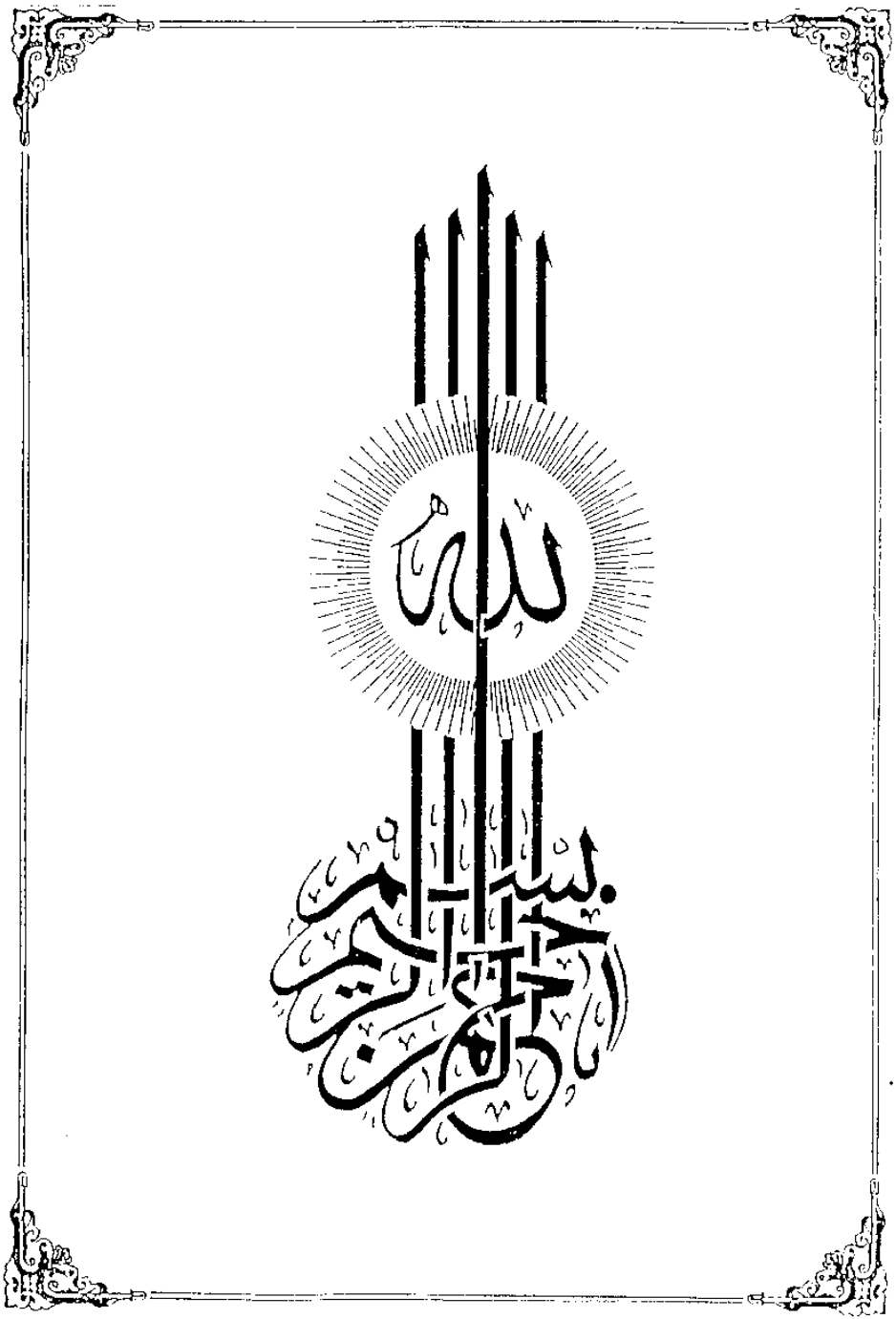

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INTRODUCTION AND AIM OF THE WORK

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Non-steroidal anti-inflammatory drugs (NSAIDs)are widely used nowadays in the treatment of rheumatic, rheumatoid and other inflammatory disorders. The modern NSAIDs are related in principle to salicylates, the oldest drugs in human use.

In 1838, salicylic acid was prepared by Piria from 'salicin". Salicin, a bitter glycoside, was the active ingredient in the willow bark that was used by the Greek and Roman physicians Celsus, Plinius, Dioscorides and Galen as a fever-lowering and behaviour-improving agent. In 1860, Kolbe was the first to synthesize salicylic acid from sodium phenolate. Sodium salicylate was first used as an antipyretic by Buss in 1875. Its value in the treatment of rheumatic fever was discovered in 1876 by Stricker and MacLagan. In 1879, See observed that salicylates increased the urinary excretion of uric acid, and that property was utilized in the treatment of gout by Campbell in the same year. Acetyl salicylic acid (aspirin) was synthesized by Hoffmann in 1897, and was introduced into medicine as an analgesic, antipyretic and antirheumatic agent by Dreser in 1899.

The first NSAID introduced after salicylic acid was phenylbutazone in 1952. Although phenylbutazone was effective in the treatment of rheumetoid arthritis and related disorders, its toxicity precluded its use in long-term therapy.

In 1963, indomethacin was synthesized and was soon introduced for treatment of rheumatoid arthritis and related inflammatory diseases. Meanwhile, competitive compounds such as ibuprofen and mefenamic acid were also introduced. At that time, scientists decided to develop a new anti- inflammatory

drug that would have high activity and outstanding tolerability. Out of more than 200 analogues synthesized, diclofenac sodium exhibited the best physico-chemical properties (Sallmann, 1985).

The marketed use of diclofenac sodium began in 1974 in Japan and had extended to 120 countries and used by more than 150 million patients (Catalano, 1986).

Although NSAIDs were often chemically unrelated, they shared common therapeutic actions and side effects. The most prominent side effects of NSAIDs were gastrointestinal in nature, including gastrointestinal bleeding and ulceration (Brune and Otterness, 1988).

As most of the studies concerned with the effect of diclofenac sodium on the gastric mucosa were clinical, endoscopical and biochemical studies, the aim of the present work is to investigate the early histological effect of diclofenac sodium on the fundic mucosa of the adult albino rat as well as the effect following repeated daily dosing of the drug.

REVIEW OF LITERATURE

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Rheumatic diseases represent a problem of major clinical importance and are essentially treated by non-steroidal anti-inflammatory drugs (NSAIDs). Recently, a wide number and variety of these drugs are encountered. The term NSAID was first used in 1952, when phenylbutazone was introduced into clinical practice. kuzell, Schaffarzick, Brown and Mankle (1952) described the side effects of phenylbutazone as rash, oedema, nausea, vertigo and activation of a pre-existing peptic ulcer with resultant perforation or massive haemorrhage. However, Krainin (1953) reported the occurrence of gastric ulcer with massive haemorrhage in a patient with no history of previous peptic ulcer after receiving phenylbutazone therapy in a dose of 400mg/day for one month. He concluded that phenylbutazone could reactivate as well as initiate gastric ulceration. Furthermore, Steinberg, Bohrod and Roodenburg (1953) added that agranulocytosis was another serious side effect of phenylbutazone that caused death of a patient after 26 days of receiving phenylbutazone in a dose of 400mg/day.

Varro, Csernay and Javor (1959) observed that stimulation of gastric acid secretion by histamine or atropine in dogs did not alter the frequency or severity of phenylbutazone-induced ulceration. They concluded that decreased gastric mucosal resistance was the major factor in the ulcerogenic action of phenylbutazone.

Roth, Valdez and Pieses(1963) studied the effect of direct contact of acetyl salicylic acid with the gastric mucosa of cats by placing the drug tablet in the stomach through a gastrotomy for 2-3 hours. Most of the tested cats showed localized gastric mucosal damage.

Menguy and Masters (1965) studied the effect of parenteral administration of aspirin to rats as well as its oral administration to dogs on the gastric mucus secretion using both histological method (PAS staining of sections of gastric mucosa) and biochemical method (direct measurement of gastric mucosal content of hexosamines and fucose). They observed decrease in the amount and carbohydrate content of mucus following administration of the drug.

Kent and Allen (1968) observed that oral administration of salicylic acid had an inhibitory effect within two to three hours on mucus glycoprotein biosynthesis in both human gastric mucosa and sheep colonic mucosa.

The study of Menguy (1969) on the rats revealed that oral administration of aspirin, indomethacin, phenylbutazone and cortisone reduced the secretory rate and altered the composition of the gastric mucus. This alteration involved a reduction in the concentration of its carbohydrates particularly sialic acid and hexosamines.

Benson (1971) reported that oral administration of aspirin caused gastric mucosal damage observed both gastroscopically and experimentally. He added that 40% of patients with upper gastrointestinal haemorrhage have had aspirin within 48 hours.

Sleisenger and Fordtran (1973) concluded that ulcerogenic drugs as aspirin, ethanol and indomethacin had little or no influence on gastric acid secretion. The authors suggested that these drugs caused gastric ulceration through breaking the gastric mucosal barrier.

Ganong (1973) stated that the insoluble, buffering mucus-bicarbonate coat of the gastric mucosa plus the surface membranes of the epithelial cells and the tight junctions between them constituted the "mucosal bicarbonate barrier" that protected

it from acid-pepsin digestion. He reported that ulcerogenic drugs had a damaging effect on this barrier

Bockus (1974) stated that the gastroduodenal mucosa in certain patients seemed to be more vulnerable to the deleterious effects of the ulcerogenic drugs. He suggested two different mechanisms for producing gastroduodenal ulceration. Reduced mucosal resistance played a primary role in the ulcerogenicity of salicylates, phenylbutazone, indomethacin and glucocorticoids. However, histamine, reserpine and caffiene produced ulceration mainly through excessive stimulation of gastric acid secretion, which on prolonged contact with vulnerable areas in the gastroduodenal mucosa, produced their ulceration.

Uthgenannt (1976) measured faecal blood loss in human subjects given therapeutic doses of aspirin, naproxen and diclofenac sodium for 3 weeks. They found that faecal blood loss was greater with aspirin and naproxen than with diclofenac sodium.

Glarborg (1977) recorded from his study on patients with perforated peptic ulcers that most of them had taken aspirin, phenylbutazone, indomethacin or glucocorticoids, mostly for a short period (12 hours) before perforation of the ulcer. He concluded that these drugs played an important role in perforation of peptic ulcers and in gastrointestinal bleeding.

Lehtola and Sipponen (1977) compared the effects of therapeutic doses of diclofenac sodium and naproxen administered for 8 days on the gastric mucosa of healthy volunteers, using gastroscopy, gastrophotography and histological examination of mucosal biopsies. They found that the mucosal lesions as well as the subjective symptoms were greater with naproxen than with diclofenac .

In 1978, Bijlsma studied the effects of administration of therapeutic doses of diclofenac sodium and indomethacin given orally for 6 months to patients suffering from rheumatoid arthritis. It was observed that diclofenac sodium showed greater improvement and less side effects than indomethacin.

The study of Robert, Nezamis, Lancaster and Hanchar (1978) on the rats revealed that prostaglandin E at a dose very much lower than that needed for inhibiting gastric secretion, had a cytoprotective action against various substances noxious to the gastric mucosa.

The work of ciccolunghi, chaudri and Schubiger (1979) on patients treated with diclofenac sodium for 3-24 months revealed that the side effects were transient, occurring during the first few months of treatment and were mainly gastrointestinal, central nervous system, dermatological and cardiovascular side effects. The long-term therapy with diclofenac demonstrated good laboratory tolerability. Few patients showed minor changes in liver and kidney function tests and decreased haemoglobin concentrations .

The 3-month comparative study of ciccolunghi, Schubiger and Reddrop (1979) revealed that orally administered therapeutic dose of diclofenac sodium was better tolerated than that of indomethacin. Patients receiving diclofenac had less frequent and less severe gastrointestinal and central nervous system side effects than patients receiving indomethacin.

Ciucci (1979) reported that the most frequent side effects occurring with diclofenac were gastrointestinal in nature, followed by dermatological and central nervous system effects. Few haematological side effects were reported, including agranulocytosis and aplastic anaemia. Few cases of liver function abnormality were also recorded.

Diclofenac sodium was chemically designated as sodium-[0-[2,6-dichloro-phenyl-amino]-phenyl] acetate, based on analysis of the structure-activity relationships of the other anti-inflammatory drugs (John, 1979). Diclofenac sodium was the active ingredient in Voltaren, a potent non-steroidal anti-inflammatory, analgesic and antipyretic drug (Maier, Menasse', Riesterer, Pericin and Ruegg, 1979). Orally administered diclofenac sodium was almost totally absorbed from the gastrointestinal tract, metabolized then excreted mainly in the urine. Small amounts were excreted in the bile (Willis, Kendall, Flinn, Thornhill and Welling, 1979).

Osnes, Larsen, Eldsaunet and Thom (1979) investigated the influence of therapeutic doses of diclofenac sodium and naproxen given for one week to human subjects on the gastroduodenal mucosa by endoscopic examination. They found that diclofenac caused significantly less gastritis, haemorrhagic and erosive lesions than naproxen.

Caruso and Porro (1980) concluded from their gastroscopic study on patients with rheumatoid arthritis and osteoarthritis treated with 12 different NSAIDs for 3-12 months that all NSAIDs caused gastric mucosal damage, as they inhibited prostaglandin synthesis. The greatest offender was aspirin and the least was sulindac and diflusinal. Ketoprofen, naproxen and diclofenac sodium were not significantly better tolerated than the classical drugs. They reported that the correlation between dyspeptic symptoms and the presence of ulcerative lesions was not always existing.

Ingemanson, Carrington, Sikstrom and Bjorkman (1981) proved by clinical study that diclofenac administered in an oral therapeutic daily dose was effective in relieving dysmenorrheal pain and associated symptoms such as excessive bleeding, nausea and oedema, owing to its anti-prostaglandin effect.

Tympner (1981) measured the transmural electric potential difference of the stomach wall (which was an indicator for efficiency of the gastric mucosal barrier) before and after administration of therapeutic doses of diclofenac, indomethacin and phenylbutazone to human subjects for 4 weeks. They found that these drugs caused significant reduction in the gastric potential difference, indicating decreased functional efficiency of the gastric mucosal barrier.

The comparative study of Lundstam, Leissner, Wahlander and Kral (1982) showed that single intramuscular therapeutic dose of diclofenac was superior in efficacy to a therapeutic dose of a narcotic-spasmolytic combination (Spasmofen) in relieving renal colic.

Rainsford (1982) observed that benoxaprofen, fenclofenac and azapropazone given to rats and pigs for one and ten days in different doses showed lower ulcerogenicity than equivalent doses of aspirin, indomethacin and diclofenac sodium. He attributed this to their lower activity for inhibiting gastric mucosal prostaglandin synthesis.

Rainsford and Willis (1982) found that repeated oral administration of therapeutic doses of aspirin, indomethacin, sulindac and diclofenac to pigs for 10 days caused significant reduction in gastric mucosal as well as plasma prostaglandins, coincident with gastric mucosal damage. However, they found that therapeutic doses of the less ulcerogenic drugs flufenamic acid, azapropazone and fenclofenac, significantly reduced plasma prostaglandins without significant reduction of mucosal prostaglandins. Therefore, they concluded that the drug ulcerogenicity paralleled its reduction of the mucosal prostaglandins rather than plasma prostaglandins.