EFFECT OF NEWER NONSTEROIDAL ANTI-INFLAMMATORY DRUGS ON KIDNEY FUNCTION

THESIS

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BY

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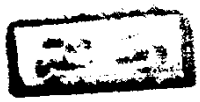

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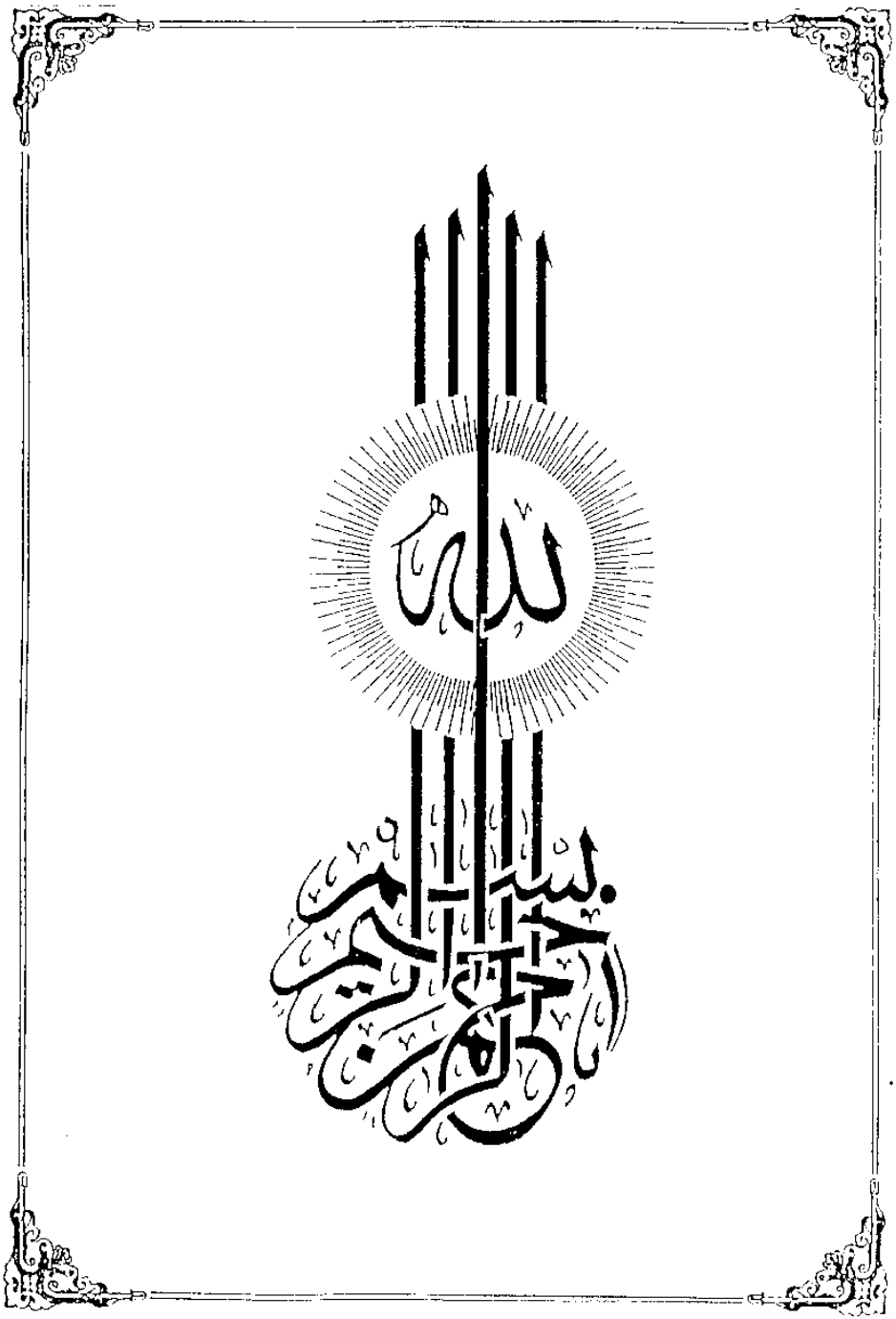

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Several newer nonsteroidal anti-inflammatory drugs (NSAIDs) are now available for the management of various rheumatologic conditions. These NSAIDs are classified into structural classes including : salicylates, propionic acids , fenamates, pyrazolones, and oxicams. Approximately 50 agents within these classes have been used. They have in common, the ability to inhibit prostaglandins synthesis from arachidonic acid by blocking the enzyme cyclo-oxygenase.

Prostaglndins are synthesized in several organs iclud-ing the kidney.

In addition to their role in inflammation, prostaglandins (PGs) affect various physiologic functions and they may be important in the regulation of renal hemodynamics (Anderson et al., 1976). So, the inhibition of PGs sythesis by drugs may explain the changes in the renal functions that these drugs may induce.

Accordingly, one might expect some changes in the renal functions secodary to the administration of NSAIDs which are inhibitors of PGs synthesis. On the other hand, the kidney

is so discriminated against and so vulnerable to drug toxicity because of many reasons .

As it is not possible to experiment with all NSAIDs , so, ibuprofen and proquazone - being newer than the generation of aspirin and indomethacin - have been chosen to be the object of this study . Therefore , ibuprofen and proquazone will constitute the practical part of this thesis, while the effects of the other NSAIDs on kidney functions will be reviewed.

REVIEW

MECHANISM OF NEPHROTOXICITY

A number of factors make the renal tubules and interstitium particularly prone to toxic injury .

These factors are :

1- Large blood flow:

The kidney receives 25% of the cardiac output . This large amount of blood is directed to an organ constituting a small percentage of the body weight (0.4%) . Consequently, substances circulating in very small concentrations in the blood stream become heavily concentrated when they enter the micro-circulation of the kidney .

The ratio of blood flow to tissue mass in the kidney is even higher in the renal cortex which receives more than 90% of the total renal blood flow. Therefore, it will be electively damaged by nephrotoxic substances .

2- Direct toxic effect by concentration in the medullary tissue of the kidney:

It was found that the first lesion in cases of analgesic

nephropathy occurs in the long loops of Henle and vasa recta areas where higher concentrations of these drugs occur .

Indirect support to the direct toxic effect of analgesics has been provided by the elegant experiments of Hardy (Hardy , 1970) and Brown (Brown et al.,1968).

3- The role of anoxia :

The kidney has a great metabolic activity; it has the highest oxygen consumption per-gram and the highest glucose production per-gram,of any tissue in the body(Lornoy et al., 1979). The large amount of O_2 required by the metabolism of the kidney makes this organ highly sensitive to anoxia inducing agents (Mery and Fillastre , 1979).

The oxygen tension in the human kidney is known to fall from 100 mm Hg in the cortex to about 20 mm Hg in the medulla (Leonhardt et al.,1963). The medulla, therefore, is clearly vulnerable to ischaemia.

Anoxia may result from the following changes in the vascular tree:

a)reduction in blood flow by vasoconstriction or mesangial thickening.

b) platelet aggregates.

c) occlusion of the blood vessels by interstitial hyperplasia.

d) changes in the oxygen affinity of hemoglobin .

e) changes in blood viscosity.

Nanra et al., (1973) have demonstrated that aspirin (500 mg/ Kg/day) , phenylbutazone (10 mg/Kg/day),mefenamic acid (100mg/Kg/day), all lowered the medullary flow, mefenamic acid being the most active in this respect. Endothelial necrosis and vascular obliteration have also been reported in animals but not in man (Abrahams et al.,1963).

A specific microangiopathy was reported to occur in the renal vascular tree in some patients using NSAIDs (Abrahams, 1976).

Nanra and Kincaid-Smith in 1973 reported that there were some platelate aggregates in the vasa recta of some patients under NSAIDs treatment. In 1969, Saker and kincaid-Smith observed adherent platelets in the vasa recta of some patients under NSAIDs treatment but no thrombi were found.

In the view of the known effects of the NSAIDs on platelet aggregation and adhesion, it would seem very unlikely that they would induce aggregation or thrombosis.

4- The renal vascular rete mirabile concetrates active compounds in the interstitium of renal papilla to a degree not found in other interstitial tissues of the body . (Sabour , 1965)

5- Trascellular transport :

Trascellular transport may increase the concentration of some substances within the cells or at their surfaces.

Concentration of these substances at the cell extremity bordering the tubular lumen is also enhanced by water reabsorption along the tubules (Mery and Fillastre , 1979).

6- Toxic substances may interfere with several enzymes essetial for epithelial cells activity (Mery and Fillastre, 1979).

7- Immunological causes:

Recently, much attention has been focused on the possibility of immunologically mediated renal diseases as a mechanism of adverse drug reactions. It seems likely that many drugs will be added to those currently identified as causing immunological damage, paticularly to tubular

basement membrane (Porter et al.,1981). Murray et al. , (1975) postulated - on the basis of the glomerular deposits and positive staining of glomeruli incubated with fluorescent anti-serum - that there is an immunologic basis and that the amino group contained in most analgesics may be responsible for it .

8- Prostaglandins :

The renal papilla is the main source of PGs in the kidney. As "aspirin-like" drugs inhibit PGs biosynthesis , it is thought that this inhibition is relevant to the genesis of analgesic nephropathy . (Smith et al.,1975 - McGiff et al., 1971).

The degree of inhibition of PGs synthesis by NSAIDs depends very much on the substrate employed (Flower, 1975).

The rank order of inhibition of prostaglandin synthetase - in the guinea pig - by NSAIDs is as follows: meclofenamic acid > niflumic acid > mefenamic acid > flufenamic acid > naproxen > phenylbutazone > aspirin or ibuprofen (Dereadt,1976) .

As PGs may be important for the regulation of renal hemodynamics (Anderson et al.,1976),so, the inhibition of PGs synthesis by NSAIDs may explain the changes in the renal functions that these drugs may induce .

PROSTAGLANDINS

CHEMISTRY :

Prostaglandins (PGs) are series of closely related 20 carbon unsaturated fatty acids containing a cyclopentane ring . They were first isolated from seminal fluid, but have now been shown to be synthesized in most and possibly all organs of the body .

The different PGs fall into several main classes : E , F , A , B , C , and D , distinguished by the constituents of the cyclo-pentane ring . The main classes are further subdivided according to the number of the double bonds in the side chain , this is indicated by the subscripts 1,2, 3,..., for example : the E series may be E_1 or E_2 according to the number of double bonds (Anderson et al., 1974).

Synthesis of PGs is accomplished in a stepwise manner by a complex of microsomal enzymes referred to as "prostaglandin synthetase" .

PGs are synthesized from arachidonic acid, and other essetial fatty acids via endoperooxides . The first enzyme