HEPATO-RENAL TOXICITY OF SOME ANALGESIC ANTIPYRETICS

THESIS

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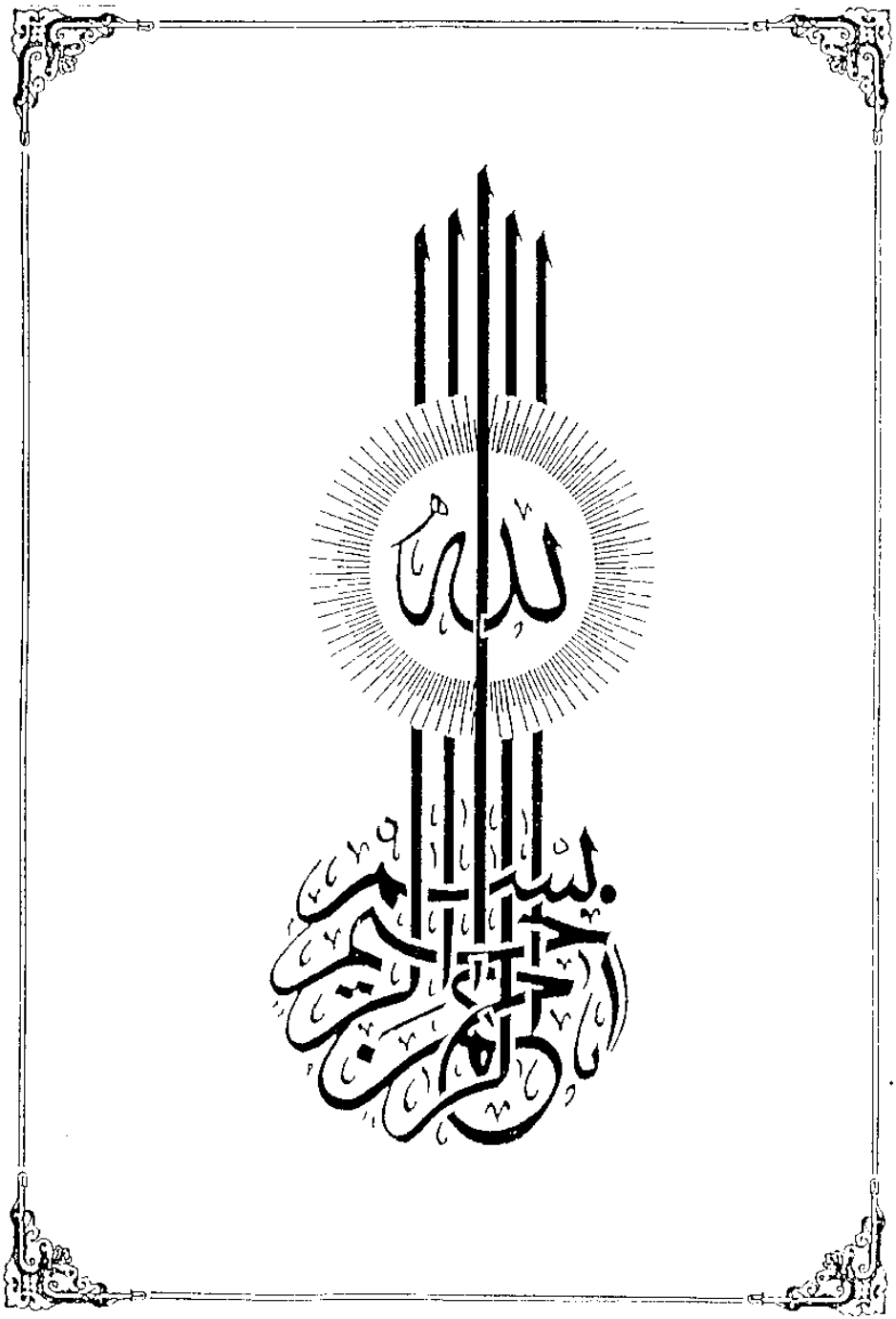

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AIM OF THE STUDY

The analgesic antipyretic drugs have become of universal use. However there is still basic disagreement between experts as to the nature and frequency of some of their major adverse reactions. According to Dukes's opinion (1980), there are several reasons why this should be so. Firstly, some of the more serious complications result not from reasonable use but from abuse, amounting sometimes to frank habituation. Secondly, these drugs are largely employed for self medication without obtaining a reliable information from the physician or the pharmacist regarding their use and effects. Thirdly, the analgesic antipyretics have to a large extent been used in combinations whether fixed or not, and accordingly it has become difficult to decide to which component a given adverse reaction is attributable. Finally, most of these drugs were developed and marketed long before modern techniques of investigation and so fundamental studies of their properties have not been undertaken in a coordinated fashion.

In this study, we concern with two of the most commonly used analgesic antipyretic drugs namely acetylsalycilic acid (aspirin) and N-acetyl-p-aminophenol (acetaminophen - paracetamol).

Aspirin is one of the cheapest, most easily available and most widely used drugs in the world as it is well known that people tend to overdose on whatever medication is most readily accessible. Nickander et al. (1979), reported that aspirin products alone account for app-

roximately 200 million dollars of all sales of pharmaceutical products and are currently the first choice of treatment for mild pain and arthritis. In the United Kingdom more than two million kg of aspirin are consumed per year (about 2 tablets per week for every member of the population) and about 4 tablets are ingested by every person in the U. S.A. per week (Bowman and Rand, 1980). Aspirin gains its popularity due to its long history of safety and tolerance. However, it may be involved in analgesic nephropathy. The acute nephrotoxicity of aspirin has been proved experimentally in man (Dukes, 1978). On the other hand, Macklon and Graft (1974) and Burry et al. (1976) found that significant long term damage is propably unusual. Also in Maher's studies (1984), chronic renal toxicity of salicylates has been detected in two cases only and this may be due, in his opinion, to the fact that the disease was previously overlooked and doubted even by those who should always be wary of drug toxicity; the physicians.

There are also increasingly frequent reports that aspirin has deletorious effects on hepatic function (Anonymous, 1974, Goodman and Gilman, 1980 and Davis, 1982).

Another analgesic antipyretic drug which has become increasingly popular in recent years is acetaminophen. It is generally con-

sidered to be one of the safest of all minor analgesics when taken in the usual therapeutic doses (Dukes, 1980). It is usually promoted as an effective alternative to aspirin due to its reported low incidence of gastro-intestinal side effects (Hoftiezer et al., 1982). However, aspirin is still a head of acetaminophen, in both sales (Beck et al., 1982) and the incidence of overdosage (Poison control statistics 1962-1975), but the gap is narrowing as its share of the pain reliever market has increased from 6 to 37 % in the last 6 years (Beck et al., 1982). When acetaminophen is taken in large amounts, it may produce fatal hepatotoxicity. On the contrary, the drug was considered harmless to the liver, when chronically abused. Several recent reports render it necessary to revise this view (Dukes, 1980). Similary in analgesic nephropathy, there has been very little evidence involving acetaminophen, but in a few recent studies, isolated renal failure has been reported following chronic ingestion (Krikler, 1967, Edwards et al., 1971 and Rogers et al, 1982).

Quite apart from the individual toxicity of aspirin and acetaminophen, their combination whether fixed (benorilate, an ester of both drugs) or non fixed, is not uncommon for those who seek more analgesia or antipyresis and the review of the adverse effects shows that they are not merely the sum total of those of each drug (Dukes , 1980).

The objective of this study is to evaluate the hepatorenal effects of repeated administration of toxic doses of both drugs, individually and in combination. In addition, aspirin has a well known damaging effect on gastric mucosa while acetaminophen is devoid of such effect, but in the contrary, it significantly decreases acute mucosal damage due to aspirin or other damaging agents (Kontureck et al., 1982). In this study, we are interested to assess if this protective effect exists also with repeated doses of aspirin or not.

REVIEW OF LITERATURE

CLASSIFICATION OF ANALGESIC ANTIPYRETICS

Analgesic antipyretics are a group of chemically unrelated drugs which produce similar pharmacological effects by inhibiting the synthesis of prostaglandins. These pharmacological effects include reducing the elevation in body temperature during fever (antipyretic) and experience of pain without loss of conciousness (analgesic). Many of these drugs are also capable of reducing symptoms of inflammation (anti-inflammatory). So this group of drugs may be termed "nonsteroidal anti-inflammatory antipyretic - analgesics" to differentiate them from the steroidal anti-inflammatory drugs, or "non narcotic analgesics" to distinguish them from the narcotic analgesics.

Goth (1984), classified the nonsteroidal anti-inflammatory antipyretic analgesic drugs according to their therapeutic uses into:

(1) **Salicylates:** (anti-inflammatory antipyretic analgesics)

1- Acetylsalicylic acid (ASA, aspirin).

2- Saligenin (Salicyl alcohol).

3- Sodium and magnesium salicylate.

4- Salicylamide.

5- Diflunisal (a new salicylate derivative).

6- Choline magnesium trisilicate.

7- Salicylic acid (keratolytic and antiseptic used topically for wart and corn removal).

8- Methylsalicylate (oil of wintergreen, used as a counter irritant in ointment). The last 3 drugs have systemic effects but are only used locally.

(2) **Salicylate - like anti-inflammatory agents** :

1- Arylalkanoic acid derivatives which include naproxen and fenoprofen.

2- Tolmetin.

3- Pyrazolone derivatives which comprise phenylbutazone and oxyphenbutazone.

4- Indol derivatives which include indomethacin and sulindac.

(3) **Salicylate-like antipyretic analgesic** :

1- p-Aminophenol derivatives which include acetaminophen and phenacetin.

2- Mefenamic acid.

3- Zomepirac sodium.

(4) **Analgesic combinations and mixtures** :

1- Narcotic and antipyretic analgesics (codeine and aspirin or acetaminophen).

2- Antipyretic analgesic mixtures (aspirin and acetaminophen).

3- Caffeine and antipyretic analgesics (APC - aspirin phenacetin and caffeine). Acetaminophen has replaced phenacetin in many of these mixtures due to the latter's renal toxicity.

4- Sedatives and antipyretic analgesics (phenobarbital or promazine and aspirin).