ANALGESIC NEPHROPATHY

AND

POSSIBLE EFFECTS OF INDOMETHACIN ON KIDNEY FUNCTIONS

T H E S I S

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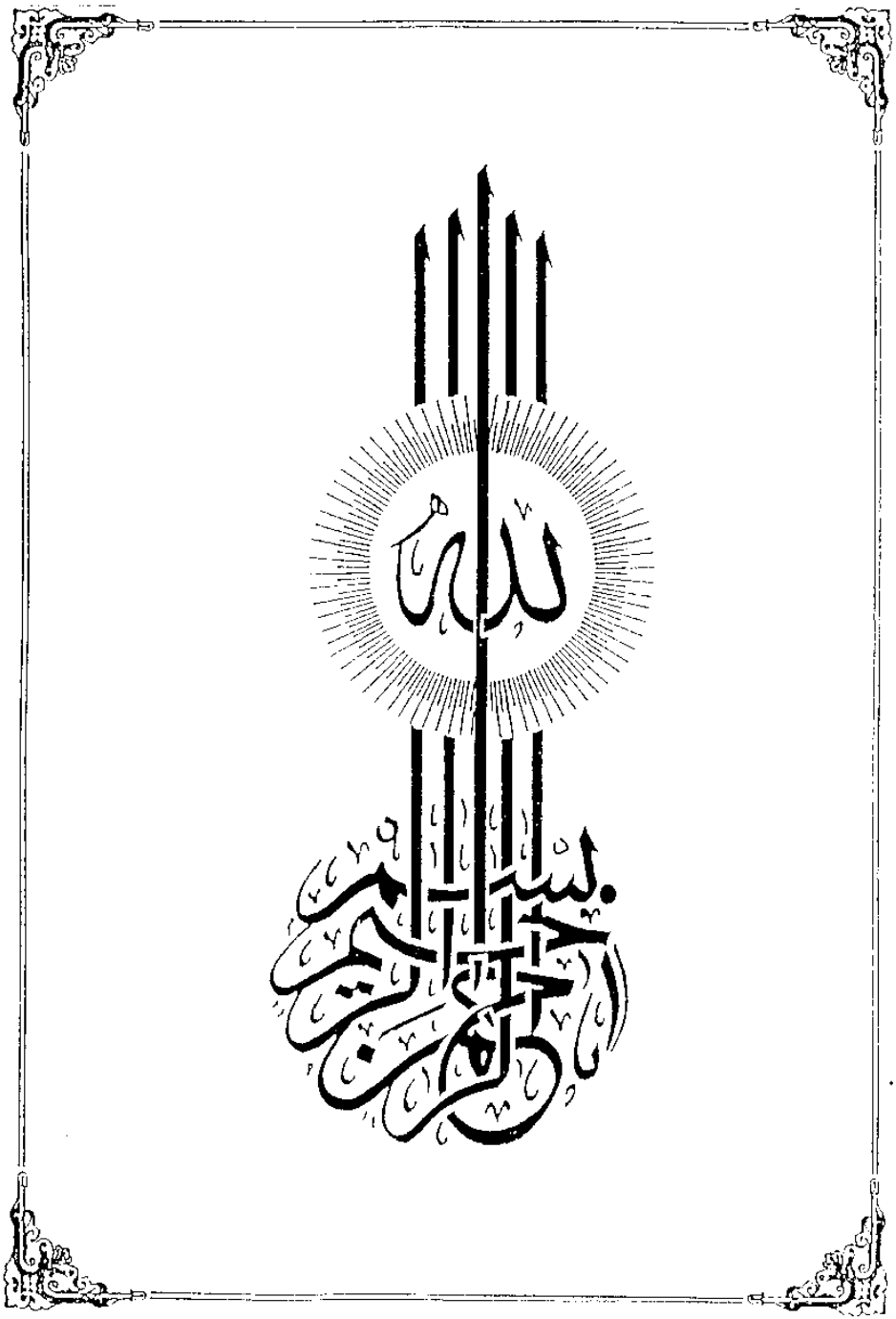

TO MY PARENTS .....

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CHAPTER I

INTRODUCTION

AND

REVIEW OF LITERATURE

INTRODUCTORY NOTE

As it is not possible to experiment with all analgesics, INDOMETHACIN, being a common non-steroidal analgesic, anti-inflammatory and anti-rheumatic drug, has been chosen to be the object of this study. Therefore, INDOMETHACIN will constitute the practical part of the thesis, while analgesic nephropathy, in general, will be reviewed.

I N T R O D U C T I O N

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

One of these reasons is that a large blood flow (25 % of cardiac output) is directed to an organ constituting a small percentage of body weight (0.4 %). In consequence, substances circulating in much smaller concentrations in the blood stream become heavily concentrated when they enter the microcirculation of the kidney.

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. (Lorncy et al., 1979).

At its vascular surface (which has one of the highest endothelial concentration of any organ in the body), are many enzyme systems for blockade. By virtue of its counter current system, it can thus raise concentrations of substances to greater than blood concentration levels. Furthermore, the kidney has the mechanism for protein unbinding as well as normal transcellular transport processes that facilitate drug entry into the cell. Drugs, therefore, exist intracellularly in a totally different environment from extracellularly, a conceptual phenomenon that is relatively new to pharmachology, i.e. intracellular separation of drug from its normal transport carrier protein (Schreiner et al., 1981).

REVIEW OF LITERATURE

INTRODUCTION

Since 1953, when Spuhler and Zollinger reported from Switzerland the association of chronic interstitial nephritis with the ingestion of certain analgesic drugs, analgesic-associated nephropathy has been established as an important cause of chronic renal disease in many parts of the world.

By 1970, reports of chronic renal disease in patients taking large quantities of either on-the-counter remedies or prescription medications containing various analgesics, appeared from many countries in Western Europe as well as from Australia, South Africa and Canada (Goldberg and Murray, 1978).

Renal failure is commonly associated with this condition, and pathologically an almost uniform finding is necrosis of the renal papilla (Gault et al., 1968).

Kincaid-Smith, (1967), has suggested that papillary necrosis is the primary factor in the pathogenesis of this disease.

Absolute proof of the causal relationship between analgesics and renal didease is lacking, but circumstantial epidemiologic as well as experimental studies in animals has convinced most observers that analgesic-associated nephropathy is a specific entity with potentially important implications from the standpoint of public health and preventive medicine (Cecil Text Book of Medicine, 1979).

Simultaneously, the whole concept of analgesic-induced nephropathy came under review, and suggestion was made that the observed chronic interstitial nephritis was just another form of chronic pyelonephritis. As subsequent experience has shown, however, distinct differences between these two entities exist, and considerable evidence now indicates a causal relationship between prolonged consumption of analgesic and renal disease (Wadi and Garahed, 1976).

ETIOLOGY

Although a great number of drugs are used for analgesia, those that are commonly considered as possible causes of renal disease in North America (correctly or incorrectly) when abused are aspirin, phenacetin, acetaminophen, caffeine and codeine (Murray and Goldberg, 1975). Although the latter two drugs are commonly ingested in concert with the others listed, there is little to support the contention that they contribute significantly to the development of renal disease (Shelley, 1967).

Early reports assume that phenacetin was the cause of the renal disease because it was the single drug common to the many analgesic mixtures ingested by almost all the well documented cases (Spuhler and Zollinger, 1953). However, that such an assumption was unwarranted since most of the reported cases had all ingested the phenacetin in combination with other drugs (Shelley, 1967 ; Kincaid-Smith, 1967 ; Gilman, 1964). However, at least one patient has been reported to develop papillary

necrosis, a major manifestation of this disease, after the excessive consumption of phenacetin alone (Lindenberg, 1958).

A major reason for the difficulty in attributing analgesic abuse nephropathy specifically to phenacetin is that this compound is generally not utilized as a single drug, but more commonly is available in combination with other analgesics, particularly aspirin. Although direct proof that phenacetin alone can cause renal damage in the human is not available, such a conclusion is not rolled out by the clinical data (Murray and Goldberg, 1975).

Since aspirin is a component of the analgesic mixtures in most of the reported cases, it has been also considered a possible cause of the renal disease. At least 5 patients have developed papillary necrosis associated with the ingestion of aspirin alone (Shelley, 1967; Murray et al., 1971). There is, however, a recent study that suggests that the incidence of papillary necrosis and/or renal function impairment are both extremely rare consequences of the use of aspirin alone even in very high doses for prolonged periods of time (Murray & Goldberg, 1975). It is clear, however, that the ingestion of aspirin and phenacetin together, with or without, other drugs, has most commonly been reported to be associated with the development of papillary necrosis or renal function impairment in the absence of other known reasons of renal disease.

This fact has several implications; it is theoratically possible, e.g. that aspirin is the toxic drug, but that only those patients who ingest combination analgesics ingest enough aspirin to cause damage. Surveys of patients who have ingested large

amounts of aspirin alone, however, make this an unlikely explanation (Newzealand Rheumatism Association Study, 1974).

It is also possible that ingestion of one drug modifies the metabolism or alters renal tissue response of the other drug in such a manner as to increase its toxicity, thus the abuse of combinations of drugs may be necessary to produce the nephropathy. Finally, it is still possible that phenacetin is the primary cause of the renal damage, but that its major availability for patients is in combination form.

Acetaminophen (N-acetyl -P-amino-phenol - APAP)is presently being used in increasing amounts either alone or in combination with aspirin. Since it is also the major metabolic product of phenacetin in the human (more than 90 % of ingested phenacetin is converted into this form within one hour), the risk of its excessive use being associated with the development of renal disease should be considered. There are so far relatively few patients reported, who have ingested massive amounts of acetaminophen, but there have been three patients described with papillary necrosis after its long-term ingestion, two after acetaminophen and aspirin in combination (Newzealand Rheumatism Association Study, 1974, and Prescott, 1966), and one patient after acetaminophen alone (Krikler, 1967).

Thus, until further experience accumulates to the contrary, this drug, too, should be considered potentially related to the development of kidney disease at least in combination with aspirin.

The acidic non-steroidal, anti-inflammatory agents such as

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The acidic non-steroidal, anti-inflammatory agents such as

indomethacin, phenylbutazone, and mefenamic acid appear to have a number of common action to that of aspirin, and serious consideration should be given to their potential role in analgesic induced renal disease (Kincaid-Smith and Nanra, 1979).

In animals, all non-steroidal, anti-inflammatory agents given in high dosage produce papillary necrosis, and it is likely that they may also cause damage in man if dosage is high and prolonged (Kincaid-Smith, 1978).

Schreiner et al., (1981), pointed out that papillary necrosis, the most dramatic form of analgesic nephropathy, has been reported in experimental animals and humans after use of a wide variety of drugs (aspirin, antipyrine, acetaminophen, phenylbutazone, indomethacin, ibuprofen, phenoprofen, alclofenac, and phenacetin. Most of these drugs and many new ones having anti-inflammatory and analgesic properties can produce papillary necrosis in some animal species. There is certainly no over-the-counter analgesic preparation that can be regarded as safe on the basis of existing clinical and experimental data.

The incidence of analgesic-associated nephropathy varies widely from country to country. It is found extremely frequently at necropasies in Australia. The incidence in different series has varied between 3.7 % and 21 %.

The following table illustrates the incidence of analgesic nephropathy in some of the countries where the disease frequently occurs.

Table 1

Country	Date	Renal Papillary necrosis per 100 Necropasies
U. S. A.	1947 - 1961	0.2
U. K.	1961 - 1967	0.16
Switzerland	1938 - 1947	0.76
	1948 - 1957	1.32
	1955 - 1972	1.0
	1971 - 1976	1.1
Australia	1962	3.7
	1964	9.9
	1968 - 1969	8.7
	1973 - 1974	21.4
	1976	20.0

Incidence of Analgesic Nephropathy in Different Countries

(Compiled from various publications)

(Kincaid-Smith, 1978)

In contrast, in the United States and the United Kingdom, in only 0.2 and 0.1 % respectively of necropasies has papillary necrosis been found. Even so, analgesic nephropathy cannot be