# NON-STEROIDAL ANTI-INFLAMMATORY DRUGS
# ( DICLOFENAC SODIUM «VOLTAREN» )
# IN
# THE TREATMENT OF RHEUMATIC FEVER

## THESIS

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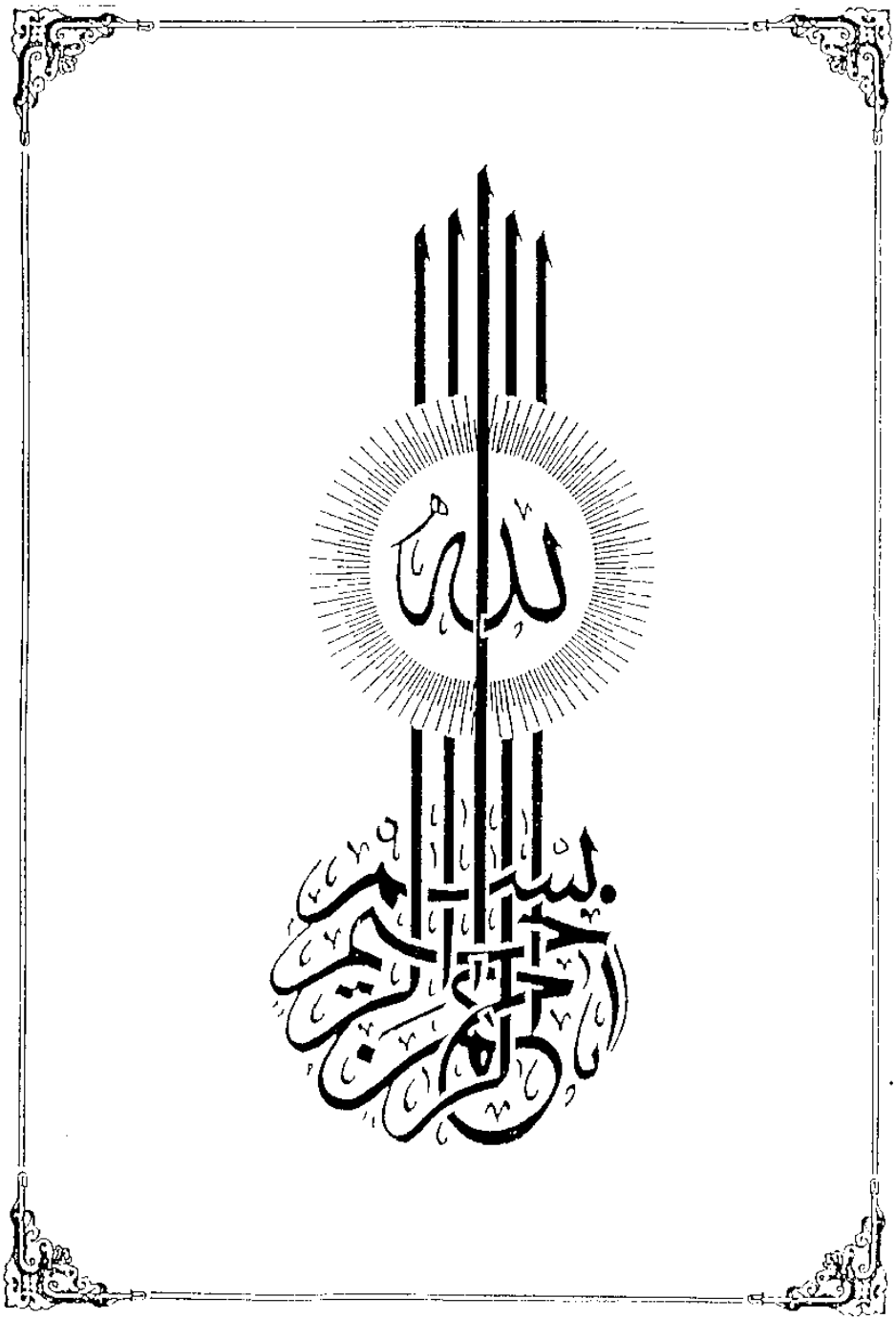

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# INTRODUCTION

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Rheumatic fever is a systemic febrile illness affecting connective tissues, particularly of the heart and joints (Abudjaja and Khan,1983). It occurs predominantly in children between the ages of 5 and 15 years. It is rare before age of 4 and after 50 years.

It mainly affects children who live in overcrowded low socioeconomic conditions associated with rapid urbanization and industralization (WHO, 1978). The prevalence in such communities appears to be related to the increased transmission of streptococcal infection (Edginton and Gear,1982). The available data from developed countries suggest that the incidence of rheumatic fever and rheumatic heart diseases declined by 80-90% during the period from 1958-1977 (Agrawal, 1981).

In Africa, Asia, the Middle East and South America, the prevalence is well over 1 per 1000 school children, while in developed countries, the rate is less than 1/1000 except in pockets of poverty (WHO,1978).

Rheumatic fever develops in 0.3-3% of individuals with untreated streptococcal infection, the high 3% attack rate being associated with epidemics of streptococcal infection (Kaplan et al.,1977).

## AIM OF THE WORK

It is known that anti-inflammatory drugs were suggested by rheumatologists for the treatment of acute rheumatic fever. Marini and Pinca (1962) studied the effect of "phenylbutzone" in the treatment of rheumatic fever. Also, Vignau (1965) studied the effects of "Indomethacin" in rheumatic fever

The idea of using non-steroidal anti-inflammatory drugs (NSAIDS) is to find a drug with anti-inflammatory effect at the expense of antipyretic analgesic action, and comparing its effect with that of aspirin for the treatment of patients with acute rheumatic fever

Diclofenac is the nonsteroidal anti-inflammatory drug which is selected for this comparative study.

Vercesi and Focesi (1977) proved that salicylates have a deleterious effect on cardiac metabolism. Therapeutic doses of salicylates may induce congestive heart failure or pulmonary oedema if used in acute rheumatic fever with active carditis. The following factors conspire to cause this: increased oxygen consumption with increased peripheral uptake of oxygen This is met by increased plasma volume

(of uncertain cause )which may be enhanced by increased sodium intake where sodium salicylate and not aspirin has been used (Laurence and Bennette,1980). So it is necessary to find a nonsteroidal anti-inflammatory drug taking this deleterious effect.

To start with, Diclofenac will be studied on acute rheumatic fever cases with fleeting arthritis

# PATHOGENESIS

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## RHEUMATIC FEVER AND STREPTOCOCCUS

### Streptococcal structures and corss-reactive antigens:

Each streptococcal cell is surrounded by several layers:

1. Capsule.
2. Cell wall; subdivided into:

    a) protein layer (M,R,and T)

    b) Group A carbohydrates

    c) Mucopetide layer

3. Protoplast membrane (Lewis and Zabriskie,1985).

### The M Protein:

This protein antigen is seen on the outer surface as fimbria. It serves as a marker for the immunologic subclassification of group A streptococci into specific types (Lewis and Zabriskie, 1985).

There are over 80 serologic types of "M" protein, each of which is capable of stimulating specific protective antibodies as well as sharing a common property of being able to avoid phagocytosis by the host's immune system. Fischetti and Colleagues (1980) have noted a marked

structural homology between the M-protein molecule and the muscle protein tropomyosin. Yet, antisera raised against M protein or tropomyosin do not give the same pattern of staining seen in acute rheumatic fever sera. Dale and Beachey (1982), noted that antibodies raised against the pepsin fragment of the type 5 M protein moiety was not only protective in the opsonic assay but also crossreacted with sarcolemmal tissue.

Group A Carbohydrate Moeity:

N-acetylglucosamine cross-reacts with the mammalian valvular glycoproteins (Goldstein ,1968). This cross-reaction may be quite important in the pathogensis of valvular disease in patients with rheumatic fever.

Cell Wall Mucopeptide:

Current work suggests that it may be partly responsible for the chronic, remittant, nodular lesions of connective tissue after a single injection of disrupted group A streptococci ( romartie et al., 1960).

The Final Inner Layer; of the streptococcal cell is a highly complex antigen lipoprotein it contains approximately 72% protein, 25% lipid and 20% carbohydrate

by weight. Its antigens are quite different from those in the streptococcal cell wall (Lewis and Zabriskie, 1885).

These Findings are Summarized as Follows:

1. Cell membranes and extracts from group A streptococci cross-react with human glomerular basement ambrene antigens (Rapaport et al., 1969).

2. Rabbit antisera to these streptococcal membrane structures will bind to rabbit and human muscle sarcolemmal membrane antigens, including cardiac muscle (Kaplan and Frengley,1969 ; Zabriskie,1966). They also bind to smooth muscle of blood vessels.

3. Guinea pigs immunized with a number of different types of groupA streptococci developed a sensitivity indistinguishable from that produced by sensitization with allogenic tissues (Rapaport,1964). Antigens shared by streptococcal membrane and mammalian tissue appear to includ mammalian histo-compatibility antigens. There is also, close biochemical similarity between mammalian histo-compatibility antigens, certain structural glycoproteins, and streptococcal membrane antigens (Robert et al.,1972).

Patients with rheumatic chorea possess an antibody that stains caudate nuclei and can be absorbed by streptococcal membrane antigens (Husby et al.1976), indicating that streptococcal antigens share antigenic determinants with brain antigens (Kingston and Glynn,1976).

Antisera bind to skin fibroblasts as well as to thymocytes ( Lyampert et al.,1979). This cross- reactivity could be important in the host's immunoregulation to streptococcal antigens.

Pathogenetic Concepts of Rheumatic Fever:

Most investigators concerned with the pathogensis of rheumatic fever now favor the concept that the disease is a result of an abnormal immune respone (humoral and/or cellular) on the part of the host to a given streptococcal infection. For instance, patients with rheumatic fever have higher antibody titres to streptococcal antigens such as "streptolysin"O"than do subjects without rheumatic fever (Stollerman,1975).

In addition, the sera of patient with acute rheumatic fever contain antibodies that react with constituents of human cardiac tissues(Zabriskie et al.,1970; Kaplan

et al.,1961). Antibodies are present in very low titers or are absent in uncomplicated streptococcal infections. Elevated titres of antibodies to streptococcal antigens may reflect a greater antigenic challenge,although it should be emphasized that an asymptomatic streptococcal infection, so mild that the patient can not recall the symptoms of pharyngitis, will precipitate an attack of rheumatic fever (Lewis and Zabriskie, 1985).

Several observations support the idea that cell-mediated immunity is also important in the rheumatic process:

1. The rare occurrence of the disease before 4 years of age suggests that several infections with the streptococcus are needed to sensitize the susceptible individual (Rantz et al.,1953).

2. Streptococcal antigens can be shown to induce delayed hypersensitivity in both animals and man (Francis et al.,1976).

3. Examination of the human heart from patients with acute rheumatic fever reveals numerous lymphocytic infiltrates, both perivascular and between muscle bundles (Lewis and Zabriskie,1985).

Humoral Immunity:

1. Carditis:

Examination of a number of sera from patients with recent streptococcal infections and their sequelae revealed heart-staining antibody in most of them. However, the amount of antibody detected in individuals with rheumatic fever at the onset of their disease was strikingly different from that in patients convalescing from uncomplicated streptococcal infection. Two to three weeks after uncomplicated streptococcal infections, sera from the latter had little or no heart reactive antibody, whereas, sera from patients with acute rheumatic fever had antibodies detectable at a ten fold dilution. The presence of these high titers of heart reactive antibodies has been an important additional diagnostic tool in cases of suspected rheumatic fever. Also these has been helpful in the differential diagnosis of other rheumatic disorders eg. systemic lupus erythematosus (Zabriskie et al.,1970).

Serial studies of the sera obtained from patients with acute rheumatic fever reveal that the antibody titers decline rapidly during the first 3 to 6 months after the initial attack, then more gradually over the next 2 to 3 years. At the end of 5 years the vast majority of patients