THE TOXICOLOGIC BRUNT OF SOME ANTIRHEUMATIC DRUG COMBINATIONS

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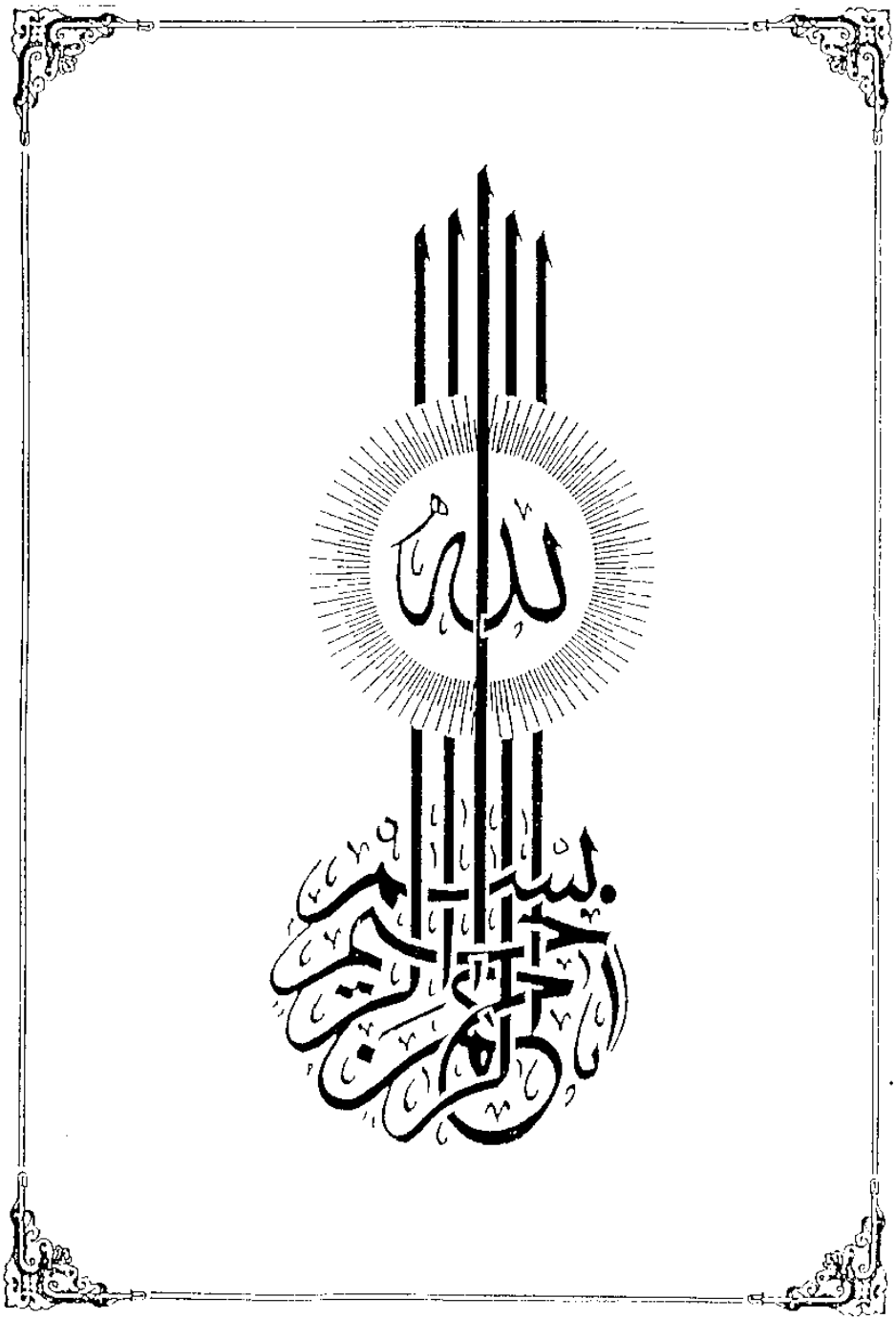

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OBJECTIVE

O B J E C T I V E

Rheumatic diseases, are chronic ailments, known since ancient times, affecting a considerable number of the population, and to which medecine are prescribed to the patients to alleviate their pains. In the field of rheumatology, the choice between antirheumatic drugs is largely empirical, since a large variation in the response of individuals to the different anti-inflammatory agents do exist (Goodman and Gilman, 1980).

Self prescription is becoming a new chalenge, favouring the untoward reactions of these drugs and often escaping the medical supervision. Patients suffering from rheumatic diseases exchange their experience with these medicines, shifting from one drug to another and often taking more than one antirheumatic agent to get a better relief without medical consultation. In addition, a beneficial effect gained on a short term therapy might produce toxic effects on long term therapy. We are sorry to admit that such a hazardous combination invaded the medical prescription. This iatrogenic ethusiastic use, whether by dose augmentation, combination with drugs or continuance of administration could prove to be toxic.

This present study aims to depict the toxic hazards of three commonly used anti-infammatory agents and to reveal the subchronic toxicity resulting from different drug combinations as compared with the toxicity of individual drugs. Phenylbutazone, indomethacin and ketoprofen are experimented upon for the popularity they gained in the treatment of rheumatic diseases and other non rheumatic medical illnesses. Phenylbutazone deserves a special reputation in the treatment of superficial thrombophlebitis and is the drug of choice in muscle sprains and trauma. Indomethacin was as well included in this work for the popularity it gained in the treatment of rheumatic diseases, as well as for the reputation in its ability to alleviate dysmenorhea and produce remissions in glomerulonephritis (Vihert et al, 1973). The recently introduced drug, ketoprofen, is as well assessed for its possible toxic effects.

Haematotoxic, hepatopathic and nephropathic effects of these drugs are going to be looked for.

The first part of this thesis will be concerned with reviewing the pharmacological and toxicological profile of the chosen antirheumatics. The experimental design and its implementation is to be presented. The results of the

subchronic toxicological experimentation will be documented, statistically analysed and discussed to arrive to a pertinent conclusion on the toxic hazards of the single and combined antirheumatics as executed on the experimental animal.

INTRODUCTORY REVIEW

HISTORICAL REVIEW

Sementically, the term antirheumatic is composed of, the work "rheum". It originated from the Latin "rheuma" which literally means "flow" or "flux" denoting the discharge from the nasal and conjunctival mucosa. The Latin rheumatismus is defined by Webster (1973) as any of various conditions characterised by pain in muscles, joints, or fibrous tissues. Guillaume de Baillou, the father of rheumatism was the first who coined this term in his work "liber rheumatismus" published in 1642 (Copeman, 1970).

In the ancient times, man tried to alleviate his "douleur" by mystic, physical then actual therapeutic agents. The goddess Hygie was worshiped by the Greeks because they though that she offered health and relief. Antiphlogistic measures were used to ameliorate pain and inflammation. This term was derived from the Greek "phlogistos" or inflammable because the root "phlog" means flame. Hot water bathes were used as well to relieve painfull conditions by Egyptians and all civilisations around the Egan sea where remains of the bathes masonry dates back from 3000 to 1200 B.C. (Arabic Encyclopedia, 1953). The use of turkish steam baths and hot water dips were in common practice as antirheumatic physical measures since the third century A.H. untill now. Therapeutic

exercises in water is one form of treatment for rheumatic joint diseases. The buoyancy of water relieves pressure on the joints, making movements easier (Miller, 1965). physical methods of treatment advocated by Greeks and Romans, may have approximated to modern practice so far as hydrotherapy, counterirritation, soothing local applications and massages are concerned.

The drugs which were put to use in the eighteenth and nineteenth centuries included sulfur, guaiacol, colchicum and quinine. Colchicum autumnal was first recommended by Alexander of Tnalles (525-605), subsequently forgotten, but reintroduced by Von Stork in 1763. Its active principle, the alkaloid colchicine was discovered in 1820 (Copeman, 1970). Acetylsalicylic acid was later employed in the treatment of rheumatic pains in the form of herbal preparations containing the shrub Spirae, and hence the name Aspirin (Webster, 1973).

Phenylbutazone, a congener of antipyrine and aminopyrine, was employed originally as a solubilizing agent of aminopyrine. It was introduced in 1949 for the treatment of rheumatoid arthritis and allied disorders (Goodman and Gilman, 1975). It was widely used in doses up to 1200 mg daily before 1954 when the first reports of bone marrow depression, and agranulocytosis were published. A reluctance to use the drug became prevalent in the late 1950's

untill it became apparent that the bone marrow reaction was most often dose-related, and that smaller amounts could be used safely and effectively for relatively long periods of time (Kantor, 1977).

Chinese herbal medicines, imported illegaly, gained great popularity in USA during the early 1970's. They were widely used for the treatment of arthritis, rheumatic and back pains, for promotion of circulation, for sexual rejuvenation and as a general tonic. The medicines were said to contain a wide variety of Chinese herbs and other organic substances including scorpion powder, tiger bones, rhinoceros horn, turtle shell and male mouse droppings. Life threatening agranulocytosis, occured frequently while taking these herbal preparations since they were shown to be adulterated with both aminopyrine and phenylbutazone to ensure symptomatic improvement in the treated individuals. This urged local authorities to withdraw these highly dangerous preparations from the American market (Ries and Sahud, 1975). Phenylbutazone was also known as "bute" among racetrack personnel, jockeys, and trainers. Its abuse for muscle aches and bruises is not surprising considering its easy availability and effectiveness (Ramsay and Gold, 1975).

Indomethacin was the product of a laboratory search for drugs with more effective anti-inflammatory properties and musch less toxic potential. It was introduced in 1963 for the treatment of rheumatoid arthritis and related disorders (Goodman and Gilman, 1975).

Keptoprofen, of research designation 19.583 R.P. belongs to the group of new non steroidal anti-inflammatory drugs, which have been developed during the past few years. The compound has been synthetised by Farge, Messer and Moutonnier (French Patent 1546478) in 1967 and the basic research ofthe biodchemical and pharmachokinetic properties has mainly been carried out by the Rhone-Poulenc laboratories research group under the leadership of Julou (Fossgreen, 1976).

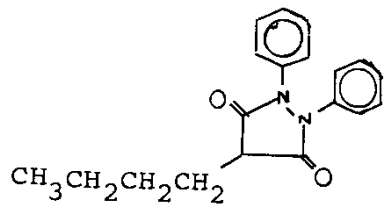
The longstanding reputation and clinical application of the three, comparatively recent antirheumatic, based their implementation in this current research.

PHARMACOKINETICS AND PHARMACODYNAMICS

PHENYLBUTAZONE

Phenylbutazone is a white or almost white, odourless crystalline powder which is tasteless at first but has a slightly bitter after taste. Phenylbutazone is practically insoluble in water, but soluble in aqueous solutions of alkali hydroxides and very soluble in acetone. Its solubility in other media vary, soluble 1 in 28 alcohol, 1 in 1.25 chloroform; and 1 in 15 of ether. (Wade and Reynolds, 1982). On passing the official tests, 11 out of 12 brands of phenylbutazone tablets had disintegration times within the official limits, but dissolution rates in simulated intestinal juice varied widely. Considerable variations in the time at which peak serum concentrations occured, were also observed (Searl and Pernarowski, 1967).

Chemically, phenylbutazone is 3.5-dioxo-1.2-diphenyl-4n-butylpyrasolidine.



(Goodman and Gilman, 1980).

Decomposition of phenylbutazone seems to be directly related to the hydroxyl value of the basis. Decomposition products ranging between 3 and 21%, were found in preparations containing phenylbutazone and aluminium hydroxyde. However, in other prepatations, the percent of decomposition products did not exceed 0.5% in 32 out of 33 brands of phenylbutazone tablets (Wade and Reynolds, 1982).

Routes of Administration and Dosage

Phenylbutazone is administered by mouth in a total daily dose of 200 to 400 mg in 3 or 4 divided doses preferably taken with meals or milk. A sodium-free antacid might reduce the distressing gastric disturbances. Up to 600 mg has been given daily, but a daily dose of 400 mg of phenylbutazone is now rarely exceeded since higher doses seldom produce a greater therapeutic effect, but augment the toxic hazards (Wade and Reynolds, 1982). It has even been claimed that by using doses as low as 200 mg daily the toxic effects can be diminished without loss of therapeutic action (Bruck et al, 1954). When improvement is