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THESIS

Drug-induced neuromuscular disorders

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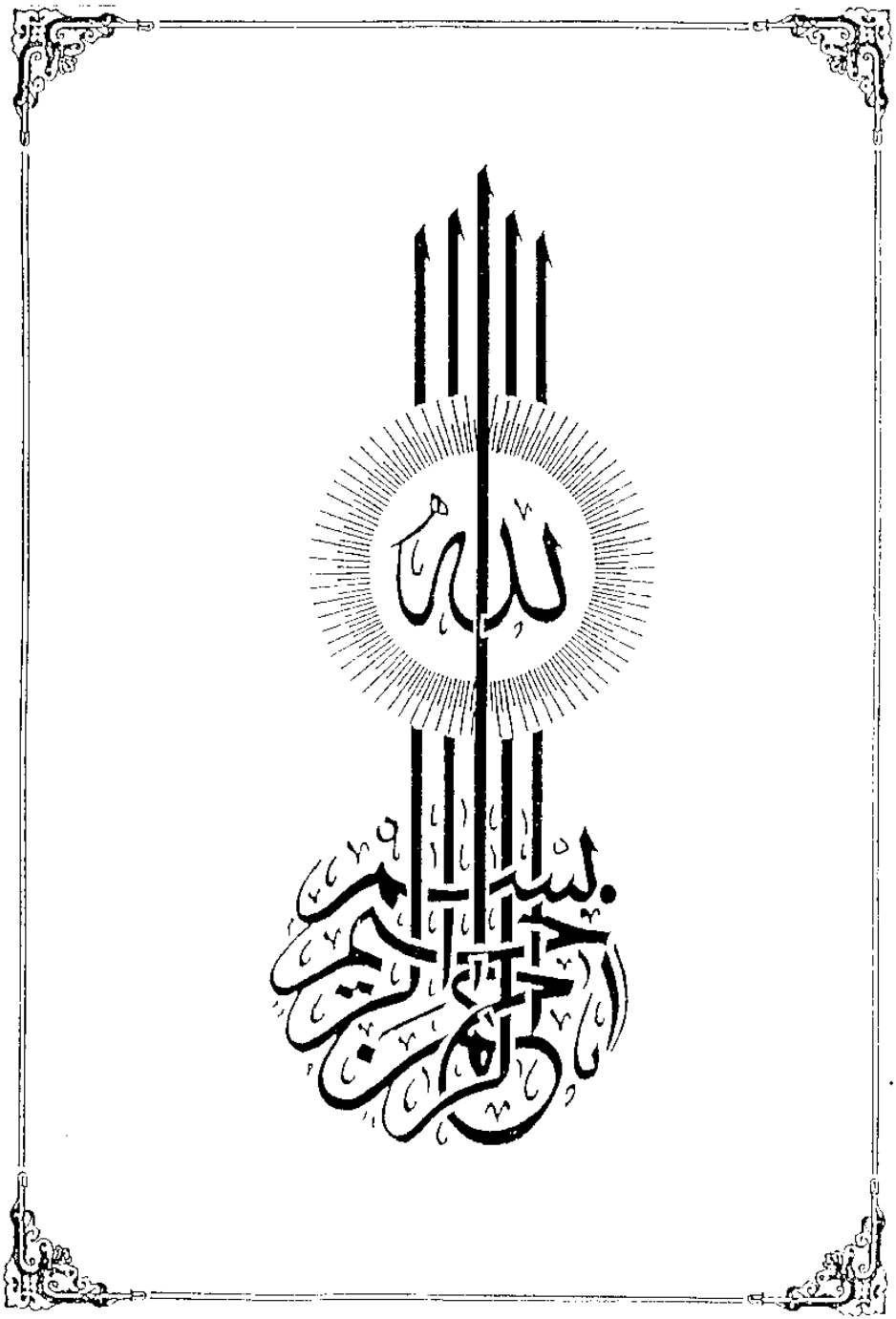

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LIST OF ABBREVIATIONS

cAMP	cyclic adenosine monophosphate
CNS	central nervous system
CPK	creatine phosphokinase
CT	computerized tomography
EACA	epsilon aminocaproic acid
2,4-D	2,4-dichlorophenoxyacetic acid
EMG	electromyography
ESR	erythrocyte sedimentation rate
LSD	lysergic acid diethylamide (lysergide)
MG	myasthenia gravis
MH	malignant hyperpyrexia
NMS	neuroleptic malignant syndrome
SFEMG	single fibre electromyography
SMON	subacute myelo-optic neuropathy
SR	sarcoplasmic reticulum
TCE	trichlorethylene
TOCP	tri-orthocresyl phosphate

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INTRODUCTION

An increasing number of therapeutic drugs, occupational and environmental agents have been recognized to have deleterious effects on the neuromuscular system. Some have a selective effect on the structure and function of muscle (Lane and Mastaglia,1973), while others interfere with neuromuscular transmission (Argov and Mastaglia, 1979a), or are neurotoxic (Argov and Mastaglia,1979b ; Schaumburg,Spencer and Thomas,1983). Certain drugs such as vincristine and chloroquine are both myotoxic and neurotoxic, while others such as D-penicillamine may lead to the development of either a myasthenic syndrome or an inflammatory myopathy through different mechanisms (Mastaglia,1984).

The frequency of drug-induced neuromuscular disorders in clinical practice is difficult to establish, as the association with the drug is not always recognized, and subclinical involvement may be more prevalent than is generally appreciated (Mastaglia and Argov,1981).

Awareness of the possible effects of drugs on the neuromuscular system is of increasing importance both because the range of therapeutic agents introduced into clinical practice continues to expand, and because the resulting syndromes though usually reversible at

the outset, may progress if the offending drug is not withdrawn, and lead to unnecessary morbidity and even to a fatal outcome in a potentially reversible condition (Lane and Kastaglia,1973).

Aim and Methods of the Work

Review of the literature on the drug-induced neuromuscular disorders, the resulting pathological effects and the different clinical presentations ; with the aim of determining the usefullness of the various investigatory procedures intended to be of help in early diagnosis of the underlying pathology.

Chapter 1

ADVERSE REACTIONS TO DRUGS

A drug is defined as any chemical agent, with the exception of food, that is capable of interacting with living organisms to produce biological effects (Gerald,I93I).

Drugs are generally metabolized before excretion. Where as the major proportion of drug metabolic reactions are carried out by tne microsomal enzymes of the liver which are relatively nonspecific in their affinity for different substrates, yet many other tissues have some metabolizing activity (Gorrod,I979). The fate of most drugs undergoing metabolic transformation is conveniently classified into two phases. In phase I compounds undergo oxidation, reduction or hydrolysis. These processes expose or add functionally reactive groups which are tnen available for the synthetic (conjugating) mechanisms of phase II. The activity of microsomal enzymes is one of tne most important determinants of variability in drug response (Smith and Rawlins,I973).

Most adverse reactions to drugs may be classified into one of two groups. The most frequent are those that result from the exaggerated but predicted pharmacologic action of the drug which may result from an abnormally high tissue concentration of the drug due to variability in its pharmacokinetics, or due to enhancement of its pharmacologic effect by concomitant

administration of anotner drug. Other adverse reactions, the so-called idiosyncratic reactions, ensue from toxic effects on cells that result from mechanisms unrelated to the intended pharmacologic actions. These therefore are often unpredictable and frequently severe. Some of the mechanisms of extrapharmacologic toxicity include direct cytotoxicity due to irreversible binding of the drug or its metabolites to tissue molecules by shared electron (covalent) bonds , the initiation of abnormal immune responses through reaction with cellular proteins , and the perturbation of metabolic processes in individuals rendered susceptible by genetic enzymatic defects (Wood and Oates,1933).

Genetic factors affecting side effects of drugs :

Specific proteins are involved in the complex sequence of events determining a particular response to a drug. Genetic differences in the formation of any one of tnese proteins could lead to idiosyncratic reactions (Boobis,1979).

Pharmacogenetic disorders comprise disorders of drug nandling and those of drug response. In disorders of drug handling, an inappropriately high drug concentration in tissues may result from genetically determined alterations in its specific routes of metabolism. An example is tne polymorphism that exists for drug acetylation by the liver enzyme acetyltransferase ,

individuals being either slow or fast acetylators, with considerable racial differences in the frequency of slow acetylation phenotype which ranges from 0.22 in Canadian Eskimos to 0.9I in Egyptians (Boobis, I979). Other examples include defective metabolism of phenytoin, with subsequent toxicity, due to an abnormality of cytochrome P-450 @ dependant mixed-function oxidase activity (Kutt et al., I964) , and the prolongation of succinylcholine apnoea in individuals who have a variant form of plasma cholinesterase with decreased capacity to metabolize succinylcholine (Boobis, 1979).

Disorders of drug response comprise incidents of altered sensitivity to drugs, and atypical drug responses. The latter include incidents of drug-precipitated porphyric attacks in patients with latent porphyria (Boobis, I979) , haemolytic anaemia in subjects with deficiency of glucose 6-phosphate dehydrogenase (Vesell, I972) , and malignant hyperpyrexia (Gronert, I980).

Enzyme induction and inhibition :

The liver microsomal enzymes detoxicate and deactivate drugs , yet they can catalyse the converse reaction and so render drugs more toxic. Repeated dosing with a variety of drugs leads to enhanced activity of these

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@ Cytochrome P-450 is a haem-containing protein that is necessary for the functioning of the liver microsomal mixed-function oxidases.

microsomal enzymes as a result of increased enzyme synthesis. However, high substrate concentration will lead initially to inhibition of these enzymes followed by increased synthesis, hence inhibition and induction are related phenomena. Drugs most slowly metabolized such as phenobarbitone are potent enzyme inducing agents (Parke,1979). Many naturally occurring substances are both inhibitors and inducers of microsomal drug-metabolizing enzymes. Cigarette smoking was found to cause induction of these enzymes (Hart et al.,1976).

Where drugs are being activated instead of detoxicated by metabolism, enzyme induction may enhance toxicity. The long-term administration of enzyme-inducing drugs, with consequent continued high rate of enzyme synthesis, poses a high demand on folate which may not be adequately supplied by dietary intake. Thus induction decreases and toxic effects of the drug become manifest due to its continued high dosage.
This is seen in long-term administration of anticonvulsant drugs which may also cause vitamin D deficiency and osteomalacia presumably due to enhancement of deactivating mechanisms of 1,25-dihydroxycholecaciferol, the biologically active co-enzyme (Parke,1979).