MONITORING DIGOXIN LEVEL IN CARDIAC PATIENTS WITH IMPAIRED KIDNEY FUNCTION

THESIS

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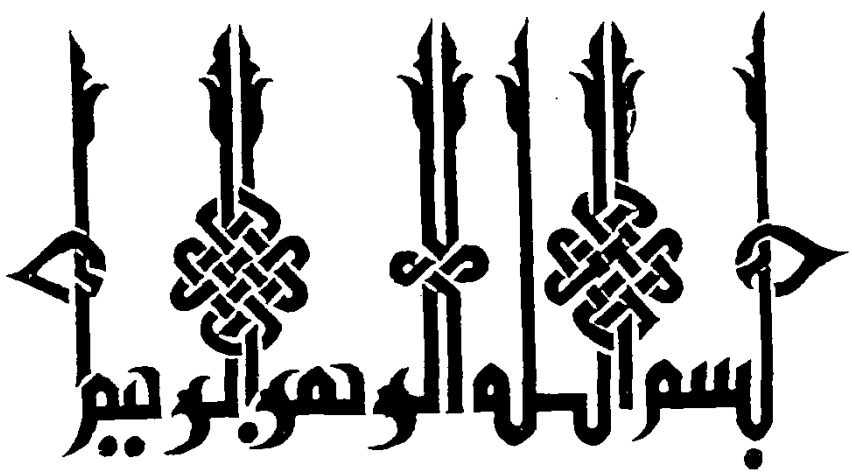

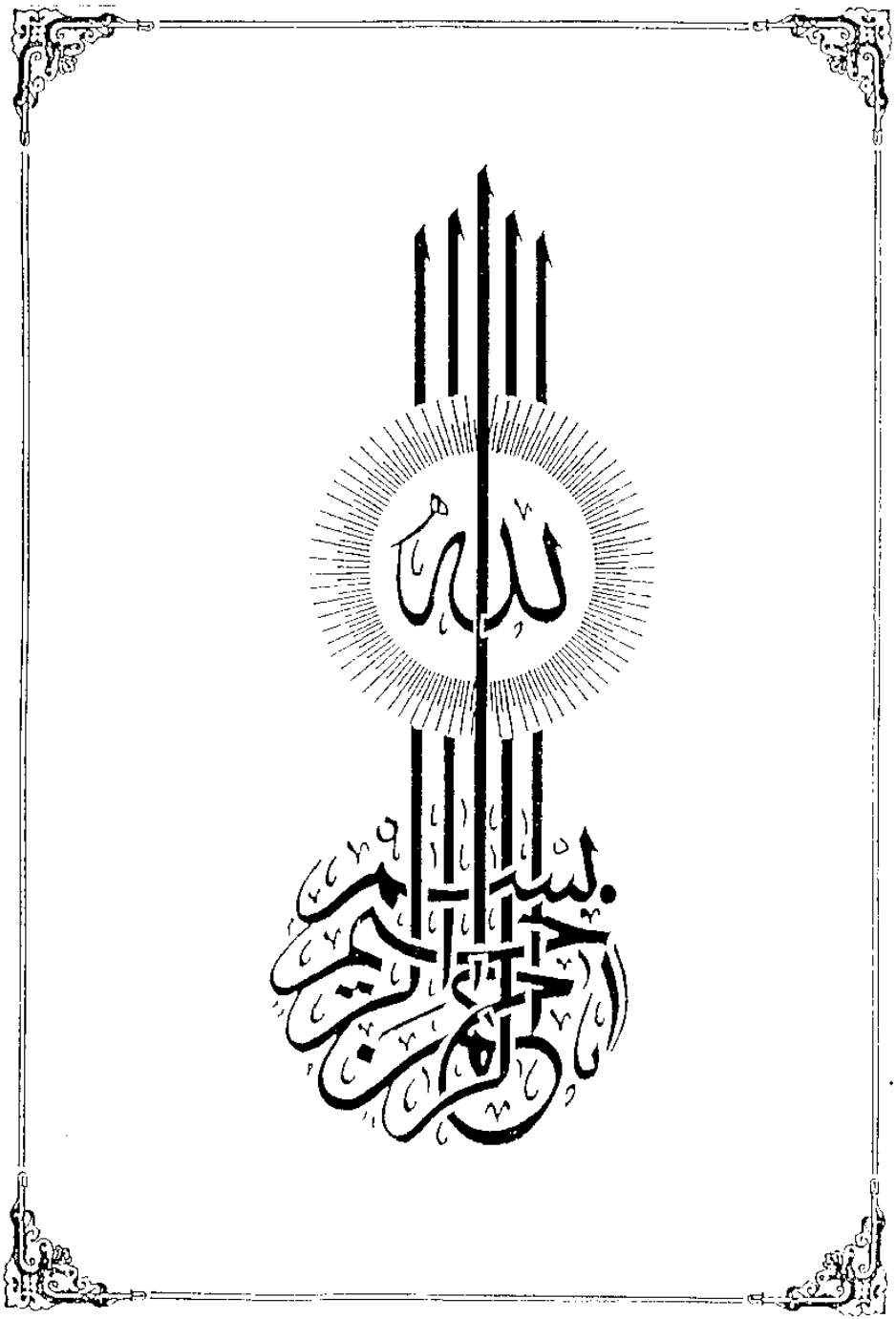

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REVIEW OF LITERATURE

REVIEW OF LITERATURE

Over the past 25 years, more than 500 new drugs have been released worldwide for clinical use . In the wake of their development , knowledge of the mechanism of action and metabolic fate of these and other more established drugs has gradually accumulated (Brodie and Ramsay,1984).

In the last decade, improved techniques for measurement of tissue response, receptor identification and drug assay have resulted in substantial progress in understanding the ways in which drugs act and are handled within the body . Detailed pharmacodynamic and pharmacokinetic data are now available for many drugs in current clinical use . When applied to patient care, this flood of information has the potential for improving prescribing practice by refining the therapeutic use of drugs and avoiding potential toxicity (Brodie, 1984) .

Many of the drugs commonly prescribed can now be detected and measured in plasma and other biological fluids; this is a consequence of the increasing sophistication of laboratory techniques in recent years . Careful studies have shown good correlations in normal volunteers and patients between serum concentrations and the intensity of pharmacological effects of many important drugs (Tognoni et al.,1980).

The relationship between drug concentration and effect has fostered the study of the factors influencing drug movement in the body i.e., pharmacokinetics . Pharmacokinetics is the mathematical description of the line course of drug absorption, distribution, metabolism and excretion. It aims to relate these parameters to the therapeutic and adverse effects of drugs . Clinical pharmacokinetics has proved particularly valuable for those drugs with a narrow margin between toxic and therapeutic effects and a close correlation between plasma concentration and toxic or therapeutic effects (Brodie , 1984) .

Pharmacokinetics and drug monitoring are very useful in assessing patient compliance, enable drug regimen to be tailored to the needs of individual patient and help to explain treatment failures and unexpected adverse effect (Campbell, 1981 and Brodie, 1984) .

Many drugs are excreted unchanged by the kidney, and others have active or toxic metabolites that require renal excretion . In patients with renal failure, adjustment is often necessary to achieve safe but effective therapy . In addition, the biochemical derangement present in renal failure may modify a drug's bioavailability, distribution , pharmacological action or elimination (Bennett et al., 1980) .

The cardiac glycoside digoxin and its metabolites are normally excreted largely in the urine (Gault et al.,1979). In renal impairement, firstly there is diminished excretion of digoxin and secondly there may occasionally be a diminished apparent volume of distribution (Gault et al., 1980) . Both of these effects result in increased plasma digoxin concentration at a given dose . Plasma concentration of digoxin may be useful in determining correct dosage or when there is concurrent administration of either quinidine or of spironolactone (Aronson, 1981) .

Principles of Therapeutic Drug Monitoring

Individual variations in the response to drugs are well recognized. A dosage regimen may be effective in some patients while being ineffective or toxic in others. However, for virtually all drugs, the achievement of optimal therapy i.e., the maximum efficacy without undue toxic effects, requires that drug administration be tailored to the individual patient's requirement . This has been most commonly achieved by monitoring clinical drug effects .

Unfortunately, there are many drugs and clinical settings for which patient response is not constantly available or reliable guide to optimal dosage . The intensity of pharmacological effect of such drugs can not be readily quantified in clinical practice (Mira et al., 1985) . An alternative method of monitoring drug therapy is by measurement of the drug concentration and/or its active metabolites in blood or plasma and , in certain circumstances, its concentration in saliva, urine or cerebrospinal fluid (Benvenuta et al., 1978; Dykeman and Econbinchon, 1979; Danhof and Breiwe,1983).

Although drug levels vary among different patients, a given dosage regimen yields remarkably constant serum levels in the same patient. The relative constancy of drug serum levels in the same individual, together with a common range of therapeutic concentration, form the basis of therapeutic drug level monitoring (Sadee, 1980) .

Determination of the serum concentration of drugs can be useful in the management of intoxications, for the detection of non-compliance and in bioavailability studies . However, their value is far less uniform in pharmacotherapy (Koch-Weser, 1981). Determination of serum levels is unnecessary for drugs whose dosage not need be individualized or whose intensity of action is readily monitored in clinical practice (Koch-Weser, 1980) . Even for many drugs whose dosage should be individualized and whose intensity of action is difficult to judge, serum concentration information is unfortunately of little value ; The reason lies in the fact that serum concentration is not predictably or constantly related to the intensity of the pharmacological action (Koch-Weser, 1981) . There are few people who are quite sensitive to the therapeutic effect of most drugs, responding to lower levels, whereas others are sufficiently refractory . Serum drug concentration determinations become useful as clinical guide only when the range of therapeutic concentrations has been established . This is particularly so when there is a narrow range between the plasma levels yielding therapeutic and adverse effects(Oates and Wilkinson, 1987) .

The clinical usefulness of the relationship between serum concentration and effects has been accomplished for many valuable drugs. These include cardiac glycosides (Weintraub, 1977), major antiarrhythmics (Ochs et al., 1980) , and

anticonvulsants (Amdisen, 1977), many other psychoactive agents (Amesterdam et al., 1980), theophylline (Ogilvie, 1978), a few anti-inflammatory drugs and many antibiotics (Barza and Lavermann, 1978) . However, it should be mentioned that a drug level is virtually impossible to interpret without additional information including the dosage regimen, the compliance of the patient, the length of time the patient has been taking medication , the method of administration , the time of sampling, other drugs being taken , and the method of assay used (Brodie, 1984) . Accurate and precise timing, both in administering the drug and obtaining each blood sample, are of utmost importance in therapeutic drug monitoring (Mira et al., 1985) . However, a concentration of drug measured in a sample taken at virtually any time during the dosing interval will provide information that may aid in the measurement of drug toxicity. During long-term therapy, blood samples should be taken in the steady state, i.e. after treatment with a constant dose over at least 4 half-lives . Concentrations of drugs in samples obtained shortly after administration can be uninformative or even misleading . This is the case when changes in the effects of drugs are delayed relative to change in plasma concentration because of a slow rate of distribution or pharmacodynamic factors. When the goal of measurement is adjustment of dosage regimen, the sample should be taken just before the next planned dose, i.e. when the concentration is at its minimal value . There is an exception to this approach.

Some drugs are nearly completely eliminated between doses and act only during the initial portion of each dosing interval . For such drugs, determination of both maximal and minimal concentrations is recommended especially when low clearance is suspected as in cases of renal failure (Benet and Sheiner, 1985) . Individual variations do exist in the relation between dose administered of a drug and its serum concentration achieved . This can be explained on pharmacokinetic basis . It is clear that pharmacokinetic process of absorption, distribution, biotransformation and excretion of most drugs are highly variable among patients and in the same patient with time . This process is influenced both by the genetic make up of the individual and by a host of environmental factors, including the effects of the disease and of concomitant administration of other drugs (Weser , 1975; El-Sayed and Sadee, 1983) .

Other difficulties of interpretation of drug concentrations arise from problems with specificity of assays. Some assays for drugs measure not only the active compound but other substances or metabolites as well . When this is so, the usual relationship of concentration to effect may appear to change over time (e.g. as metabolites that are devoid of metabolic activity accumulate) . The opposite results from

accumulation of active metabolites that are not measured by a specific assay . As specific and sensitive assays for drug and metabolites are developed, such problems should decrease (Benet and Sheiner, 1985) .

Gas chromatography is essentially a method of separating mixtures of similar substances in order that one or more of those substances may be analysed qualitatively or quantitatively (Wicks and Toseland, 1981) . Gas liquid chromatography techniques were further refined and improved . More recent advances in the development of detectors, particularly the nitrogen phosphorus detector, have improved the sensitivity of the instruments to such an extent that microsampling by gas liquid chromatography is now possible on a routine basis . Nitrogen detection serves as a successful means of monitoring nanogram quantities of drugs and has been applied to therapeutic drug monitoring of antiepileptic, anti-arrhythmic and anti-depressant drugs . One of the major disadvantages of gas liquid chromatography had been the complexity of the instrumentations, which necessitated a highly trained and skilled analist (Pippenger, 1979).

The development of radio-immunoassay techniques permitted quantitation of drug concentrations in microvolumes of serum.