COMPARATIVE PHARMACOKINETIC STUDY OF PIPECURONIUM AND ORG (9426) IN NORMAL AND IN PATIENTS WITH HEPATIC INSUFFICIENCY

THESIS
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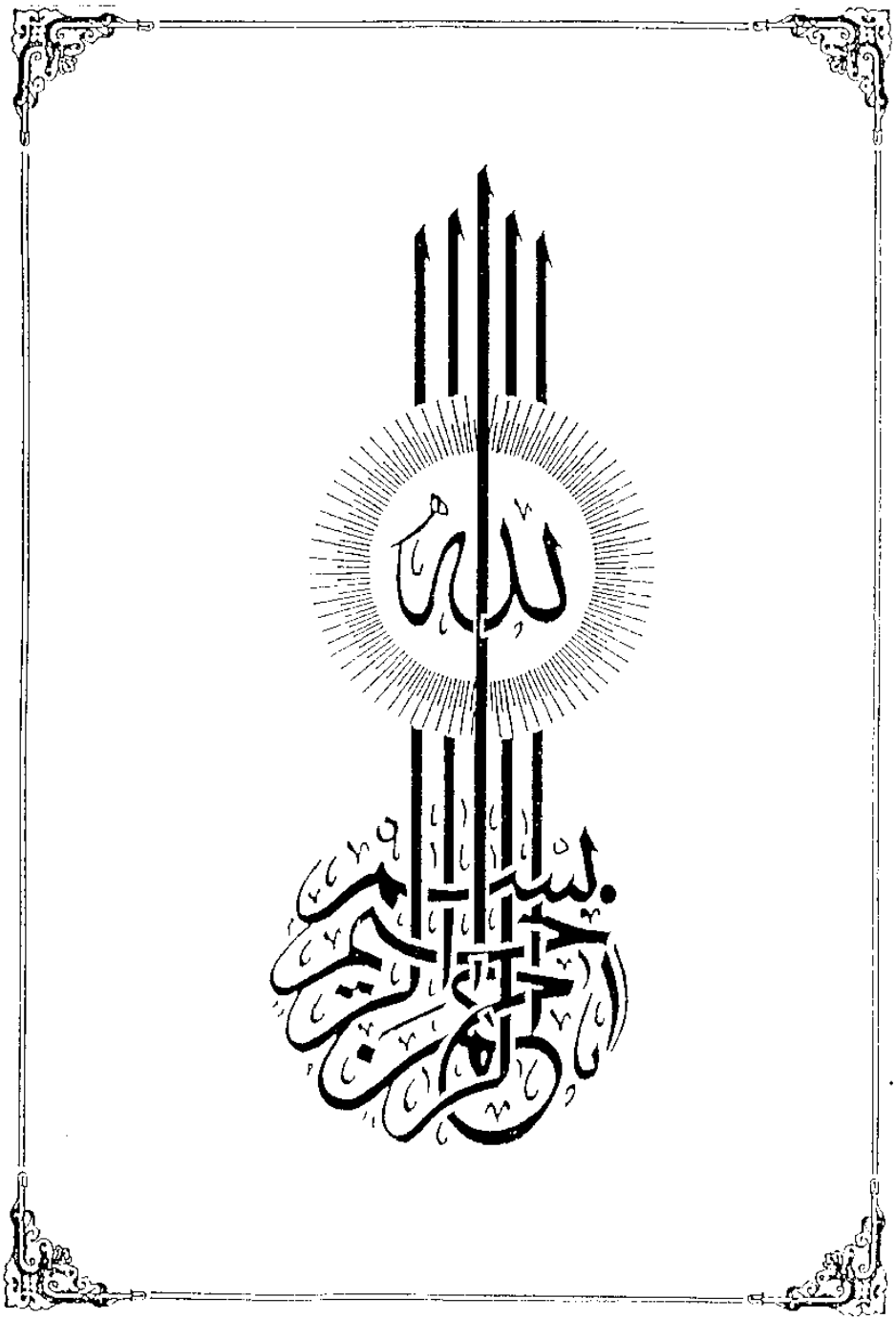

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CONTENTS

INTRODUCTION

[INTRODUCTION]

Neuromuscular blocking agents , have got an impressive impact in the development of anaesthesia and surgery. When Griffith and Johnson introduced curare into clinical practice in 1942, they revolutionised anaesthetic practice . During the years which followed the introduction of d.tubocurarine there was continuous research for an ideal relaxant that would have the following characteristics :

* Short, noncumulative .
* Non depolarising .
* Rapid onset and recovery .
* Reversible by an appropriate antagonist.
* Lacking clinically important side effects.

Pipecuronium and Rocuronium are non-depolarising muscle relaxants with steroid nucleus which resemble pancuronium and vecuronium respectively. Pipecuronium has the advantage of being devoid of haemodynamic secondary effects where rocuronium has the advantage of rapid onset of action that may approach succinylcholine.

The response to muscle relaxants is often altered in patients with liver disease, Increased resistance and prolonged effect are the two main anomalies reported in patients with hepatic dysfunction. The mechanism that explains this different behaviour was :

(1) Reversed Albumin /Globulin ratio .

(2) Sequestration of muscle relaxants in huge liver and spleen .

(3) Decreased liver blood flow during anaesthesia and surgery.

Different pharmacokientic studies of muscle relaxants in patients with hepatic dysfunction which showed differences in pharmacokientic parameters .

Also, recent studies in man proved the excretion of important amount of vecuronium in bile.

Pharmacokinetics of Drugs Administered Intravenously

Pharmacokinetics is the quantitative study of drug disposition in the body. It includes processes of ***absorption***, from site of administration ***distribution*** to body tissues and fluids, ***biotransformation*** to pharmacologically active or inactive metabolites and ***excretion*** of the drug and its metabolities from the body.

Drug Disposition

It is generally true that there is a direct relationship between the dose and the resulting concentration of a drug at its site of action and the intensity of its actions. This relationship can be represented as follows :

Drug (concentration)+ Receptor ⟶ Drug receptor complex ⟶ EFFECT

Under ordinary circumstances of acute drug therapy the number of available receptors is constant and the effect is dependant only on concentration of the drug at its site of action that could be represented by plasma concentration.

[Factors Affecting plasma concentration]

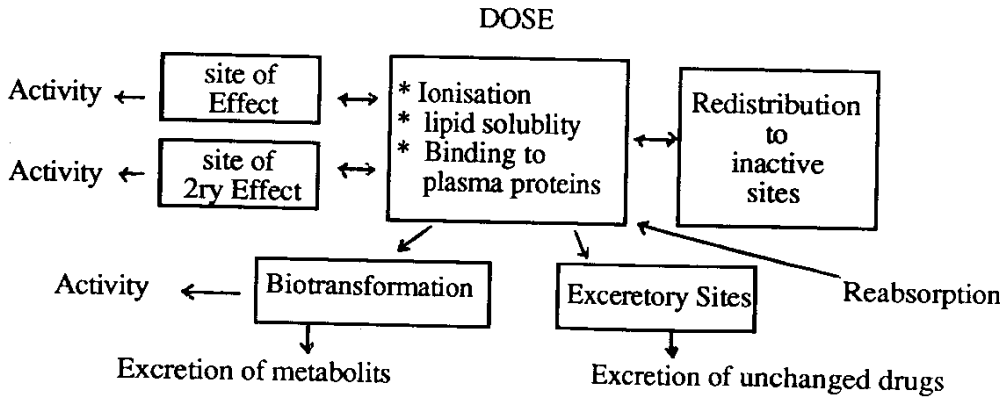

Fig (1) Some of possible pathways for the uptake, distribution and elimination of an active drug (Hull 1979)

Three factors determine drug plasma concentrations :

A) **Mode of drug administration and its physicochemical properties :**

In cases of single bolus dose administered intravenously plasma level depends on the dose size. The progressive decline in plasma concentration occurs because drug enters body tissues and organs. Thus the major determinant of exit of drug from plasma is the rate at which drug penetrates biological membranes. By far most drugs penetrate most membranes by dissolution and diffusion in the lipoproptein matrix of membranes .

The physicochemical properties that govern the rate of diffusion of drugs across membranes are :

1- Lipid Solubility:

This is the most important property, the greater the lipid solubility, the more rapidly the drug penetrates all types of membranes.

2- Ionisation :

Ionisation of a drug limits its rate of penetration because ionisation both reduces its lipid solubility and cause it to be repelled from similarly charged portions of the membrane or attracted and bound by oppositly charged membrane components. Ionisation is complete for certain drugs (e.g) muscle relaxants with quaternary nitrogen atom and is partial for weak acids or bases with a pK close to the range of pH values found in physiological fluids.

3- Molecular size :

Molecular size is a feature of considerable importance in terms of penetration of membranes by way of pores. Capillary membranes restrict the penetration of large molecules such as proteins. Almost all drugs are bound to some degree by plasma proteins, especially albumin. It is the unbound i.e free drug which diffuses across membranes and causes the effect .

B) **Uptake of drugs by body tissues :**

The uptake of drugs by tissues can be characterised in terms of *rate* and *capacity* . **Blood flow determines the rate of delivery** of the drug to and removal from tissues. Immediatly after intravenous injections when the plasma concentration of the drug is highest, the entry of the drug into tissues is most rapid . As soon as some of the drug enters the tissue, the concentration gradient is reduced and the rate of entry slows. As the concentration builds up in tissue and continues to fall in plasma a point will be reached at which the concentrations in plasma and tissues are equal . With continous elimination of the drug from plasma, the gradient will be reversed and the net exchange of the drug will be from tissue to plasma . **Factors that determine the capacity are** the tissue plasma partition coefficient which represents the affinity of the tissue for drug and can be estimated by dividing the drug concentration in the tissue by that in plasma at steady state. It is important to note that the capacity is a function of both the partition coefficient of the drug and the mass of the tissue . Thus skletal muscles may have only a moderate affinity for a drug compared to other tissues, but they nevertheless assumes a dominant role in the disposition of most drugs because of its large mass (50% of body weight) .

C) **Elimination of drug from the body :**

The processes of elimination include *biotransformation* and *exerction* . They begin almost immediatly after drug administration.

* **Biotransformation :**

The liver is the primary site of biotransformation. The aim of biotransformation is to transform lipid soluble drugs into water soluble ready for urinary excretion. Metabolities may be active or completly inactive. The intrinsic rates of biotransformation reactions are determined by a large number of factors affecting enzymatic activity and cofactor

avaliability e.g, (genetics, presence of other drugs, nutrition and hypoxia).

* **Excretion :**

Excretion of drugs in urine by the kidney removes them from the body The rate of excretion is determined by renal blood flow and by the rate of three renal processes *glomerular filteration, tubular secretion* and *tubular reabsorption.* Free drugs pass through the glomerulus at a rate dependent on its concentration and on the volume of the glomerular filterate. Tubular secretion involves active transport processes which are selective for certain drugs and drug metabolites . Tubular reabsorption removes drug that has entered tubular fluid by glomerular filteration and tubular secretion. One frequent consequence of biotransformation is the production of more polar compounds less able to penetrate cell membrane i.e less susceptible to renal tubular reabsorption.

KINETICS

Kinetics can be defined as the rate of change and can be expressed as units of amount per unit of time .

* **Linear Kinetics**

First order kinetics i.e the rate of change in drug concentration is dependent on drug concentration.

$$\frac{dc}{dt} = - kc$$

Where C = Concentration of the drug

k = first order rate constant

t = time .

If the concentration is plotted against time in logaritmic manner the equation will be .

$$\log C_t = \log C_o - \frac{kt}{2.303}$$

Where C_t = Concentration at any time .

C_0 = Concentration at time 0

2.303 = Conversion factor for common logarithms.

K = Rate constant

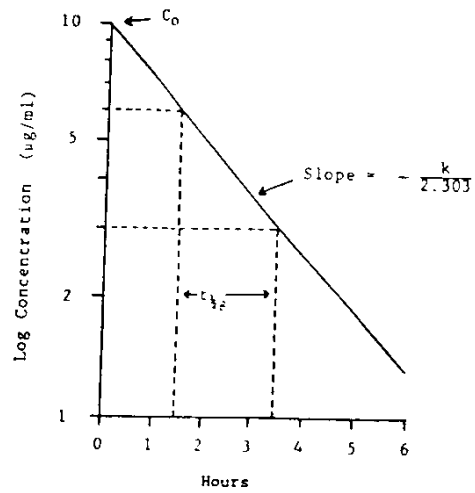

Fig. (2) First order process (Hug C.C . 1978).

First order process is often described in terms of its half-time rather than by its rate constant (k) . The half time of a first order process can be estimated graphically by choosing any point on the straight line and measuring the time interval to a point representing one half that value on the same line .

$$t_{\frac{1}{2}} = \frac{0.693}{k}$$

Where k is the first order rate constant and 0.693 is the natural logarithm of 2 .

The Two Compartment Pharmacokinetic model :

The first major assumption of the two compartment model is that the body can be resolved into a central compartment of small apparent volume and a peripheral compartment of large apparent volume . Fig (3) These compartments do not necessarily correspond to specific anatomic entities.

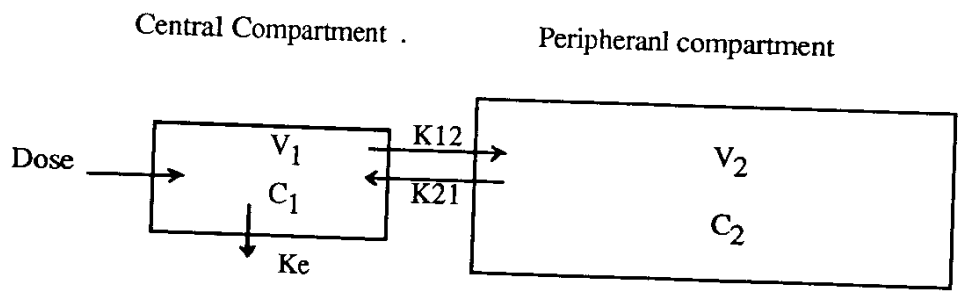

Fig.(3) Schematic diagram of the two-compartment open model C + C_2 represent drug concentration in, V_1 and V_2 represent apparent volumes of central and peripheral compartments. K_{12} and K_{21} are first order rate constants of drug transfer between central and peripheral compartments. Ke is the first order rate constant for drug elimination from the central compartment. (David et al., 1975)

Principles of Pharmacokinetic analysis :

The simplist method of drug administration for pharmacokinetic analysis is very rapid administration of a single dose (D) directly into the central or serum compartment. Assuming instantaneous distribution throughout the central compartment, the concentration there (C_1) immediatly after injection is equal to the dose divided by the volume of central compartment . At the same time the drug concentration in the peripheral compartment is zero thus :

at time 0, $C_1 = D/V_1$ and $C_2 = 0$

A plot of the logarithm of C_1 versus time yields a curve with two distinct linear components Fig (4) .

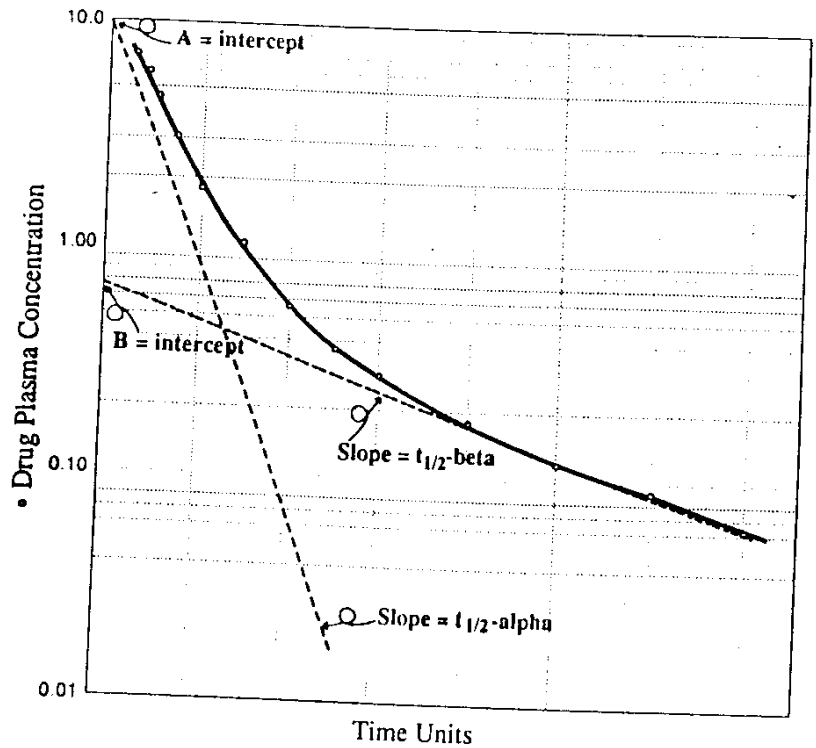

Fig. 4. Computer simulation of a drug with two-compartment kinetics. The curve displays the expected plasma drug concentrations on a logarithmic concentration scale versus time. Two distinct phases of drug plasma concentration changes are visually apparent: the initial rapid decline in drug level during the distribution phase and the slower decline in concentration during the elimination phase. (Hug . C.C. 1978)