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TOWARDS OPTIMAL UTILIZATION OF DRUGS

By

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1. INTRODUCTION

Mr. Vice-chancellor, Sir, distinguished ladies and gentlemen, it is with pleasure and immense gratitude to God that I stand before you today to deliver this inaugural lecture. In the Department of Pharmaceutical Chemistry there are sub-specialties of which Biopharmacy is one. This is an aspect of Pharmaceutical Sciences encompassing Pharmaceutical Analysis, Drug Metabolism and Pharmacokinetics. Thus, Biopharmacy, which is my area of specialization cuts across other disciplines in biomedical sciences. Such inter-disciplinary approach is necessary where the research thrust is geared towards generation of knowledge relevant for optimization of the therapeutic utility of drugs.

Let me begin by posing the question: What is a Drug? A drug is any substance (other than a food or device) intended for use in the diagnosis, cure, relief, treatment, or prevention of disease or intended to affect the structure or function of the body. Since drugs are chemical compounds, their actual names are usually too complex and cumbersome for general use. So usually, an official body assigns a simple name to a drug and this is called its generic name.

The success of drug therapy is highly dependent on the dosage regimen design. In the design of an appropriate dosage regime, the objective is to achieve drug concentration at the site of action that produces an optimal therapeutic response with minimum adverse effects. Optimization of drug therapy is dependent on a good understanding of the principles of **Pharmacokinetics, Biopharmaceutics** and **Pharmacodynamics**. A brief introduction of these concepts is required to facilitate comprehension of this lecture.

1.1 Basic Concept of pharmacokinetics

The word "pharmacokinetics" is derived from 'pharmacon' which is a Greek word for drug, and kinetics. Its ordinary meaning therefore is the time-related movement of drug within the body. Thus, pharmacokinetics deals with the fate of a drug in the body or how the body handles a drug following administration. When a pharmaceutical dosage form is

administered, the following steps take place (Fig 1): (a) If the drug is not introduced directly into the vascular system, it must then be absorbed. (b) This process is followed by the drug distribution through the blood and different body fluids, to various tissues and organs of the body, including the site of drug action. One might ask the question: *How does the drug know where to go after absorption?* The physicochemical property of the drug and the physiology of the body guide the distribution of the drug. E.g. If a drug is lipophilic, it tends to distribute more to tissues with high lipid amount. (c) Since the drug is also distributed to organs that can excrete or metabolize them, these two processes (metabolism and excretion) also contribute in determining the fate and duration of drug activity. All the events are dynamic and intertwined, and the demarcation into phases is, with regard to the process that is dominant at each stage. Drugs undergo metabolism, primarily within the liver, to produce more soluble forms as a means of activation or inactivation and subsequent elimination through renal excretion.

The principles of pharmacokinetics are applied in different disciplines. In Biopharmacy, pharmacokinetics is employed for the development of a drug dosage regimen and for optimization of drug therapy in which the dose, dosage regimen, or dosage form may be altered to produce the desired drug concentration in the body.

Two basic approaches have been used to evaluate how much drug and how often to administer it for a given therapeutic purpose. One of the approaches is the empirical approach which involves evaluation of therapeutic response following the adjustment of both dose and dosing interval. After experience with a sufficient number of subjects, fairly accurate predictions can be made. The disadvantage with this approach is that much information must be gathered and in the process, some dosage regimen may have produced toxicity while others may have been ineffective. The second approach is the kinetic method and it is based on the principles of pharmacokinetics.

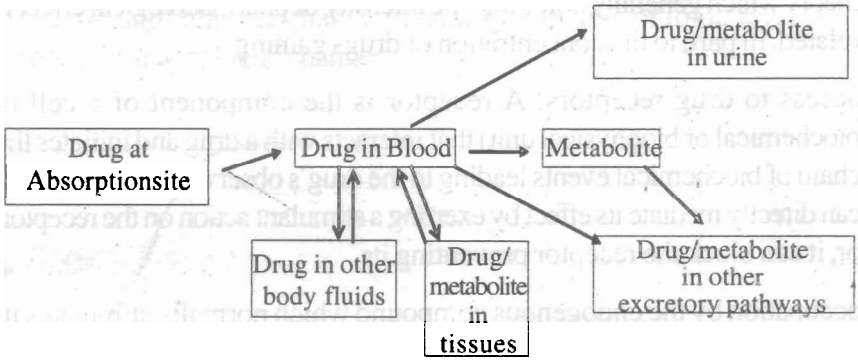


Fig.1: A scheme depicting the relationship between the different processes involved in drug disposition.

1.2 Basic concept of Biopharmaceutics

Generally, drugs are combined with other excipients in the process of drug formulation, which may be a solid or liquid dosage form. The formulation or finished dosage form in which the active drug is contained is referred to as the *'drug product'*. It has since been known that the way a drug product is prepared could affect the potency of the active drug. This led to the development of the field of Biopharmaceutics. This is the study of the relationship between the physicochemical properties of the drug and the formulation variables on the delivery of the drug to the body. Thus, a major concern in Biopharmaceutics is the *bioavailability* of the drug which refers to the rate and extent to which the active drug reaches the systemic circulation. Biopharmaceutics studies allow for rational design of drug products with the aim of enhancing the delivery of the active drug and thereby optimize the therapeutic efficacy of the drug.

1.3 Pharmacodynamics

The term pharmacodynamics specifically refers to the relationship between plasma concentration and pharmacological or toxicological effects of drugs.

Put simply, it may be considered as "what a drug does to the body" while pharmacokinetics may be considered as "what the body does to a drug". Pharmacodynamics is linked to pharmacokinetics by the drug-receptor theory which generally holds that the intensity of pharmacological effect is related, in part, to the concentration of drugs gaining

access to drug receptors. A receptor is the component of a cell (a biochemical or biophysical unit) that interacts with a drug and initiates the chain of biochemical events leading to the drug's observed effects. A drug can directly mediate its effect by exerting a stimulant action on the receptor, or, it can block the receptor preventing its

occupation by the endogenous compound which normally stimulates it. As the drug dose increases, the concentration of drug at the receptor site increases, and the pharmacological response (effect) increases up to a maximum effect. (Fig 2). For many drugs, the plot of log dose or log concentration versus response shows a linear relationship between 20 to 80% of the maximum response, and this includes the therapeutic range of many drugs. Thus, a mathematical relationship can readily be established between *response* and drug *concentration.*

Drug response profile of a drug can change over time in an individual. The factors responsible are related to what are called **'Receptor dynamics':** Receptors may undergo dynamic changes with respect to density (number of receptors per cell). This is caused by continuous or repeated exposure to a drug resulting in reduction in the number of receptors (down-regulation), or an increase in the number of receptors (up-regulation). Down-regulation is responsible for **pharmacodynamic tolerance** where increasing doses of a drug are required to produce a given magnitude of effect. The rapid development of pharmacodynamic tolerance is called **tachyphylaxis.**

It is important to understand the pharmacodynamic characteristics of a drug so that it would be possible to determine whether an observed change in drug response is due to pharmacokinetic factors such as change in elimination or distribution, or due to pharmacodynamic factors such as tolerance or tachyphylaxis. If there is a therapeutic failure and plasma

drug concentrations obtained following standard dosage regimen are monitored and found to be within the therapeutic window, then the cause of the failure is attributable to pharmacodynamic changes. On the other hand, a standard regimen that yields sub-therapeutic or toxic levels is linked to pharmacokinetic changes.

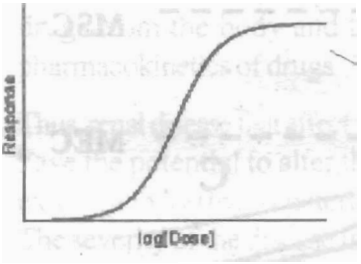


Fig. 2: Typical Dose versus pharmacological response (effect) relationship

1.4 Need for Optimization of drug therapy

Doses and dosage regimen are designed so as to achieve serum concentrations that are maintained within the therapeutic range for the drug. The therapeutic range is defined as the range of serum drug concentrations associated with the desired therapeutic effect and a low risk of toxicity in the majority of patients. Pharmacokinetics of drugs are affected by:

(a) age (infants and elderly);

(b) different diseases states (eg renal impairment, hepatic dysfunction, congestive heart failure, some infections etc);

(c) body weight (e.g. obesity);

(d) some physiological conditions (e.g. pregnancy);

(e) drug-drug interactions, and

(f) genetic differences in drug metabolism.

When standard doses are administered in these conditions, there are bound to be variations in drug response since the pharmacokinetics of the drug are altered by the conditions. The possible alterations in plasma drug levels

are depicted in Fig. 3. This necessitates determining a dosage regimen that is appropriate for such patients.

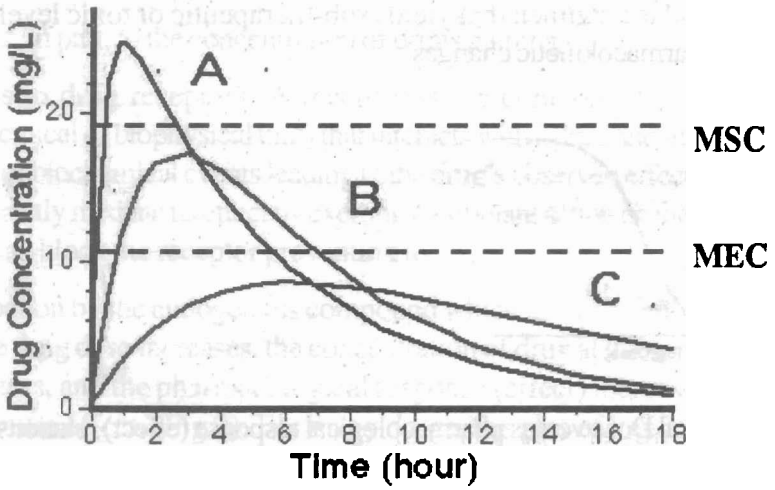


Fig.3: Plasma concentration vs time curves showing possible alterations of drug profiles. MEC = Minimum Effective Concentration. MSC = Maximum Safe Concentration.

B represents the normal concentration profile for the drug.

Profile A would result in toxicity necessitating a smaller dose while Profile C would be ineffective, necessitating increased dose.

1.4.1 *Age*

Age-related pharmacokinetic differences occur among the neonate, infant, child, adult, and geriatric adult. The differences can be attributed to changing metabolic functions and drug distribution characteristics. Neonates clear drugs very slowly, progressing to much faster in infants and children as compared to adults. As a general rule of the thumb, children metabolize drugs twice as fast as adults and need higher maintenance doses to obtain the same therapeutic effect. In geriatrics, drugs are cleared from the body at a slower rate than adults due to a combination of

decreasing metabolic activity and the inception of reduced renal function. Thus, dosages must be reduced in relation to these alterations in drug pharmacokinetics in order to avoid toxicity.

1.4.2 *Diseases*

The liver and kidney are the two major organs of elimination of drugs from the body and therefore have the most impact on pharmacokinetics of drugs

Thus, renal disease that affect the functioning capacity of the kidneys have the potential to alter the pharmacokinetics of drugs. The extent of this effect is determined by the severity of the disease. The severity of the disease is determined by how much lower the creatinine clearance in a patient is compared to the normal value of about 125 ml/min in healthy individuals. In general, clearance of a drug by glomerular filtration is reduced in patients with decreased renal function, resulting in increase in the duration of time the drug stays in the body. Increases in drug half-life may result in toxicity in patients if the amount of the dose and the dosing schedule is not suitably adapted.

The major impact of liver disease is on the reduced metabolism of drugs. Several studies have shown that the metabolic capacity of the liver is reduced in liver disease cases and alteration in the pharmacokinetics of several drugs has been demonstrated. The consequence is a reduction in clearance and increase in half lives of these drugs.

Both renal and liver diseases can also alter the degree of plasma protein binding resulting in changes in drug distribution and pharmacologic effect.

1.4.3 *Drug factor*

For drugs with narrow therapeutic window, such as digoxin, aminoglycosides (eg gentamicin, amikacin, tobramycin), antiarrhythmics (eg quinidine, procainamide, disopyramide),

immunosupressants (eg cyclosporin, tacrolimus) and other drugs like theophylline, phenytoin, and lithium, dosage individualization is very important. Since the drugs have narrow therapeutic window, individual variation in pharmacokinetics of drugs can readily result in plasma levels that are either ineffective or toxic. For this reason, the doses of these drugs are adjusted to be appropriate for each individual patient.

2. MY WORK AND CONTRIBUTIONS TO KNOWLEDGE

My research endeavours are focused on biopharmaceutic, pharmacokinetic and pharmacodynamic evaluation of mainly anti-infective agents with the overall objective of generating information relevant for optimization of the therapeutic utility of such drugs. In very few cases, where the drugs evaluated were not anti-infective agents, such studies were prompted by the need to solve prevalent pharmaceutical and drug usage problems of importance.

2.1 PHARMACOKINETIC STUDIES OF ANTIMALARIALS

The pharmacokinetics of antimalarial drugs: chloroquine, proguanil, halofantrine and quinine were evaluated in different body fluids using different experimental models. My interest in antimalarials is derived from the fact that malaria is the most dreadful tropical disease, remaining widespread throughout the tropics. It exacts a heavy toll of morbidity and mortality especially amongst children and pregnant women, and also poses a risk to travellers and immigrants. About 300 – 500 million cases occur every year with 1.2 – 2.7 million deaths and 90 % of these occur in Africa, South of the Sahara. Antimalarials are among the most commonly used medications in the tropical areas of the world. Correct use of an effective antimalarial drug will not only shorten the duration of malaria illness but also reduce the incidence of complications and risk of death. Generation of pharmacokinetic data of the drugs provides the means for determination of rational dosage regimen for optimal efficacy.

As part of the pharmacokinetic studies, the first step was development of sensitive and specific methods for analyses of the antimalarial drugs and their metabolites in biological fluids (Ogunbona *et al.* 1986; Onyeji et al,.1989 ; Onyeji *et al.*, 1992; Onyeji & Aideloje, 1997). All the analytical methods were developed using high-pressure liquid chromatographic (HPLC) systems (Fig 4). There are three main areas that determine the goodness of an analytical method, viz: (i)Extraction procedure (ii) Chromatographic conditions (iii) Method validation process.

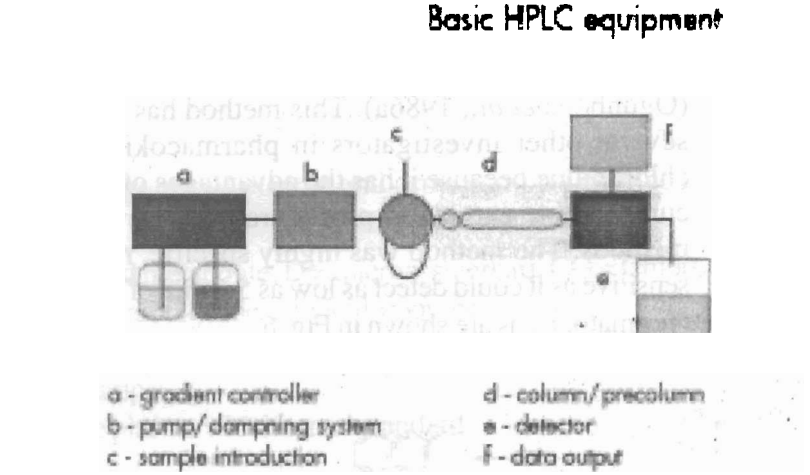


Fig 4: Diagram showing the components of a HPLC equipment

2.1.1 Pharmacokinetic Studies of Chloroquine

Chloroquine, (Fig 5) a 4-aminoquinoline, was the most frequently used antimalarial drug in malaria-endemic regions of the world when the parasite was sensitive to the drug. It is also useful in the treatment of rheumatoid arthritis unresponsive to nonsteroidal anti-

inflammatory drugs as well as in amoebiasis therapy. The use of chloroquine as a single first-line antimalarial drug treatment is now increasingly limited following the evolution of chloroquine-resistant malaria parasite. However, it remains a drug of choice in most African countries where acceptable clinical cure rate can be obtained. In some areas, the utility of chloroquine can be extended by its combination with other antimalarial drugs. Attempts to elucidate the complex pharmacokinetics of the drug had depended on analytical methods that had limitations in terms of involving time-consuming procedures or not being specific enough to separate the drug from its major metabolite. There was a need for an alternative analytical method.

In our laboratory, we developed a simple, sensitive and rapid high-pressure ion-pair liquid chromatographic method for the analysis of the drug and its metabolites in biological fluids (Ogunbona *et al.*, 1986a). This method has been adopted by several other investigators in pharmacokinetic studies of chloroquine because it has the advantages of involving a less cumbersome extraction procedure than previously reported methods. The method was highly specific, reproducible and sensitive as it could detect as low as 5 ng/ml of the drug. Typical chromatograms are shown in Fig. 6.

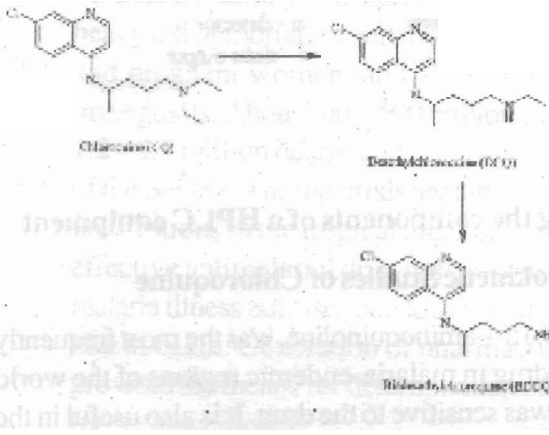
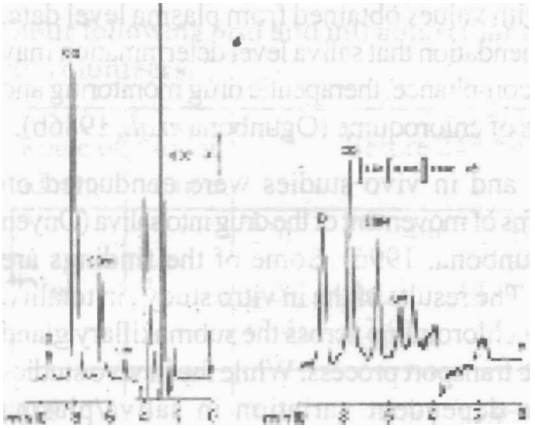


Fig. 5 Chemical structures of chloroquine and its major metabolites



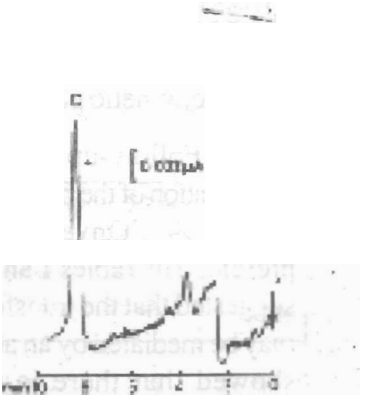


Fig. 6 Chromatograms of plasma and urine samples obtained from a subject.

UM = unidentified metabolite, D = internal standard; CQ = Chloroquine; CQM = major metabolite, desethylchloroquine
left: plasma sample
middle: urine sample
right: drug-free plasma with internal standard

(A) *Chloroquine monitoring in Saliva and Milk*

While blood is usually used for therapeutic drug monitoring, measurement of saliva concentrations may reflect blood values and also have the advantages of convenience, painlessness and non-invasiveness. Although it was known that the free form of chloroquine distributes widely throughout the body, there was no published information on its availability in human salivary secretions. We, therefore set out to determine whether chloroquine is excreted in human saliva and also elucidate the drug pharmacokinetics from saliva excretion data.

The presence of chloroquine in saliva was established and the pharmacokinetic parameters calculated from the saliva concentration-time profile were in agreement with values obtained from plasma level data. The results led to the recommendation that saliva level determination may be used in evaluating patient compliance, therapeutic drug monitoring and pharmacokinetic parameters of chloroquine (Ogunbona *et al.*, 1986b).

Follow-up in vitro and in vivo studies were conducted on investigation of the mechanisms of movement of the drug into saliva (Onyeji *et al.*, 1991; Onyeji & Ogunbona, 1996). Some of the findings are presented in Tables 1 and 2. The results of the in vitro study, in totality, suggested that the transfer of chloroquine across the submaxillary gland may be mediated by an active transport process. While the in vivo studies showed that there is time-dependent variation in saliva/plasma concentration ratios which is also indicative of active transport process in the transfer of drugs into saliva. Therefore, it is possible that some medicinal agents could inhibit chloroquine secretion in saliva thus rendering unreliable any drug monitoring of chloroquine using saliva levels. Hence, we recommended that caution should be exercised in using saliva levels for therapeutic monitoring of the drug.

Table 1: Effects of various conditions of incubation on the uptake of chloroquine by the rat submaxillary gland slices.

Incubation Condition	N	Uptake (mL/g ± s.e.m)
Control*	24	0.95 ± 0.14
4 ^{0}C	12	0.56 ± 0.06*
N_2	13	0.49 ± 0.06*
0-Nitrophenol (10^{-3} M)	12	0.43 ± 0.05*
Iodoacetic acid (10^{-3} M)	13	0.53 ± 0.03*
Cyanide (10^{-3} M)	12	0.48 ± 0.04*

*Control conditions: 6 x 10^{-6} M chloroquine; pH = 7.4; 37.5 ^{0}C bath temperature and oxygen aeration. * = $p < 0.05$

Table 2: Mean (± SD) Saliva to plasma chloroquine concentration ratios monitored in the periods before and after 24 hour following oral and intramuscular administrations of the drug to volunteers.

Route of admin.	No. of volunts.	Before 24th hour			After 24th hour		
		2 hr	4hr	6hr	48 hr	72 hr	168hr
Oral	7	8.3 (7.4)	10.7 (7.9)	14.4 (9.5)	12.1 (5.2)	11.5 (4.8)	11.9 (5.1)
IM	6	7.4 (6.1)	13.5 (8.0)	11.9 (5.7)	10.9 (2.7)	11.4 (2.4)	11.5 (3.1)

The safety of chloroquine in the chemosuppression of malaria during pregnancy has been established. It was thought necessary to investigate if the drug is excreted in human breast milk and to what extent in order to access the safety of infants being breastfed by their mothers that are on chloroquine therapy (Ogunbona et al. 1987). This study was carried out using eleven lactating mothers who received single oral doses of chloroquine. The results (Table 3) showed that the concentrations of chloroquine and its major metabolite, desethylchloroquine, were much higher in milk than in plasma as indicated from the average milk to plasma concentration ratio. However, there is a lower tendency for the metabolite to pass into the mammary gland as observed from a significantly lower metabolite level percentage of chloroquine in milk than in plasma. It was calculated that the maximum daily dose of chloroquine that can be received by the infant through breastfeeding is about 0.7 % of the maternal start dose (600 mg) of the drug in malaria chemotherapy. Since an amount of 1 – 2% of the maternal dose is considered safe to the nursing infant, based on our results, we asserted that it is safe for mothers to breastfeed their infants when undergoing treatment for malaria with chloroquine. This finding is cited widely in most international pharmacopoeia.

Table 3: Plasma, saliva and milk excretion of chloroquine and desethylchloroquine following oral administration of chloroquine

	Cm/Cp		CQM/CQ%			Cmax of CQ	Elimination half-life (days)	
	CQ	CQM	Milk	Saliva	Plasma	(mg/L)	Milk	Saliva
Mean (±SD)	6.6 (2.4)	1.5 (0.6)	6.1 (2.0)	8.2 (5.6)	31.5 (8.5)	4.4 (2.6)	8.8 (4.7)	3.9 (1.0)

Cm = Concentration in milk; Cp = Concentration in plasma; Cmax = Maximum drug concentration; CQ = chloroquine; CQM = chloroquine metabolite

(*B*) *Other Pharmacokinetic Studies of Chloroquine*

Chloroquine Interaction with imipramine

The spread of chloroquine resistant malaria parasite is a source of great concern to health authorities in the world because cross-resistance has already been demonstrated to the newer antimalarial agents. There is, thus, an increasing urgency for new antimalarial agents and drugs that can reverse the resistance. It was shown that the antidepressant drug, imipramine and its metabolite, desimipramine, restored the effectiveness of chloroquine against chloroquine-resistant strains in vitro and in vivo in monkeys. Before drugs are recommended for co-administration, there should be an examination of any pharmacokinetic interaction which might result in therapeutic failure or toxicity. Therefore, we elucidated the pharmacokinetic interaction between chloroquine and imipramine using healthy volunteers (Onyeji et al., 1993). The results revealed that the plasma concentrations of chloroquine and imipramine and their pharmacokinetic parameters were not significantly altered by each other when the drugs were co-administered. The results suggest that imipramine may be given with chloroquine in the treatment of chloroquine-resistant falciparum malaria without any fear of adverse pharmacokinetic drug interaction.

Chloroquine and pruritus

One of the few side effects of chloroquine is pruritus, which is a peculiar type of generalized itching, and occurs in up to 70 % of adult Africans. This high incidence of pruritus is reported to have a negative impact on malaria therapy with the drug in the malaria endemic regions because, pruritus-susceptible subjects feel reluctant to take the drug following subsequent attack of malaria. If the basis of the drug-induced pruritus is understood, it is possible to completely control this incapacitating side-effect. Thus, several investigators have made efforts to identify the mechanism(s) underlying chloroquine-induced pruritus. Experimental reports have shown that the pruritus is neither an allergic reaction nor due to direct release of histamine by the drug. There is a possibility of subjects susceptible to the drug-induced pruritus handling the drug pharmacokinetically different from non-susceptible subjects. Therefore, we designed a study to elucidate possible difference(s) in the disposition of chloroquine in subjects with and without pruritus (Onyeji & Ogunbona, 2001). It was also investigated whether the metabolism of the drug in pruritus-susceptible subjects is influenced by its dose. The results of the study indicate that there might be a decreased metabolism of chloroquine in subjects susceptible to chloroquine-induced pruritus following ingestion of a therapeutic dose. Comparatively higher chloroquine levels in pruritus susceptible subjects (Fig 7) may possibly be responsible for the pruritus experienced by such individuals when given therapeutic regimen. In malaria endemic regions where malaria parasite is still sensitive to chloroquine, there may be a need to establish a new lower dosage regimen of the drug for patients susceptible to chloroquine-induced pruritus.

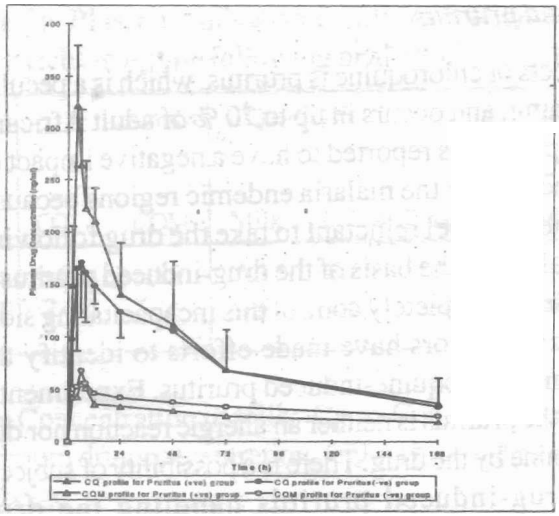


Fig. 7: Mean plasma chloroquine (CQ) and desethylchloroquine (CQM) profiles following oral administration of 600 mg chloroquine dose to two groups of volunteers, those susceptible {CQP(+)} and those not susceptible {CQP(-)}to chloroquine-induced pruritus.

Chloroquine use in Pregnancy

Some physiological changes which occur during pregnancy are known to influence the disposition of a variety of drugs, including antimalarials such as quinine, mefloquine and proguanil. In spite of the extensive use of CQ by pregnant women in many malaria endemic regions, its dosage is still empirically based as there is dearth of information on pharmacokinetics of the drug in human pregnancy. We carried out a study aimed at examining the possibility of pregnancy influencing the metabolism of chloroquine in humans, through determining blood level profiles of the drug and its major metabolite, desethylchloroquine (CQM) in women in the early third trimester of pregnancy, and comparing the values with those of non-pregnant women (Chukwuani et al., 2004). Results showed that the plasma levels of the metabolite were markedly higher in the pregnant compared

to the non-pregnant group. Also, the ratio, AUC(CQ)/AUC(CQM), was on the average, 13.6 times lower in the pregnant relative to non-pregnant women (Fig.8). These results strongly indicate an occurrence of induction of metabolism of chloroquine in the early third trimester of pregnancy leading to faster clearance of the drug. But for the toxicological importance of chloroquine metabolites, it could have been recommended that higher dosages of chloroquine be evaluated in malaria prophylaxis in pregnant women to compensate for its rapid metabolism.

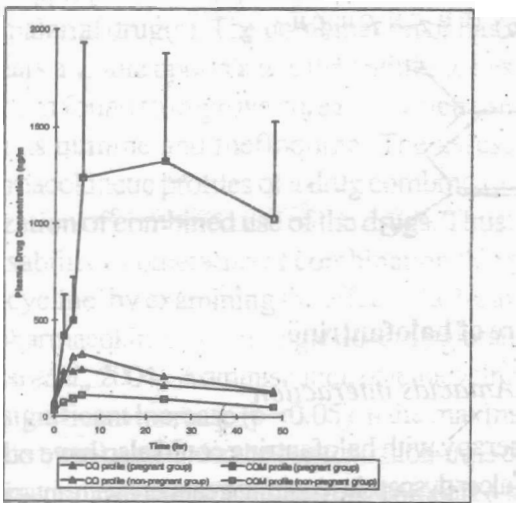


Fig. 8: Mean plasma chloroquine (CQ) and desethylchloroquine (CQM) profiles following oral administration of 600 mg single doses of chloroquine to pregnant and non-pregnant women.

2.1.2: Pharmacokinetic and Biopharmaceutic Studies of Halofantrine

Halofantrine (Fig.9), an oral phenanthrene methanol antimalarial, has been found to be effective against chloroquine and multidrug resistant uncomplicated *P. falciparum* malaria. The major drawback in the use of

halofantrine is its cardiotoxicity which reportedly has resulted in cases of sudden deaths. Optimization of the therapeutic utility of any drug requires a detailed knowledge of its pharmacokinetics. This can be achieved through the availability of methods with high accuracy and low limit of determination for the analysis of the drug in biological fluids. We thought it necessary to develop a HPLC method of analysis of Halofantrine that has all the qualities of a good analytical method and is also relatively cost-effective and involves the use of readily available materials in the analytical procedure (Onyeji & Aideloje, 1997). This method was applied in pharmacokinetic studies of the drug in varied conditions.

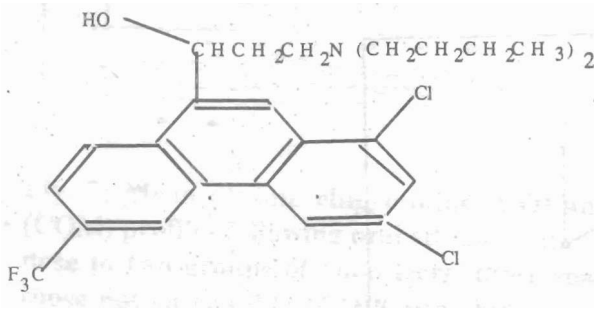


Fig. 9: Chemical Structure of halofantrine

Halofantrine and Antacids interaction

Some malaria patients on therapy with halofantrine could also have other indications like ulcer and non-ulcer dyspepsia requiring treatment with antacids. Before a concomitant administration of halofantrine and antacids could be recommended, it would be necessary to determine whether a significant in vivo interaction occurs between both compounds. The importance of such a study is underscored by the fact that antacids have been reported to markedly reduce the bioavailability of a broad range of drugs. Therefore, we conducted a study to determine whether halofantrine interacts with antacids in vitro and also to evaluate the effect of the antacid on the pharmacokinetics of the drug in man (Aideloje et al., 1998). Out of some non-systemic antacids, magnesium carbonate showed the highest adsorptive effect on the drug, the extent of adsorption being up to 83%. The effect of magnesium carbonate on the

bioavailability of halofantrine was evaluated in healthy volunteers. The results showed that the maximum plasma concentrations (C_{max}) and the area under the curve (AUC) values of halofantrine and its major metabolite were significantly reduced ($p < 0.05$). Results of this study suggest that it is not advisable to concomitantly administer halofantrine with an antacid like magnesium carbonate.

Halofantrine-tetracycline Interaction

One of such strategies that can be employed in order to safeguard efficacy of antimalarial drugs is combination therapy. Hence, to prolong the therapeutic useful life of halofantrine and also enhance its efficacy, it would seem appropriate to recommend a co-administration of the drug with other antimalarial drug(s). The combination of halofantrine with tetracycline appears a viable option since the antibiotic has antimalarial action and it has been found to improve cure rates when used with other antimalarials such as quinine and mefloquine. The assessment of the clinical and pharmacokinetic profiles of a drug combination is mandatory for rational utilization of combined use of the drugs. Thus, we set out to evaluate the advisability or otherwise of combination therapy with halofantrine and tetracycline, by examining the effect of a 7-day course of tetracycline on the pharmacokinetics of a single dose of halofantrine in healthy volunteers (Bassi *et al.*, 2004). Administration of tetracycline plus halofantrine resulted in a significant increase ($p < 0.05$) in the maximum plasma concentration (Cmax), total area under the concentration-time curve (AUC_T), and terminal elimination half-life of halofantrine, compared to values from halofantrine dosing alone (Table 4). Similarly, tetracycline caused a significant increase ($p<0.05$) in the AUC and Cmax of the metabolite. Theses results suggest that, with the increased plasma levels of the drug and its metabolite induced by tetracycline, there is an increased risk of halofantrine toxicity following co-administration of therapeutic doses of the drug with tetracycline.

Table 4: Pharmacokinetic Parameters of halofantrine in 8 volunteers following oral administration of 500 mg single dose of the drug alone, and with tetracycline (500 mg 12 hourly for 7 days).

Drug	Volunteer	T_{max} (hr)	C_{max} ($\mu g\ ml^{-1}$)	AUC_T ($\mu g\ ml^{-1}$	$T_{1/2\beta}$ (hr)	CL/F $L\ hr^{-1}$	Vβ/F $L\ kg^{-1}$
A	Mean ±SD	6.0 ±94	0.432 ±0.136	32.02 ±13.64	90.78 ±17.87	19.36 ±9.05	33.28 ±16.72
B	Mean ±SD	6.75 ±1.39	1.057 ±0.438	63.66 ±20.11	157.42 ±57.40	8.69 ±2.71	28.36 ±7.99
	P=0.05	NS	S	S	S	S	NS

T_{max}, C_{max}, AUC_T, $T_{1/2\beta}$, , CL/F and Vβ/F are standard pharmacokinetic parameters

A = Halofantrine alone; B = Halofantrine plus tetracycline

NS = No significant difference

S = Significant difference

Halofantrine-Amodiaquine Interaction

There is a renewed interest in amodiaquine as a replacement for chloroquine in the treatment of malaria, especially in sub-Saharan Africa. However, levels of amodiaquine resistance have been observed and there are reports of malaria treatment failures with the drug. Lack of adequate response to amodiaquine in malaria treatment might necessitate a switch to an alternative more effective drug such as halofantrine. In such instances, pharmacokinetic or pharmacodynamic interactions may occur between the antimalarials if there is a considerable presence of the earlier administered drug in the body before the alternative drug is given. We investigated the influence of prior administration of amodiaquine on the pharmacokinetics and electrocardiographic effect of halofantrine (HF) in healthy volunteers (Omoruyi et al., 2007). This study results suggested that prior administration of AQ does not result in a significant alteration of

the pharmacokinetics of halofantrine but may be associated with an increased risk of QT prolongation. It may be necessary to exercise caution in the use of halofantrine for malaria treatment in persons who have recently received amodiaquine.

2.1.3: Pharmacokinetic Studies of Other Antimalarials

In addition to the extensive studies done on chloroquine and halofantrine, we also evaluated the clinical pharmacokinetics of proguanil and quinine.

Proguanil (Paludrine®), is a biguanide derivative of pyrimidine (Fig 10) which was widely used as a prophylactic agent against malaria infection and is a drug of choice for malaria suppression in sickle cell anaemia patients, particularly children. With the development of resistance by malaria parasites to the drug, it is currently used for chemoprophylaxis in combination with chloroquine in areas with low prevalence of chloroquine-resistant falciparum, and for treatment of malaria in combination with atovaquone. It is also effective for treatment of malaria when given in combination with dapsone

A liquid chromatographic method was developed for the determination of concentrations of proguanil in biological fluids (plasma and saliva). This was used to monitor the drug levels in saliva and compared the levels with plasma data. The finding was that saliva level determination can be substituted for blood level determination in therapeutic drug monitoring and evaluation of pharmacokinetic data of proguanil in man (Onyeji *et al.*, 1989).The effects of antacids on the absorption of Proguanil was also investigated. Out of some antacids studied, magnesium trisilicate exhibited the highest in vitro adsorptive capacity for the drug, with the extent being up to 88%. The effect of magnesium trisilicate on the bioavailability of the drug, evaluated from saliva level data in healthy volunteers, showed that the antacid markedly reduced the extent of gastrointestinal absorption of the drug. From this study, we recommended that concomitant administration of proguanil with a non-systemic antacid like magnesium trisilicate should be discouraged (Onyeji and Babalola, 1993).

The widespread development of resistance by human malaria parasite to chloroquine prompted renewed interest in the use of quinine in malaria chemotherapy. Quinine (Fig. 10) is an alkaloid found in the bark of the cinchona tree. Used to treat malaria since the early 1600s, it was the best chemotherapeutic agent available to combat the disease until the 1920s. The cinchona tree contains more than 20 alkaloids of which quinine and quinidine are the most important. Quinidine is used to treat cardiac arrhythmias. Following our development of good HPLC method for the analysis of quinine in biological fluids, we used the method to evaluate, using a rat model, the effect of renal failure on the disposition of the drug. Three aetiologically different models of experimental acute renal failure resulted in up to 25-fold increase in the plasma levels of the drug and a marked decrease in the levels of the major metabolite. There was no correlation between increased plasma urea and plasma quinine levels. The results suggest that quinine dosage should be adjusted in patients with renal impairment. Plasma urea levels, as a measure of renal function, might not provide a suitable index for determining quinine dosage (Onyeji *et. al.*, 1992).

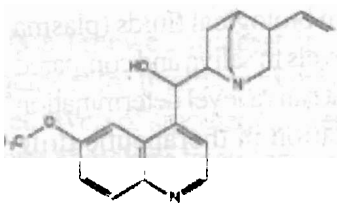
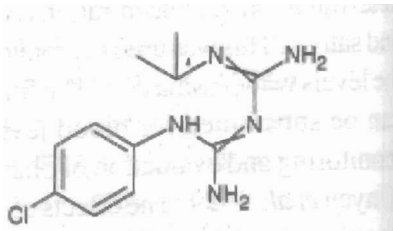


Fig. 10: Quinine.

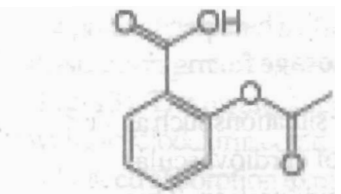


Proguanil

2.2 PHARMACOKINETIC STUDIES OF OTHER DRUGS

The drugs, aspirin and ticlopidine (Fig 11), which are effective in various platelet-dependent cardiovascular disease states, have been found to enhance the effectiveness of some antimicrobial agents. For the drugs to be used effectively to enhance antimicrobial potency, there was the

need to design appropriate dosing regimens for experimental studies of the drug with ultimate applications in man. We developed appropriate HPLC analytical methods for assay of the drugs in biological fluid and generated pharmacokinetics data in animal experimental models. The kinetics of different doses of aspirin (2.5, 10, 20, or 50 mg/kg) were evaluated in rabbits. Results obtained showed that the 20 and 50 mg/kg dosages produced serum salicylic acid concentrations that simulate those observed in humans after 600-mg and 1.2-g aspirin doses, respectively (Marangos *et al.*, 1995). Similarly, the kinetics of different doses of ticlopidine (10, 50 or 100 mg/kg) were evaluated, and the dose of 100 mg/kg produced plasma ticlopidine concentrations similar to those found in man after administration of 250 mg of the drug (Onyeji *et al.*, 1999), Therefore, 20 or 50 mg/kg doses of aspirin and 100 mg/kg of ticlopidine are the appropriate doses of the drugs for use in rabbit experimental studies with ultimate application to man. The utilization of man-adapted dosages in animal experimental models are known to optimize the clinical relevance of the results.



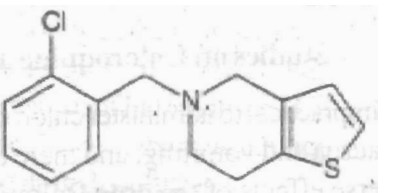


Fig. 11: Aspirin **Ticlopidine**

Some of my research activities involved collaboration with pharmaceutical companies for drug registration in Nigeria. One of such exercises was in the evaluation of bioavailability of a new oral formulation of drotaverine (Fig. 12), which is an antispasmodic agent. (Bolaji *et al.*, 1993 and 1996)

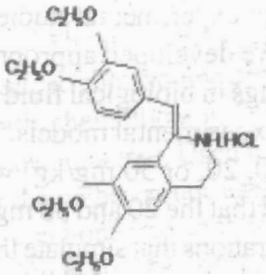


Fig. 12: **Drotaverine HCl**

3. BIOPHARMACEUTIC AND DRUG PRODUCT DEVELOPMENT STUDIES

Another important approach towards optimization of the therapeutic utility of a drug is to modify the dosage form with the aim of increasing the release and dissolution of the active drug to result in an enhanced systemic availability. In the course of my research endeavours, drug products of anti-infective agents, including antimalarials, were re-designed and evaluated.

3.1 Studies on Chloroquine and halofantrine dosage forms

It is impractical to administer chloroquine orally in some situations such as in nausea and vomiting, and there are several reports of cardiovascular adverse effects of the drug following parenteral administration. This prompted the need to explore alternatives to these routes. Thus, we deemed it worthwhile to evaluate the bioavailability of chloroquine following rectal administration of a suppository dosage form (Onyeji *et al.*, 1996). The results showed that the plasma drug concentrations after oral administration were markedly higher in comparison with the rectal route. The bioavailability of chloroquine suppositories was 63.4 ± 8.8 % relative to the tablet formulation. It was suggested, based on the results, that it may not be therapeutically reasonable to substitute chloroquine tablets by this suppository formulation with the same dose. However, further studies suggested that the rectal bioavailability of the drug can be improved by

incorporation of known absorption-enhancing agents in the suppositories (Onyeji *et al.*, 1999).

There is currently only oral formulation of halofantrine. We developed and evaluated a halofantrine rectal dosage form that can serve as a practical alternative to the oral route, which has limitations. The results showed that the extent of drug release was low but the release from water-soluble bases (polyethylene glycol and glycero-gelatin) were significantly greater than that from lipophilic bases (Shea butter and Witepsol H15) ($p < 0.05$). Incorporation of nonionic surfactants (Tweens 20 and 80, Spans 20 and 60) at different concentrations did not improve the in vitro availability of the drug from the suppositories (Oladimeji *et al.*, 2006). Further studies are underway to optimize drug release from this formulation.

The low release of halofantrine from the rectal formulation is related to the very poor water solubility of the drug. The solubility of poorly-soluble drugs can be enhanced through various strategies, one of which is by complex formation with cyclodextrins. This approach was applied in our study (Onyeji *et al.* 2007). Dissolution profile of the drug was markedly enhanced by complex formation with 2-hydroxypropyl-â-cyclodextrin and the product prepared by freeze-drying method exhibited the most superior dissolution properties compared to the other methods used in this study (Fig. 13). The results suggest that the complexation of halofantrine HCl with â-cyclodextrin could improve therapeutic efficacy of the drug through enhanced absorption expected from increased drug dissolution.

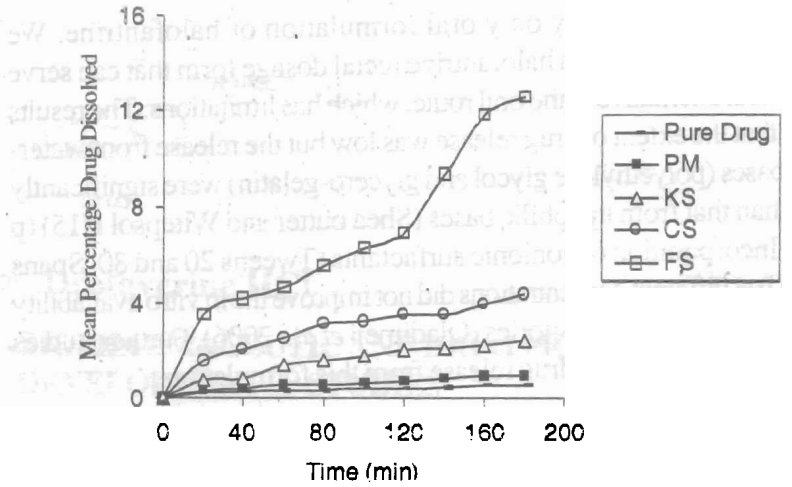


Fig. 13: Dissolution profiles of halofantrine HCl and binary systems with 2-hydroxypropyl- â-cyclodextrin in simulated gastric fluid, pH 1.2

[PM = Physical Mixture; KS = Kneaded System; CS = Co-evaporated System; FS = Freeze-Dried System]

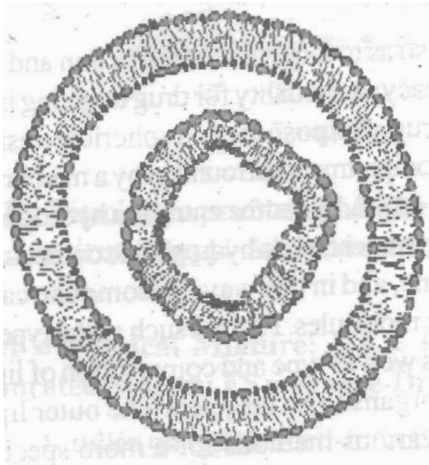
3.2 Studies on Other Anti-infectives dosage forms

The clinical failures reported for Griseofulvin, an antifungal agent, in some patients have been attributed to its highly variable low extent of absorption. Therefore, it was worthwhile to introduce a tolerable and acceptable dosage formulation that can consistently enhance the bioavailability of the drug. Our studies showed that a type of emulsion formulation (water/oil/water) of this anti-infective agent significantly increased its bioavailability compared to the tablet form. Thus, administration of griseofulvin in the w/o/w emulsion would lead to the enhancement of therapeutic efficacy of the drug (Onyeji *et al.*, 1991). Since griseofulvin is a poorly water-soluble drug, it was rationalised that its bioavailability enhancement effect with w/o/w dosage form can also apply to other poorly water-soluble drugs.

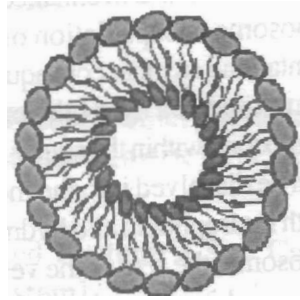
Nitrofurantoin, is a poorly water soluble anti-infective agent, with bioavailabiiity problems like griseofulvin and it also has serious GIT side effects after oral dosing. We showed that administration of this drug in w/o/w dosage form, does not only improve the therapeutic efficacy of the drug, but also reduces its GIT irritation (Onyeji & Omotosho, 1992). Follow-up studies (Onyeji & Adesegun, 1994) showed that the bioavailability and therapeutic efficacy of nitrofurantoin administered in w/o/w emulsion formulation can be further enhanced by increasing the viscosity of the formulation. The nature of the viscosity imparting agent plays a significant role in determining the extent of improvement of nitrofurantoin absorption.

Drugs can be formulated so as to target the site of action and this generally results in enhanced efficacy. A modality for drug targeting is by liposome encapsulation of the drug. A **liposome** is a spherical vesicle containing an inner core aqueous compartment surrounded by a membrane composed of a lipid bilayer (Fig. 14). A liposome entraps a hydrophilic compound within the aqueous compartment while hydrophobic compounds can be dissolved into the membrane, and in this way liposome can carry both hydrophobic and hydrophilic molecules. Factors such as the type of liposome, the size of the vesicle as well as type and composition of lipid bilayer determine the tissues or organs to be targeted. The outer lipid membrane can be modified by various methods for a more specific targeting. By delivering drugs directly to the cells needing them, drug efficacy is increased while overall toxicity is reduced. We carried out studies on how to employ liposome encapsulation to enhance drug delivery and hence the efficacy of some antimicrobials against *Mycobacterium avium-M. intracelluare* (MAI) infection. Our main interest in this microorganism was because it frequently causes opportunistic infections in patients with HIV/AIDS. MAI is primarily an intracellular organism that multiplies within phagocytic cells. Using in vitro model, our studies showed that liposome encapsulation of either ofloxacin or clarithromycin significantly enhanced the uptake of each of the drugs by human phagocytic cells and there was also enhanced activities of the drugs when compared with the antimycobacterial effects of equivalent concentrations of the free (un-

encapsulated drug. Therefore, liposome-encapsulated clarithromycin or ofloxacin is expected to be more effective than the free form of the drug against MAI infections in vivo (Onyeji *et al.*, 1994a). This study was extended to other antimicrobials with known anti-MAI activities. In agreement with our earlier study, liposome encapsulation of azithromycin and rifabutin resulted in a marked increase in the uptake of the drugs compared to the free form. Also, the antimycobacterial activity of each of the drugs was significantly enhanced when the drugs were delivered in the liposome-entrapped form (Onyeji *et al.*, 1994b).

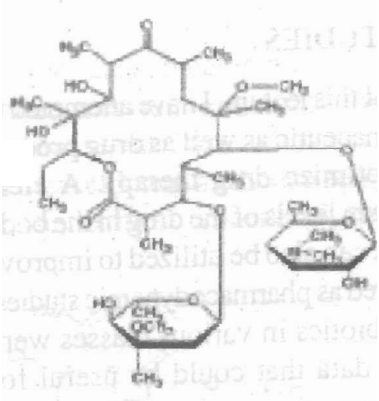


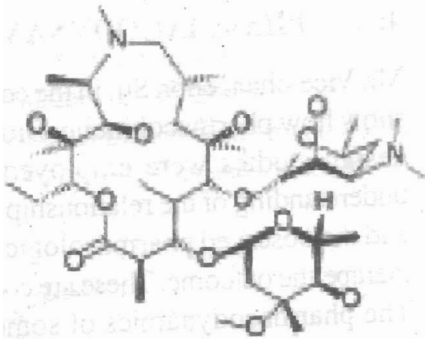
Large Multiple-bilayer Liposome



Small Single-bilayer liposome

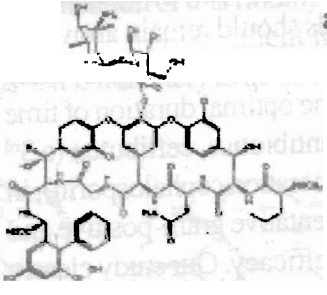
Fig. 14: .**A Picture illustrating structure and types of liposomes**



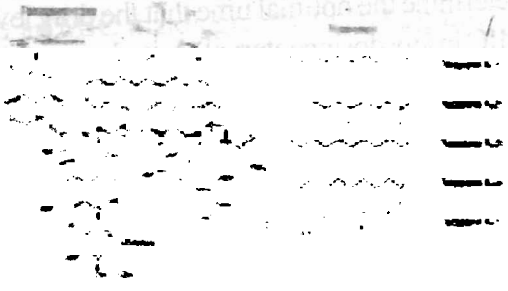


Clarithromycin **Azithromycin**

Liposome drug targeting studies were applied to improve drug efficacy against another form of intracellular infection. It had been recognized that some *Staphylococcus aureus* infections have the tendency to become recurrent and this phenomenon has been attributed to the intraphagocytic survival of small numbers of the organism. We carried out a study to determine whether liposome-encapsulation of the glycopeptide antibiotics, vancomycin or teicoplanin, can enhance the drug activity against methicilin-resistant *S aureus* (MRSA) located within human phagocytes. The results showed that liposome entrapment markedly enhanced the uptake of the drugs by phagocytes and there was a more efficient elimination of intracellular MRSA infection following treatment with liposome-



Vancomycin Structure



Teicoplanin core and the side chains which characterize the five major teicoplanin compounds

4: PHARMACODYNAMIC STUDIES

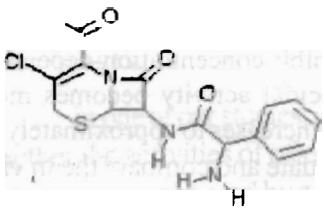
Mr. Vice-chancellor. Sir, in the course of this lecture, I have attempted to show how pharmacokinetic, Biopharmaceutic as well as drug product design studies were employed to optimize drug therapy. A clear understanding of the relationship between levels of the drug in the body and the observed pharmacologic effect can also be utilized to improve therapeutic outcome. These are considered as pharmacodynamic studies. The pharmacodynamics of some antibiotics in various classes were evaluated with a view to generating data that could be useful for enhancement of clinical utilities of the drugs.

4.1 Cephalosporins Pharmacodynamics

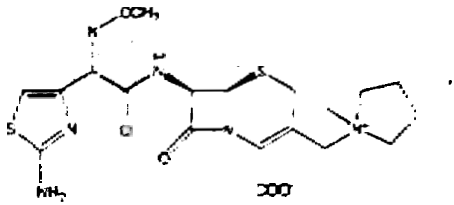
Generally, cephalosporins are grouped into "generations" based on their antimicrobial properties. Currently, four generations of cephalosporins are recognized with each newer generation of cephalosporins having greater gram negative antimicrobial properties than the preceding generation. Because of this relationship, first generation cephalosporins are useful in treating gram positive infections of respiratory tract, skin and urinary tract.

Reports from the literature showed that the major parameter correlating efficacy of cephalosporins is the duration of time the serum drug concentration exceeds the Minimum Inhibitory Concentration (MIC) of the organism within the dosing interval. However, there was no study to determine the optimal time that the drug levels should remain above the MIC in any dosing interval. A study was undertaken to investigate, using an experimentally induced infection in mice, the optimal duration of time that the concentrations of two cephalosporin antibiotics, ceftibuten (a 3rd generation cephalosporin) and cefaclor (2nd generation cephalosporin), in serum should remain above the MIC for representative gram-positive and gram-negative organisms to ensure treatment efficacy. Our study clearly confirmed that there is a significant correlation ($r > 0.9$) between drug efficacy and the time above the MIC and also showed that for maximal efficacy, the serum drug concentration does not need to be above the MIC of the organism throughout a dosing interval (Onyeji *et al.*, 1994).

Further studies on cefepime, a forth-generation cephalosporin, with extended spectrum of activity for gram-negative and gram-positive organisms, revealed that continuous infusion rather than intermittent doses is the most efficient method to administer cephalosporins and indeed β-lactam antibiotics (Tessier *et al.*,1999).

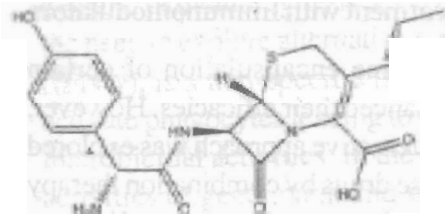


Structure of cefaclor



Structure of Cefepime

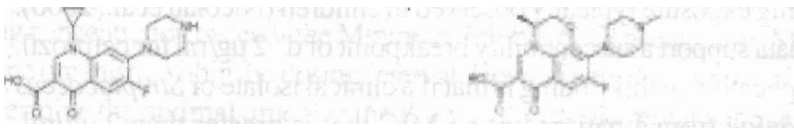
Another pharmacodynamic study was undertaken to better define the in vivo efficacy of Cefprozil, a semi-synthetic second generation cephalosporin antibiotic, against *Streptococcus pneumoniae* using a murine infection model in which human pharmacokinetic profile of the drug was simulated. The results obtained demonstrated the effectiveness of cefprozil against isolates of the pneumococcus for which the MICs are d" 2 µg/ml using drug exposure typically observed in children (Nicolau et al., 2000). These data support a susceptibility breakpoint of d" 2 µg/ml for cefprozil. The implication of this finding is that if a clinical isolate of *Streptococcus pneumoniae* from a patient has an MIC that is greater than 2 µg/ml, cefprozil is not likely to be effective in combating the infection.



Chemical Structure of Cefprozil

4.2: Fluoroquinolones Pharmacodynamics

The quinolones, just like cephalosporins, are divided into generations based on their antibacterial spectrum. The earlier generation agents have activities mainly against gram-negative microbes. The first quinolone, nalidixic acid (NegGram), was introduced in 1962. Since then, structural modifications have resulted in second-, third-, and fourth-generation fluoroquinolones, which have improved coverage of gram-positive organisms. The quinolones, unlike cephalosporins, exhibit concentration-dependent bacterial killing. This implies that bactericidal activity becomes more pronounced as the serum drug concentration increases to approximately 30 times the MIC. We undertook a study to evaluate and compare the in vivo efficacies of a then relatively new fluoroquinolone, levofloxacin (3rd generation), with ciprofloxacin (2nd generation) against clinical isolates of S. *pneumoniae* using a mouse model of experimental septicaemia. Results suggested that levofloxacin is marginally more effective than ciprofloxacin and, with some strains of S. *pneumoniae*, levofloxacin activity may be comparable to that of ciprofloxacin in the treatment of pneumococcal infections caused by susceptible strains of the organism (Onyeji *et al.*, 1999).



Ciprofloxacin **Levofloxacin**

4.3 Adjunctive Antimicrobial Treatment with Immunomodulators

Our earlier studies showed that liposome encapsulation of certain antimycobacterial agents markedly enhanced their efficacies. However, the eradication was not complete. An alternative approach was explored towards increasing the efficacies of these drugs by combination therapy with agents called **Immunomodulators**. This is called an immunochemotherapeutic regimen. An immunomodulator is a drug which may be a naturally occurring compound and is used for its effect on the

immune system. There are two types of such drugs based on their effects: **immunosuppressant** and **immunostimulants.** Since non-specific immunostimulants activate macrophages resulting in the killing of intracellular microbes, our study hypothesis was that an immunochemotherapeutic regimen has the potential to attack the microbe simultaneously by different mechanisms: the antimicrobial by direct toxicity to the organisms, and the immunostimulant via direct activation of the macrophages.

In one of our studies, we used an in vitro infection model to examine whether the activities of ofloxacin, clarithromycin and azithromycin and MAI could be enhanced by combination therapy with a naturally occurring immunostimulant – Granulocyte-macrophage colony-stimulating factor (GM-CSF). The antibiotics were applied at therapeutically achievable serum trough and peak levels. Addition of GM-CSF to the antimicrobials was associated with a significant augmentation of the antimycobacterial activity compared with the effects of the agents alone (Onyeji *et al.*, 1995). We therefore concluded that GM-CSF may be a useful adjunct in the treatment of MAI infections with azithromycin, clarithromycin and ofloxacin.

It was thought reasonable to determine whether the concept of antimicrobial combination therapy with an immunostimulant could be applied to effectively treat multiple drug- resistant organisms. Increasing antibiotic resistance in the enterococci has complicated the treatment of serious enterococcal infections. Since there was no clearly effective antimicrobial therapy for multidrug-resistant enterococci (MDRE) infections, there was the need to explore alternative treatment modalities. Interferon-gamma (IFN-γ), is a non-specific immunostimulant, that has been shown to activate phagocytes leading to an enhancement of their phagocytic and microbicidal activities. In these studies, we investigated whether the activities of gentamicin and vancomycin against multidrug resistant *Enterococcus faecalis* (MDRE) could be enhanced by a combination therapy with IFN-γ. The addition of IFN-γ to therapy with gentamicin or vancomycin, or a combination of both antibiotics, was associated with a

marked increase in efficacy compared to treatments with the agents alone. However, the same treatments made in infected neutropenic model did not show an enhancement effect by IFN-γ after a combination therapy with antibiotics, indication that the activity of Interferon is mediated through the phagocytes. In a study to examine pharmacokinetic interactions, concurrent administration with IFN-γ significantly modified the disposition of gentamicin but not that of vancomycin (Fig. 15) The results of these studies (Onyeji, Nicolau *et al.*, 1999; Onyeji, Bui *et al.*, 1999) indicate that the use of IFN-γ in combination with vancomycin or gentamicin is a new treatment option that can improve the outcome of therapy of multidrug-resistant *E faecalis* infections.

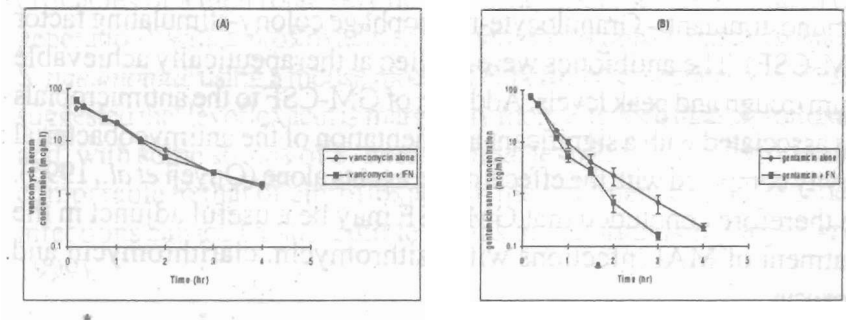


Fig. 15: Kinetic profiles of gentamicin or vancomycin with and without co-administered gamma-Interferon

Since IFN-γ was not effective in neutropenic infection model, can another immunostimulant: granulocyte colony-stimulating factor (G-CSF) which promotes proliferation of neutrophils as well as activates their microbicidal activities be effective? The answer was provided in another study which indicated that G-CSF highly augmented the effects of gentamicin and vancomycin in the treatment of multidrug-resistant *E. faecalis* infection in neutropenic condition (Fig 16). (Onyeji et al., 2000). Furthermore, we demonstrated that adjunctive application of combined immunomodulators (G-CSF and Interferon-gamma) is not more beneficial than the use of only G-CSF in combination with antibiotic in the therapy of MDRE infections in neutropenic conditions (Nicolau et al., 2001). The possibility

of pharmacokinetic interaction between G-CSF and each of the antibiotics was examined. G-CSF caused a significant decrease in the plasma concentration of gentamicin, while the disposition of vancomycin remained unmodified. Thus, for G-CSF to be administered in combination with gentamicin, the dosage of the antibiotic needs some adjustment.

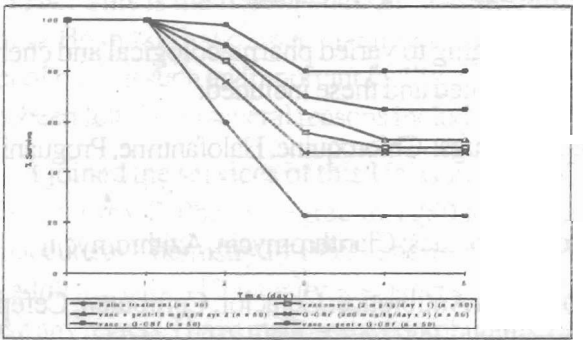


Fig. The effects of treatment with vancomycin alone or in combination with G-CSF and/or gentamicin, on survival of neutropenic mice infected with gentamicin- and vancomycin-resistant *E. faecalis*

SUMMARY AND CONCLUSION

Mr. Vice-Chancellor, Sir, the theme of my research endeavours is unambiguous, and that is : how to optimize the therapeutic effectiveness of drugs, especially anti-infective agents, using various modalities. The modalities included:

(1) Investigating how physiological conditions and disease states influence the drug pharmacokinetics to necessitate dosage adjustment so as to achieve the therapeutic drug concentrations.

(2) Elucidating how drug-drug interactions affect the disposition of the primary drug to warrant dosage adjustment or avoidance of co-administration

(3) Determining how changes in physicochemical properties of drugs as well as their dosage formulations can be utilized to improve the systemic availability and thus efficacy of the drug.

(4) Identifying, through pharmacodynamics studies, the dosing regimen of drugs that are associated with optimal efficacy, and

(5) The use of adjuvants including immunomodulators to potentiate the effectiveness of antimicrobial therapy, especially those with limited treatment options due to drug resistance.

Antimicrobial belonging to varied pharmacological and chemical classes were investigated and these included:

(A) Antimalarial Drugs: Chloroquine, Halofantrine, Proguanil, and

(B) Macrolide Antibiotics: Clarithromycin, Azithromycin

(C) Cephalosporins Antibiotics: Cefaclor, Ceftibuten, Cefepime, and Cefprozil.

(D) Fluoroquinolone Antibiotics: Ofloxacin, Ciprofloxacin, and Levofloxacin

(E) Aminoglycosides Antibiotics: Tobramycin and Gentamicin

(F) Glycopeptide Antibiotics: Vancomycin and Teicoplanin

Miscellaneous Drugs investigated included:

Drotaverine, Nitrofurantoin, Griseofulvin, Aspirin, and ticlopidine.

In this lecture, I have been able to clearly show that several factors impact on treatment outcome with a drug and the outcome can be improved upon or optimized by different approaches. In more advanced countries, the awareness on optimal use and application of drugs is very high and the practice is entrenched in their healthcare delivery systems. In these countries, almost all referral and teaching hospitals have well-equipped laboratories called "Therapeutic Drug Monitoring Laboratory" where biological fluid samples from patients are analysed for drug concentrations and necessary pharmacokinetic calculations are made, for the purpose of determining the desirability or otherwise for drug dosage adjustment for the patient. These are handled by Clinical Pharmacists. Several

retrospective and prospective studies have shown that such interventions resulted in significant reduction in the duration of hospital stay by patients with a reduction in treatment cost. In recognition of the value of optimal drug treatment, my colleagues and I in my department, through a Carnegie Grant, established a Therapeutic Drug Monitoring Lab oratory here at OAUTHC. This is the first of such a Lab oratory in Nigeria and other Teaching Hospitals have since taken a cue from us. Unfortunately, the impact of having such an important facility at our Teaching Hospital has not yet been felt due to several reasons including poor level of awareness.

I joined the services of this University as a Graduate Assistant shortly after my B.Pharm degree in 1980 and became a Professor of Pharmaceutical Chemistry in 1999. Therefore, I have spent a better part of my adult life in this University, and I can say that, by God's Grace, I do not have any regrets. I have made some contributions, not only to knowledge through my publications, but also by replicating myself through successful supervision of a handful of graduate students. Currently, I am supervising 3 PhD students that are all working on projects that revolve around generation of data for optimal drug utilization. In the area of administration and service, I have contributed my quota at various levels. I was the founding Head of Department of Clinical Pharmacy and Pharmacy Administration, a position I held for 3 non-consecutive years. I also served a 3-year term as Head of Department of Pharmaceutical Chemistry before taking up the responsibility as Dean of my Faculty.

As I am serving as an academic mentor to some people now, I also got mentored. I wish to especially acknowledge Professor F. A Ogunbona for kindling my interest in the area of Pharmacokinetics. I am deeply indebted to Professor Charles H. Nightingale, the then Vice-President for Research at Hartford Hospital, Hartford, Connecticut, USA, and Research Professor at the University of Connecticut. It was at his laboratory, where I served as a Postdoctoral Fellow and later as a Research Associate for 3½ cumulative years, that I acquired an important research technique of relating Pharmacokinetics with Pharmacodynamics. I appreciate all my teachers, colleagues in my department and all staff and students of the Faculty of Pharmacy for their support in various ways. My

academic growth would have been stunted but for the immense leverage I got in terms of research grants from various bodies/establishments including Hartford Hospital, Hartford, USA (Five Grants), American College of Clinical Pharmacy (One Grant), and Obafemi Awolowo University (Four Grants). I am grateful to these institutions. I especially appreciate my family for their love and understanding, and for always standing like the 'Rock of Gibraltar' by and with me.

Mr. Vice-Chancellor, Sir, distinguished ladies and gentlemen, I thank you all for your attention. God Bless.

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