# COMPARISON OF THE EFFECT OF A SINGLE ORAL DOSE OF CIMETIDINE AND PROPANTHELINE ON THE PHARMACOKINETIC OF PARACETAMOL IN HUMAN

BY

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A THESIS SUBMITTED TO THE POSTGRADUATE SCHOOL, AHMADU BELLO UNIVERSITY, ZARIA IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE AWARD OF THE DEGREE OF MASTER OF SCIENCE IN PHARMACEUTICAL ANLYSIS

DEPARTMENT OF PHARMACEUTICAL AND MEDICINAL CHEMISTRY,

FACULTY OF PHARMACEUTICAL SCIENCE,

ABU – ZARIA

MARCH, 2009

## DECLARATION

I, Dahiru Magaji Zarewa, hereby declare that the work reported in this thesis was carried out by me under the supervision of Professor Magaji Garba and Dr (Mrs.) M. T. Odunola. It has not been submitted anywhere for the purpose of a degree award. The information derived from literature has been duly acknowledged in the text and a list of reference provided.

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# CERTIFICATION

This thesis entitled “COMPARISON OF THE EFFECT OF A SINGLE ORAL DOSE OF CIMETIDINE AND PROPANTHELINE ON THE PHARMACOKINETICS OF PARACETAMOL IN HUMANS” by DAHIRU MAGAJI ZAREWA meets the regulations governing the award of MASTER OF SCIENCE (PHARMACEUTICAL CHEMISTRY) of AHMADU BELLO UNIVERSITY and is approved for its contribution to sciences knowledge and literary presentation.

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# DEDICATION

This work is dedicated to my late father –

*Alhaji Dahiru Ibrahim*

(Wakilin – Zarewa)

ACKNOWLEDGEMENT

I wish to sincerely thank my supervisors Prof. Magaji Garba and Dr (Mrs.) M. T. Odunola for their support and guidance at all times.

My profound gratitude to Prof. Ilyas, Dr I. Sule, Dr I. A. Yakasai, Dr Musa Gombe and Mal Iliya to mention just a few.

My thanks also go to all my classmates especially Pharm. Nuruddeen Sani Ibrahim.

Thanks to members of my family and especially my wives- Halima and Magajiya.

Also my special gratitude to all those who contributed towards the successful completion of the programme either directly or indirectly.

Above all I thanks the Almighty ALLAH for sparing my life all through.

ABSTRACT

Comparison of the effects of a single oral dose of cimetidine and propantheline on the pharmacokinetics of paracetamol were studied with paracetamol (1g) administered alone, concurrently with cimetidine (400mg), delay (1 hour) with cimetidine (400mg), concurrently with paracetamol (15mg) and delay (1 hour) with propantheline (15mg) respectively. Paraetamol concentration was measured in saliva of 8 healthy male, non-smokers and non-alcoholic volunteers. A log data and AUC curves were used to generate pharmacokinetic data and the data obtained compared pharmacokinetically and statistically. On concurrent administration of paracetamol and cimetidine, the pharmacokinetic parameters change where as follows – Cmax decrease by 16%, $T_{1/2}$ab increase by 2%, Kab increase by 9.0%, $T_{1/2}$el decrease by 1.9%, Kel decrease by 10%, lag time increase by 11% while the AUC decreases by 19%. On concurrent administration of paracetamol and propantheline the following were observed – decrease in Cmax by 11%, incease in $T_{1/2}$ab by 1.6%, Kab decrease by 9%, $T_{1/2}$el increase by 25%, Kel decrease by 17%, lag time increase by 66% while the AUC decrease by 70%. On delayed administration i.e. paracetamol (1g) admistered an hour after the administration of 15mg propantheline there was decrease in Cmax by 45% ($P>0.05$), increase in T1/2 by 67%, decrease in Kab 31% ($P>0.05$),

increase in lag time by 11% ($P<0.01$), decrease in AUC by 45% ($P>0.01$), increase clearance ($P<0.01$), and increase volume of distribution by 56% ($P>0.05$). Qualitative and quantitative differences can be said to exist between the effect of cimetidine and propantheline on the absorption kinetics of paracetamol as seen in the percentage changes of the pharmacokinetic parameters. Even with inter-individual variability accounting for some significance changes, it can be concluded that cimetidine, unlike propantheline does not alter the absorption kinetics of paracetamol on concurrent administration but delayed administration, hence no serious therapeutic implications of the combination of the two drugs in therapy. There was pronounced alteration of the absorption kinetics of paracetamol Propanthaline but are not of any clinical significance.

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## ABBREVIATIONS

| | |
|---|---|
| UV | Ultra Violet |
| Log | Logarism |
| rmp | Revolution Per minutes |
| Mwt | Molecular weight |
| Sem | Standard error of mean |
| Ug | Micrograms |
| Mg | Milligram |
| Ln | Natural log |
| L | Liter |
| SD | Standard deviation |
| PCM | Paractamol |
| Nm | Nanograme |

| | |
|---|---|
| Cv | Coefficient of Variation |
| α | Alpha |
| β | Beta |
| BNF | British National Formulary |
| $^{o}C$ | Degree centigrade |
| HCL | Hydrochloric Acid |
| PPt | Propanthaline |
| CMD | Cimetidine |

*Appendix 1*

*Phase 1: Saliva concentration of 8 healthy volunteers following oral administration of 1g paracetamol in the fasting state (concentration ug/ml)*

| s/n | | I | II | III | IV | V | VI | VII | VIII | Mean+ SEM |
|---|---|---|---|---|---|---|---|---|---|---|
| | Age (yrs) | 32 | 25 | 31 | 25 | 32 | 30 | 26 | 33 | 29.25±0.345 |
| | Weight(kg) | 57 | 50 | 65 | 54 | 55 | 58 | 62 | 70 | 58.88±0.641 |
| 1 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00±0.00 |
| 2 | 0.25 | 13.0 | 11.5 | 11.5 | 12.0 | 10.5 | 11.5 | 12.5 | 7.5 | 11.25±0.501 |
| 3 | 0.50 | 16.5 | 18.8 | 16.5 | `5.8 | 17.0 | 37.0 | 16.5 | 11.5 | 18.65±2.486 |
| 4 | 1,00 | 33.0 | 42.6 | 31.0 | 31.5 | 45,0 | 45.0 | 35.5 | 30.5 | 36.75±2.466 |
| 5 | 2.00 | 29.0 | 34.5 | 30.0 | 29,0 | 23.5 | 28.0 | 18.5 | 29.5 | 27.75±1.467 |
| 6 | 3.00 | 22.5 | 29.0 | 25.5 | 26.5 | 18.0 | 25.0 | 11.0 | 23.0 | 22.56±1.802 |
| 7 | 4.00 | 11.0 | 25.5 | 21.5 | 17.0 | 12.5 | 9.5 | 9.0 | 16.0 | 15.25±1.802 |
| 8 | 5.00 | 7.5 | 22.0 | 14.0 | 12.5 | 12.5 | 4.5 | 8.5 | 12.5 | 11.75±1.592 |

SEM = Standard error mean

Appendix 2

Phase II: Saliva concentration of 8 healthy volunteers following oral administration of 1g paracetamol + 400mg of cimetidine (concurrently) in the fasting state (concentration ug/ml)

| | No of Voiu | I | II | III | IV | V | VI | VII | VIII | Mean+ SEM |
|---|---|---|---|---|---|---|---|---|---|---|
| | Age (yrs) | 32 | 25 | 31 | 25 | 32 | 30 | 26 | 33 | 29.25± |
| | Weight(kg) | 57 | 50 | 65 | 54 | 55 | 58 | 62 | 70 | 58.88± |
| s/n | Time(hrs) | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00±0.000 |
| 1 | 0.25 | 21.5 | 10.0 | 10.0 | 19.5 | 14.5 | 5.5 | 7.5 | 7.5 | 12.0±1.802 |
| 2 | 0.50 | 35.5 | 13.5 | 12.5 | 32.5 | 16.0 | 40.5 | 15.0 | 11.0 | 22.06±3.815 |
| 3 | 1,00 | 29.0 | 36.0 | 21.0 | 34.0 | 35.0 | 32.0 | 24.5 | 30.0 | 30.81±2.248 |
| 4 | 2.00 | 25.0 | 33,5 | 7.00 | 32.5 | 32.5 | 28.0 | 17.5 | 22.5 | 24.81+3.002 |
| 5 | 3.00 | 17.5 | 23.5 | 5.50 | 24.5 | 32.0 | 18.0 | 13.0 | 18.0 | 18.94+2.364 |
| 6 | 4.00 | 14.0 | 3.5 | 2.00 | 24.0 | 20.0 | 8.00 | 9.00 | 13.5 | 11.81+2.142 |
| 7 | 5.00 | 9,5 | 3.5 | 2.00 | 14.5 | 6.50 | 7.50 | 6.00 | 7.50 | 07.38+1.454 |

SEM = Standard error mean

Appendix 3

Phase III: Saliva concentration of 8 healthy volunteers following oral administration of 1g paracetamol + 400mg cimetidine (one hour delayed) in the fasting state (concentration ug/ml)

| s/n | | I | II | III | IV | V | VI | VII | VIII | Mean+ SEM |
|---|---|---|---|---|---|---|---|---|---|---|
| | Age (yrs) | 32 | 25 | 31 | 25 | 32 | 30 | 26 | 33 | 29.25+2.322 |
| | Weight(kg) | 57 | 50 | 65 | 54 | 55 | 58 | 62 | 70 | 58.88+1.123 |
| 1 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00+0.00 |
| 2 | 0.25 | 11.5 | 7.5 | 5.5 | 19.5 | 3.5 | 16.0 | 5.0 | 4.5 | 9.13+2.126 |
| 3 | 0.50 | 19.5 | 11.5 | 7.5 | 24.0 | 5.0 | 47.5 | 12.5 | 7.5 | 16.88+4.36 |
| 4 | 1,00 | 30.0 | 32.5 | 16.5 | 30.5 | 7.0 | 24.0 | 15.0 | 26.5 | 22.75+2.692 |
| 5 | 2.00 | 24.5 | 23.5 | 7.5 | 17.5 | 20.5 | 18.5 | 24.5 | 23.0 | 18.96+1.701 |
| 6 | 3.00 | 18.5 | 19.0 | 7.0 | 4.0 | 10.0 | 13.0 | 9.0 | 19.0 | 12.44+1.741 |
| 7 | 4.00 | 9.0 | 16.5 | 4.5 | 2.5 | 7.5 | 11.0 | 6.5 | 8.0 | 08.19+1.281 |
| 8 | 5.00 | 5.0 | 12.5 | 4.5 | 2.0 | 3.5 | 6.0 | 5.5 | 6.5 | 05.69+0.995 |

SEM = Standard error mean

Appendix 4

Phase IV: Saliva concentration of 8 healthy volunteers following oral administration of 1g paracetamol + 15mg propantheline bromide (concurrently) in the fasting state (concentration ug/ml)

| S/no | | I | II | III | IV | V | VI | VII | VIII | Mean ± SEM |
|---|---|---|---|---|---|---|---|---|---|---|
| | Age(yrs) | 32 | 25 | 31 | 25 | 32 | 30 | 26 | 33 | 29.25 ± 1.22 |
| | Weight(Kg) | 57 | 50 | 65 | 54 | 55 | 58 | 62 | 70 | 58.88 ±3.123 |
| 1 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 ± 0.00 |
| 2 | 0.25 | 5.0 | 10.5 | 1.5 | 4.0 | 7.5 | 5.5 | 14.5 | 2.5 | 06.38 ± 1.378 |
| 3 | 0.50 | 5.5 | 16.5 | 12.5 | 14.0 | 19.5 | 11.5 | 28.0 | 5.0 | 14.06 ± 2.304 |
| 4 | 1.00 | 29.5 | 38.3 | 38.5 | 35.4 | 33.2 | 29.5 | 35.58 | 20.5 | 32.56±3.663 |
| 5 | 2.00 | 19.0 | 24.5 | 30.0 | 28.5 | 25.0 | 25.0 | 11.5 | 41.0 | 23.50±3.261 |
| 6 | 3.00 | 12.0 | 12.5 | 12.5 | 28.0 | 14.5 | 9.5 | 15.0 | 7.0 | 13.88±1.874 |
| 7 | 4.00 | 10.5 | 11.5 | 9.5 | 21.4 | 9.0 | 5.3 | 11.5 | 5.5 | 10.54±1.473 |
| 8 | 5.00 | 10.0 | 10.5 | 7.5 | 15.0 | 5.0 | 4.0 | 6.5 | 5.0 | 7.94±1.298 |

Appendix 5

Phase V: Saliva concentration of 8 healthy volunteers following oral administration of 1g paracetamol + 15mg propanthaline bromide one hour delayed in the fasting state (concentration ug/ml).

| s/n | | I | II | III | IV | V | VI | VII | VIII | Mean+ SEM |
|---|---|---|---|---|---|---|---|---|---|---|
| | Age (yrs) | 32 | 25 | 31 | 25 | 32 | 30 | 26 | 33 | 29.25+ |
| | Weight(kg) | 57 | 50 | 65 | 54 | 55 | 58 | 62 | 70 | 58.88+ |
| 1 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 00.00+0.000 |
| 2 | 0.25 | 5.0 | 4.8 | 1.5 | 0.00 | 0.00 | 0.00 | 3.5 | 0.00 | 01.85+0.698 |
| 3 | 0.50 | 5.5 | 22.5 | 9.5 | 0.00 | 4.0 | 0.00 | 7.0 | 4.0 | 06.56+2.298 |
| 4 | 1,00 | 5.0 | 31.0 | 11.5 | 0.50 | 8.0 | 7.5 | 6.0 | 9.0 | 10.06+2.796 |
| 5 | 2.00 | 5.5 | 31.5 | 12.9 | 18.5 | 14.5 | 7.0 | 15.5 | 18.5 | 15.74+3.588 |
| 6 | 3.00 | 5.55 | 52.0 | 17.5 | 22.5 | 27.5 | 12.5 | 17.5 | 29.5 | 23.07+4.402 |
| 7 | 4.00 | 8.0 | 37.5 | 7.0 | 8.0 | 23.0 | 5.5 | 13.5 | 19.5 | 15.25+3.492 |
| 8 | 5.00 | 5,5 | 15.5 | 2.00 | 4.00 | 18.5 | 3.0 | 11.5 | 11.5 | 08.94+1.874 |

SEM = Standard error mean

# INTRODUCTION

## 1.0 DRUG INTERACTION

A drug interaction occurs when the presence of one chemical substance changes the pharmacological effects of a therapeutically administered drug. The chemical substances may include any of the following: alcohol, foods, insecticides or dietary items.

There are different types of drug interaction:-

- Drug – Drug interaction
- Drug - Food interaction
- Drug – Disease interaction

Drugs very rarely form direct chemical or physical bonds with one another as protein does when it neutralizes the activity of heparin. Drug-Drug interaction takes place because the interaction of drug with macromolecules changes the environment of a second or third drug molecule, thereby resulting in a modified effect.

Therapeutics frequently involves “polypharmacy” which is likely to provoke such interactions. As drug therapy becomes more complex, the ability to predict the magnitude of a specific action of any given drug diminishes.

The significance of drug interactions lies in the use of knowledge to achieve the desired beneficial effects for the patient or prevent unwanted effects.

There may be a drug laboratory test interaction, where a drug causes alteration of diagnostic laboratory test. Drug-Disease interaction is a situation where a drug causes undesired effects in patients with certain disease states or the disease state can modify the action of a drug. However, it has been emphasized that trial in man is the only valid way of establishing drug interactions in man and that ideally such studies should be performed during the early stages of drug development (Brodie, 1962; Modell, 1964).

Environmental agents or smoking can sometimes influence the activity of a drug. Drug interaction may result in an increased toxic effect or reduced efficacy of drugs, any of which could have disastrous effects.

Interaction may modify the degradation of a drug by inducing or inhibiting metabolic enzymes systems, especially those associated with liver microsomes. They may intervene in the excretory processes of the drug in the kidney tubules; thus there is no phase from formulations to elimination where drug interactions are excluded (Griffin and D Arcy, 1974). Thus drug interactions may be quite

varied and complex, and in some cases, more than one mechanism may be involved (Hansten, 1979).

## 1.1 MECHANISM OF DRUG INTERACTION:

Experimental findings and clinical experience have shown that the great majority of interactions occur by a small number of relatively specific basic mechanisms (Evaluation of Drug interactions, 1976).

The mechanisms are classified into:-

a) Pharmacokinetic interaction where some agents alters the disposition of another.

b) Pharmacodynamic interaction in which the response or sensitivity of the body tissue to a particular drug is altered by another administered concurrently. Such interaction often involves drugs with similar or opposing pharmacological activity.

c) Miscellaneous interaction (Hansten, 1979).

## 1.2 PHARMACOKINETIC DRUG INTERACTIONS

Many drugs influence gastrointestinal function; the usual result of absorption interaction is a reduction in the rate of absorption or in the total amount of drug

absorbed, so that drug effect are reduced or abolished. This sort of interaction can occur at the stages of absorption, distribution, metabolism and excretion.

(a) INTERACTIONS AFFECTING DRUG ABSORPTION

In order for a drug to reach blood stream from the alimentary canal, it must be absorbed. The absorption refers to drug transfer from the site of administration (the GIT) to the systemic circulation. The absorbing system in the GIT is the mucosal epithelium which extends from the oral cavity to the anus, forming a continuous cellular barrier for orally administered substances. For drugs the most important process of absorption is that of passive diffusion (Binns, 1971), where no energy is required.

Generally, whenever a drug must penetrate biologic membranes to gain entry into the vascular fluids there are three important factors governing the rate and extent of access:-

i. Physicochemical characteristics of the drug and its dosage form

ii. Nature of the biologic membrane(s)

iii. Physiological characteristics of biological system near the site of drug absorption.

Knowledge of each of these factors and the interactions among these factors is essential for predicting and explaining their influence on absorption (Mayersolin, 1979).

Many drugs influence GIT function, thereby causing absorption drug interaction. Most of these interactions results in decreased rather than increased drug effects and they are not considered to be of much clinical importance.

Drug interaction during the absorptive phase result in either or both of the following potential clinically significant effect (Barr, 1969).

a. Alteration in the rate of absorption

b. Alteration in the amount of drug absorbed.

(i) CHANGES IN PHYSICOCHEMIACAL FACTORS

PH CHANGES:-

The extent of absorption of a drug from the stomach or duodenum depends on the Pka of the drug and the gastric or intestinal PH which may modify certain drugs.

Alkalinizing agents such as sodium and potassium bicarbonate decreases the absorption of weak acids (NSAIDS, Vitamin K antagonist, oral active penicillin), and in general all acids having a Pka of between 2.5 and 7.5.

Acidifying agents such as citric or tartaric acid affect the absorption of weak bases particularly those with Pka between 5 and 11. For example, the simultaneous administration of Tetracycline and sodium bicarbonate reduces the absorption of Tetracycline (Barr, 1971).

ADMINISTRATION OF CIMETIDINE AND TETRACYCLINE (TCN):-

Cimetidine is a potent inhibitor of gastric acid secretion. The absorption of tetracycline after dissolution at low $P^H$ is primarily duodenal. Thus, hence, Cimetidine by increasing gastric $P^H$ decreases the plasma concentration of tetracycline and the total amount absorbed after a single oral dose but after chronic administration, the bioavailability of tetracycline is unchanged due to increase gastric emptying (Labaune, 1989).

COMPLEXATION AND CHELATION

Drugs may interact to form complexes that are poorly absorbed e.g. tetracycline with calcium, magnesium iron or aluminum ions which are present in many antacids.

Example Cholestyramine binds with cholesterol to prevent its absorption and decrease its level in the blood and this type of interaction occurs with all acidic compounds or with free hydroxyl groups. Kaolin based drugs also affect absorption through complexation of drugs like digoxin.

## II CHANGES IN PHYSIOLOGICAL FACTORS

### a) GASTRIC EMPTYING:-

The importance of gastric emptying with regard to drug absorption is readily apparent since most drugs, irrespective of $P^H$ and weather they are acidic, basic or neutral have shown to be best absorbed from small intestine (Levine, 1970; Prescott, 1974). Changes in the gastric emptying modulate the duration in which a drug remains in the stomach and so influence absorption process. An increase in gastric emptying will favour absorption while a decrease will make the process more difficult. The longer a drug remains in the stomach, the slower will be the rate of absorption.

For example, with paracetamol, the following occurs:-

- Prophanthaline reduces the rate of absorption but has no effect on the amount absorbed (Nimmo, 1976).
- Metaclopramide increases the rate of absorption of paracetamol (Nimmo, 1976).

- Pethidine and dimorphine delays absorption but quantitatively, there is no effect (Nimmo, 1976).

b. INTESTINAL BLOOD FLOW:-

For most lipophylic substances, intestinal blood flow is the rate limiting step whereas for more impermeable sunstance, the rate of absorption may be independent of blood flow. Changes in blood flow may have the following consequences:

- Decrease in blood flow brings about change in the concentration gradient between the intestinal lumen and serosa.
- Increases results in the acceleration of absorption of very permeable substance.

III ACTIVE TRANSPORT BLOCKADE

Drugs actively absorbed like folic acid is inhibited by phenytoin which blocks the transport system. The clinical implication of this varies depending on which of these procession modifies absorption.

In summary, the absorption of drugs from gastro intestinal tract is a complex process that is influenced greatly by physiological and physicochemical factors.

Absorption interactions are often unpredictable, and one drug may enhance the absorption of a second drug but interfere with the absorption of a third drug. Drugs are absorbed much more slowly from the stomach than from the small intestine and absorption may often be limited by the rate of gastric emptying. Atropine, prophantheline and etoclopramide alter the rate of gastric emptying in man and have significant effects on the rate of absorption of other drugs. Many other therapeutic agents influence gastrointestinal motility and gastric emptying and could cause absorption interactions through a similar mechanism.

## 1.3 DRUG DISTRIBUTION INTERACTION

Drug distribution is the act of spreading out of a drug in an orderly manner once it reaches the circulation. Drug distribution is defendant on the following – (Rawlins, 1977 (a)).

a) The partition coefficient of drug between blood and tissues.
b) Regional blood flow
c) Binding to plasma proteins and tissue macromolecules.
d) Active transport.

It is important to note that only the free fraction of a drug is pharmacologically active and that only the free fraction can be distributed in the tissues. This sort of

interaction occurs when two drugs with high affinity for plasma proteins are simultaneously or successively administered. This occurs either by competitive inhibition (for drugs that share same binding site) or by non - competitive inhibition (when one drug alters the configuration of albumin).

I INTERRACTIONS IN THE PLASMA – EXAMPLE:

- Warfarin – phenylbutazone leads to increase in pharmacological activity of the anticoagulant and to the appearance of hemorrhagic accidents. This is due to the free fraction of warfarin increasing as the drug is displaced from its protein binding sites by phenylbutazone.
- Tolbutamide – Sulhaphenazole: - the hypoglycemic effect of Tolbutamide is potentiated as the free fraction of Tolbutamide increases. In addition the ability of sulphaphenazole to inhibit the metabolism of Tolbutamide is also an important factor.

II INTERACITONS IN THE TISSUE: - EXAMPLE

QUINIDINE AND DIGOXIN: There is a sharp increase in the plasma concentration and a significant fall in the renal clearance of digoxin when it is administered concomitantly with Quinidine. The mechanism is either

- Through redistribution of digoxin from its tissue binding sites leading to an increase in the plasma free fraction or
- Through a decrease in the tissue binding of digoxin giving rise to higher plasma levels and less tubular secretion thus explaining the drug in renal clearance (Dalquist, 1980).

Certain diseases are associated with altered drug distribution Lignocaine is cleared from the circulation to the extent of about 70% at each transit of blood through the liver (Stenson et al, 1971). Thus patients with cardiac failure eliminate lignocaine more slowly than normal subjects because of the reduction in iver blood which accompanies these disorders (Thomson et al, 1973).

Propranolol is another drug with a high first pass clearance by the liver (George et al, 1976). Propranolol reduces both its own plasma clearance and that of lignocaine as a result of dose-related reduction on cardiac output and therefore a reduction of liver blood flow (Branch et al, 1973).

### 1.4 DRUG EXCRETION INTERACTIONS

Change in renal function can modify a number of pharmacokinetic processes in the body and thereby lead to unanticipated drug effects or interactions

(Rendenberg, 1974). Urinary excretion of drugs involves the process of glomerular filtration, tabular reassertion and tabular secretion. Flomerular filtration plays virtually no role in drug interaction.

RE-ABSORPTION

Only the non-ionized form of a drug is re-absorbed in the tubule. The elimination of weak acids increases when the urine is alkanized particularly if their Pka lies between 3 and 7.5. If the urine is acidified, the urinary excretion of weak base will be favored.

Examples of drugs that alter urinary $P^H$ are thiazides diuretics and acetazolamide (as alkalizing agents.)

SECRETION:

Tubular secretion of acidic drugs is mediated by a relatively non-specific active transport system, and a variety of endogenous and exogenous compounds are potential substrates. Competition for tubular secretion may lead to a major drug interaction involving the kidney for substances whose major route of elimination is via this pathway, for example, probenicid inhibits the tubular secretion of penicillin delaying elimination and prolonging its action (Kabins, 1972).

The excretion of penicillin is also retarded by pheylbutazone, sulphyl pyrazone, ASA, indomethacin and sulphaphenazole, Decoumarol, and phenylbutazone prolongs the effect of chlorpromazine (Thomson, 1970).

The inhibition of tubular secretion also affects bases e.g. renal clearance of purcainamade is reduced when co-administered with ranitidine or cimetidine (Samogyl and Bochner, 1984).

IMPLICATIONS:-

This type of drug interaction modifies the rate of elimination as a result of changes in clearance and half life. If elimination is accelerated, the duration of action is shortened and therapeutic activity may be lost. If elimination is retarded, accumulation may occur leading to the appearance of secondary toxic effect. In both cases, the dose regimen is inadequate and must be revised.

## 1.5 DRUG METABOLISM INTERACTIONS

Most drugs are eliminated almost entirely by metabolism. Biotransformation takes place largely in the liver, but may also occur in the intestine and lungs.

Enzyme inducers enhance enzyme activity while inhibitors decrease enzyme activity.

Example of enzyme inducers are:- Barbiturates, Antipyrine, Primidone, Tricyclic-antidepressant (TCA), Rifampicin, Phenytoin, Carbamazepine, Glutethimide and Phenylbutazone.

Barbiturate with anticoagulants leads to decrease level of warfarin to three times less than the initial level. Phenobarbital and phenytoin are both enzyme inducers – the metabolism of phenytoin is enhanced leading to a shorter half life but this is not always seen. This may be because Phenobarbital induces the synthesis of the enzyme responsible for the metabolism of phenytoin but at the same time, inhibits the action of this enzyme.

Drugs can also enhance their own metabolism after chronic administration e.g. sulphonylpyrazone (Labaune, 1989)

ENZYME INHIBITION:-

This occurs by competition between two drugs for the same enzyme or due to inhibitor acting in the enzyme responsible for metabolism.

Examples of enzyme inhibitors include: - Dicoumoral,

Phenylbutazone, sulphamethiazole, Cimetidine, Disulfuram, Isoniazid, chloramphenicol and Sulphadiazozine (Christensen, 1969).

IMPLICATIONS:-

Drugs with high excretion ratio (E>1) are virtually unaffected by induction or inhibition when compared to poorly excreted drugs (E<1).

ENZYME INDUCTION:-

This can decrease the duration of a drug leading to total loss of therapeutic effect. This explains tolerance associated with same drugs especially those that stimulate their own metabolism. For active metabolites, it may give rise to increase concentration, e.g. for parcetamol; one of its metabolite covalently reacts with liver protein inducing severe hepatic necrosis. This effect will be increased by any drug which increased the production of this metabolite. This is also true for carcinogenic metabolites.

INHIBITION:-

The decrease elimination and increase concentration may give rise to toxicity. This will however depends on the therapeutic index of the drug.

## 1.6 PRINCIPLES OF PHARMACOKINETICS

Definition:-

Pharmacokinetics is the quantitative and qualitative study of the fate of a drug in the organism to which it is administered. It is concerned with the action of the organism on the drug. It involves the studies of the rate of absorption from the various loci of administration, or distribution in the body, of metabolic transformation and of the elimination (Van de kleijn and Vree, 1979). The application of the information obtained from theoretical and experimental pharmacokinetics for the treatment of patients is further specified. (Vander Kleijn and Vree, 1979).

The rates at which pharmacokinetic processes occur simultaneously are characteristics for every drug with the restriction of a numbers of variables.

Before a drug can exert a pharmacological effect, it must reach its site of action. Thus, it must first reach the general circulation and this requires the crossing of physiological barriers (GIT) for orally administered drugs and the process being known as absorption while its fraction absorbed is known as the absorption coefficient of the drug.

The drug enters the portal circulation after absorption, then to the liver where it is metabolized or transformed into metabolites that are more water soluble hence more easily eliminated, a phenomenon known as hepatic first pass effect which determines greatly the bioavailability of a drug.

On reaching the systemic circulation a drug will first interact with erythrocytes and all tissue to a different extent and this phase is referred to as the distribution phase of the drug. After the distribution of drugs into the various tissues, several elimination processes occur. These processes include urinary excretion, billiary excretion and conversion into metabolites by organs like the liver, intestine, lungs, and kidney. These elimination processes sum up what is known as the "Total Clearance" of the drug.

To ensure the pharmacokinetics characteristics of a drug, the different stages of absorption, distribution and elimination must be quantified and denoted by specific parameters that can be determined mathematically using methods based on plasma and/ or urinary kinetic data obtained after the administration of the compound for different routes.

The pharmacokinetic parameters that are considered most important in drug absorption are:-

- ✓ First pass effect
- ✓ Area under the curve (AUC)
- ✓ Half life

These parameters determine to a large extent the pharmacological responses of individual patients. Pharmacokinetics helps to determine the frequency of administration while excluding any risk of toxicity, physiological state of the individual related to the age, sex, genetic makeup, morphology in trying to estimate the effect on the pharmacokinetic properties of the drug, the pathological state of the patient whether transient or permanent in order to evaluate the influence.

## 1.7 COMPARTMENTAL MODELS:-

Once a drug is absorbed, it disperses to a variety of locations within the body. The rate of distribution into a tissue depends on its vascular perfusion, the permeability of the tissue and blood. These complex procedures may be simplified by considering the body to consist of a number of compartments. These are postulated to account for the experimental observations that drugs are distributed into various fluids and tissues at different rates (Paxon, 1981).

A compartment is defined as a kinetically distinguishable “pool” in terms of the drug concentration – time profile. The number of compartments which can be defined in any particular case will ultimately depend on the number of areas with different rates of drug penetration. Experimentally it is difficult to demonstrate more than 3 compartments, and usually only 2 can be differenced (Paxon, 1981).

The basic approach used in pharmacokinetics is to fit experimental data on drug concentrations on plasma to mathematical equations that represent the flow of drugs and their metabolites through the discrete compartments of a model system. Although each individual drug possesses its own unique properties, it is possible to apply certain general principles to the manipulation of pharmacokinetic data, resulting in a precise description of drug disposition.

Before any equations may be derived from these models, several assumptions have to be made (Paxon, 1981).

Firstly, drugs enter the system only via the central compartment, and are eliminated only from that compartment. Secondly, a reasonable transfer occurs between central and peripheral compartments and thirdly, the exit of drugs from all compartments in the system is described by first-order kinetics. Under this last

assumption the rate at which a drug is removed from a compartment is directly proportional to the drug concentration in it.

### 1.7.2 ONE COMPARTMENT OPEN MODEL

After administration, a drug may distribute into all of the accessible regions instantly. In such a case the body is considered to be a homogenous container for the drug and the disposition kinetics of the drug can be described as one compartment open model. It is called “one compartment” because all of the accessible sites have the same distribution kinetics as if the drug dissolved in a beaker containing a single solvent. It is “open” because unlike the beaker model the drug is eliminated from the container.

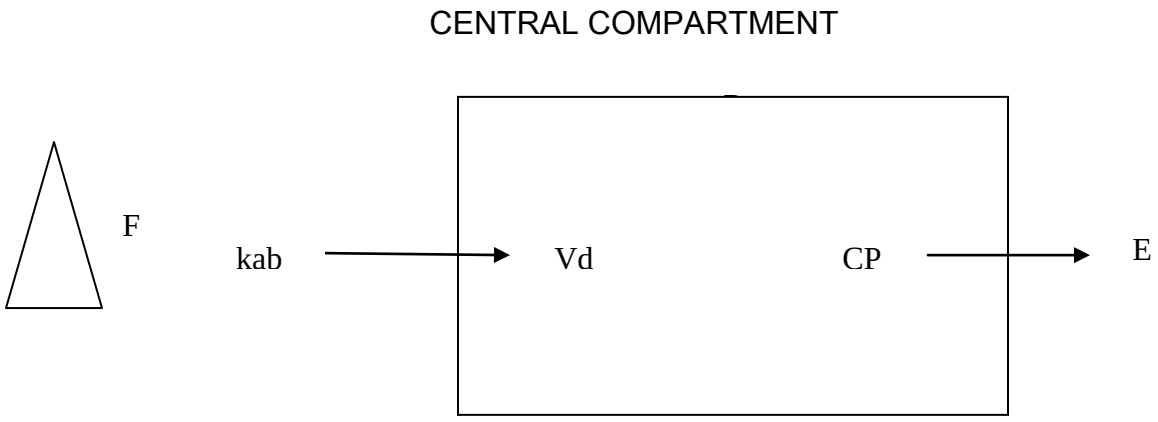

Fig 1.1 Characteristics of a single-compartment open-model

D = Dose of drug administration

F = Bioavailability

Kab = Absorption rate constant

B = Body, composing of blood, body fluids and tissues

Vd = Volume of distribution

Cp = Drug concentration in plasma

Kel = Elimination rate constant

E = Routes of drug elimination

The assumptions that, the body behaves as one compartment does not mean that the drug concentration in all body tissues at any given time are the same. However, a one-compartment model does assume that any changes that occur in the plasma quantitatively reflect changes occurring in tissue drug levels. We assume an instantaneous distribution after an IV injection of a drug into this model.

This equation then holds true

Co = D/Vd

Where: Co = concentration in the plasma immediately after injection

D = Dose

Vd = apparent volume of distribution

The time course of a drug which is handled in the body occurring to a one compartment open model depends upon the concentration which was initially introduced into the body (Co) and $K_{E.}$ Note $K_{E.}$ Is the fraction already eliminated at time (t).

$C = Coe^{-KEt}$

A plot of C versus t will be curve linear on a linear paper and will be linear on a semi-log paper

$$\text{Log } c = \log co \frac{kt}{2.303}$$

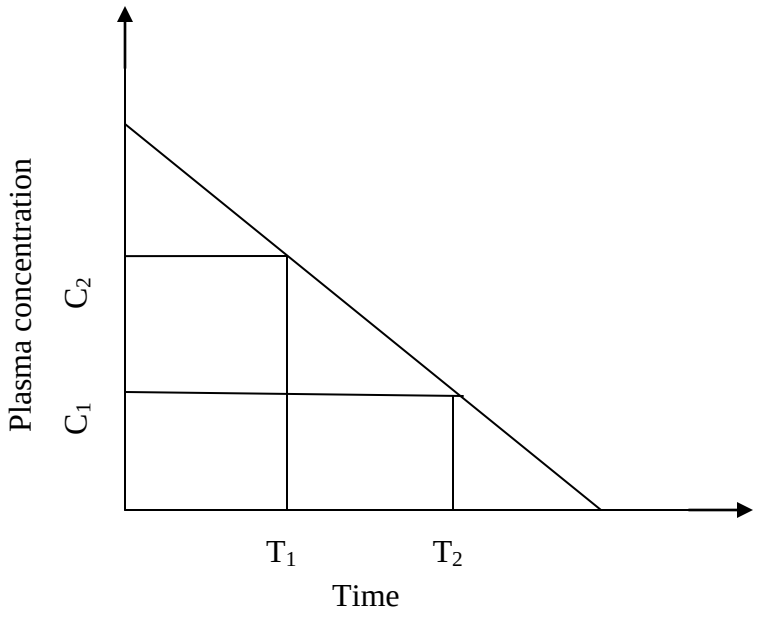


Fig 1.2 Plots of plasma drug concentration against time for a single compartmental model on a logarithm scale.

### 1.7.3 MULTIPLE COMPARTMENTAL MODELS

Very seldom a drug may follow a true one compartment open model. Upon administration drugs usually distribute into the vascular space and some readily accessible peripheral spaces in a much faster rate than into deeper tissues. In such cases the drug is being taken out of the vascular system not only via elimination but also through distribution to other tissues.

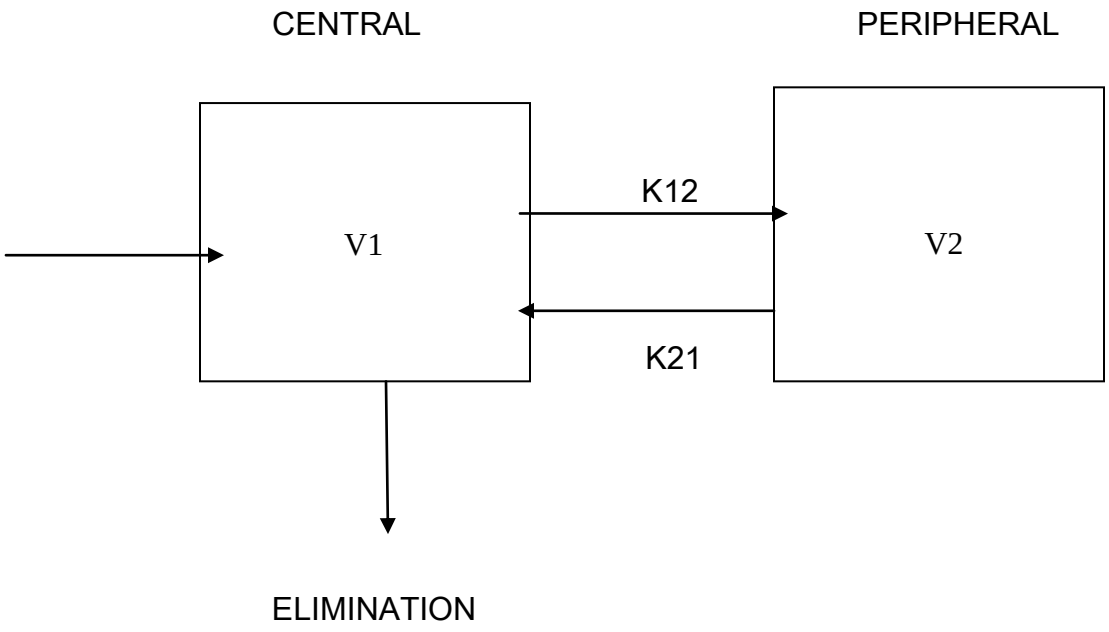


Fig 1.3 Characteristic of multiple compartment models

V1&V2 = Apparent volume of distribution

K12&k21 = Distribution constant

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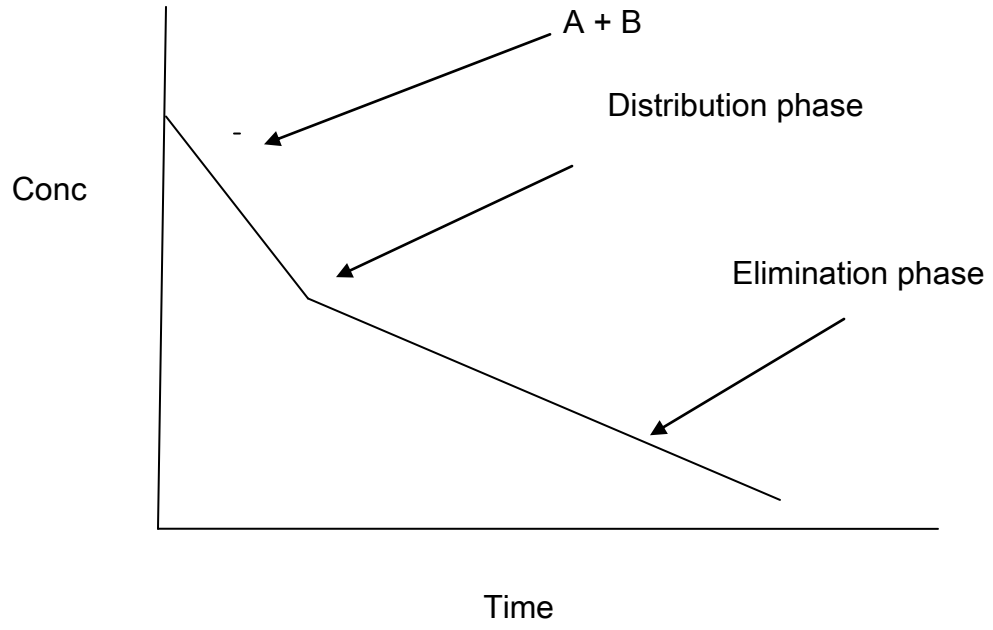



Fig 1.4 Plot of plasma drug concentration against time for a two compartmental model on logarithm scale.

These may be represented by the equations below:-

$Ct = Ae^{-\alpha t} + Be^{-\beta t}$

The coefficient B is the intercept on the ordinate obtained with extrapolation of the elimination phase.

A + B is the actual intercept of the concentration curves at t = 0

α and β are the distribution and elimination rate constants respectively.

A two compartmental model may be expanded to contain additional compartments which can be described mathematically as the sum of many individual exponent functions as there are relevant compartment.

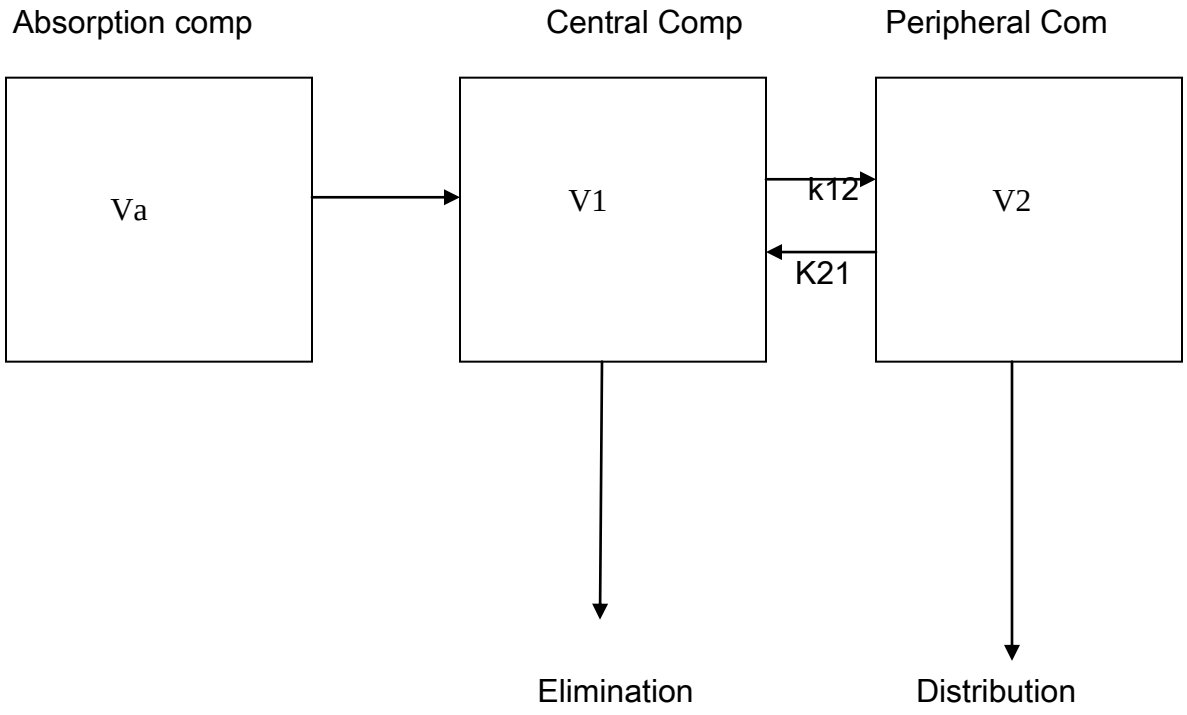



Fig 1.5 3compartment model after a single

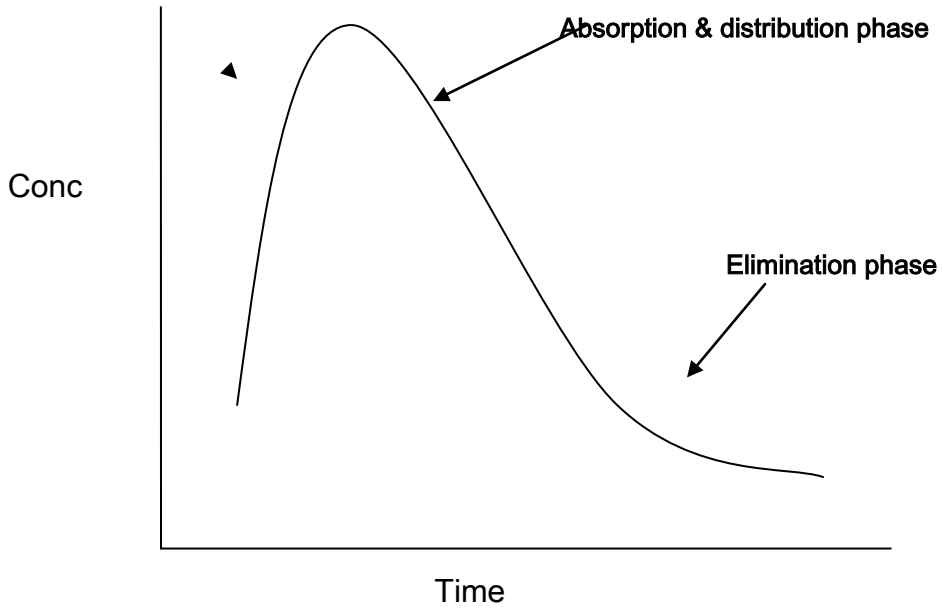



Fig 1.6 plot of plasma drug concentrations against time for a three compartmental model on a logarithm scale.

## 1.8 PHARMACOKINETIC PARAMETERS

Drug absorption and disposition are characterized by the following parameters – volume of distribution (Vd), rate constants for absorption and elimination, and the biological half life of the drug. These parameters determine to a large extent the pharmacological response of individuals. Mathematical formulas have been

developed for calculating these parameters when the concentrations of drug in the plasma and urine are known (Levy, 1963). Other important parameters are area under curve (AUC), clearance and absorption half life.

### 1.8.1 ABSORPTION RATE CONSTANTS ($K_\alpha$)

This is the rate constant of the entire process of drug transfer into the body through all biological membrane. It has units of reciprocal of time $h^{-1}$

$$K = \frac{0.693}{t_{1/2\alpha}}$$

### 1.8.2 ELIMINATION (PLASMA) HALF LIFE ($t_{1/2}$el)

This is the time required to change the amount of drug in the body by one half during elimination (Holfard and Benet, 1995) and can be calculated using the equation.

$$t_{1/2el} = \frac{0.693}{kel}$$

Where, kel is the slope of the first order plot based on the equation for a one compartment model or the final slope of the biphasic plot based on the equation

for a two compartment model. Half life can be determined graphically from a plot of the drug concentration in the blood against time on a log-scale.

### 1.8.3 AREA UNDER THE CURVE (AUC)

This is the area defined by the axis and the curve of blood or plasma concentration versus time. It may be limited to a specific time or be extrapolated to infinity. It is the total blood or plasma drug concentration from tine zero to infinity. It measures the quantity of the drug, which has been absorbed and has entered the general circulation. Thus it is a measure of the amount of circulating drug. It has unit of mg/hr/ml. It can be calculated by the trapezoid method whereby trapezoid between two sampling points are drawn and the areas of trapezoid determined according to the formula.

$$\text{Area} = \frac{C_1 + C_2}{2} \times (t_2 - t_1)$$

$$\text{AUCo-}\alpha = \text{AUCo-t} + \frac{Ct}{\beta}$$

β = Elimination rate constant

Mathematical method

After striping the curve, it is determined by the formula

$$AUCo\text{-}\alpha = \frac{A}{\alpha} + \frac{B}{\beta}$$

### 1.8.4 ELIMINATION RATE CONSTANT (Kβ)

This is the rate constant of the process leading to the elimination of the drug from the body. It is the sum of all individual elimination rates constant. It has units of reciprocal of time $h^{r-1}$.

### 1.8.5 ABSORPTION HALF LIFE ($t_{1/2}\alpha$)

This is the time taken for half of the total absorption to be achieved (half of the difference between theoretical and experimental values). It has units of time in hr.

### 1.8.6 ABSORPTION LAG TIME

This begins where the extrapolated straight line and that of the residual intercepts. It reflects the time taken between the administration of a drug and the time absorption begins. It has units of time in hour.

1.8.7 VOLUME OF DISTRIBUTION (vd)

(i) Initial volume of distribution:- This is in the ratio of the administered dose to the plasma drug concentration extrapolated to zero time after an IV injection.

(ii) Apparent volume of distribution:- This is hypothetically defined as the volume of body water which would be required to contain the amount of drug in the body if it were uniformly present in the same concentration in which it is in the blood or plasma.

Volume of distribution (Vd) relates the amount of drug in the body to the concentration of drug in blood or plasma and has unit of L or L/kg.

Initial Vd = V = D/Co

D = Dose administered by rapid IV injection

Co = theoretical blood coven at time O.

Apparent Vd = $V = Vp + \frac{VT \times FU}{Fur}$

OR

$$V = Vp + \frac{V1\ FU}{FUI} + \frac{VT\ FU}{FUT}$$

Where:- Vp = Plasma Volume

VT = Tissue Volume

V1 = Volume of intestinal fluid

FU = Free faction plasma

FUI = Free faction in intestinal fluid

FUT = Free faction in tissue fluid

### 1.8.8 TOTAL BODY CLEARANCE (cl)

This is the capacity of the organism to eliminate a substance after it has reached the general correlation. It is the total sum of all the individual clearances by the various organs. It reflects the volume of blood completely cleared of a drug by the organ per unit time.

Total clearances = Cl renal + Cl hepatic + Cl other organs of metabolism.

Clearance by any organ depends on the blood flow through the organ and the extraction ratio of the drug by the same organ.

$$Cl = \frac{\text{dose IV}}{AUC_{0-\alpha}} = \frac{f \times \text{oral dose}}{AUC_{oral}}$$

Where f = Bioavailability

Rate of elimination = clearance x concentration

### 1.8.9 ABSORPTION COEFFICIENT

This reflects the fraction or percentage of the administered dose that is absorbed in the GIT mucosa, but does not distinguish between the parent form of the drug and its metabolite. It has unit fractions between 0 and 1.

### 1.9.0 EXTRACTION RATIO

This is the fraction of the drug extracted by an organ and removed from general circulation at each transit through the organ.

$$E_{org} = \frac{Cl_{org}}{Q_{org}}$$

Where Q org = blood flow through the organ.

Units = it assumes any value between 0 and 1

### 1.9.1 MEAN RESIDENCE TIME

This characterizes all kinetic processes, which determine the fate of a drug in the organism. It can be calculate after an IV injection, IV perfusion or oral administration.

MRT = 1/k

It is the inverse of the elimination rate constant. It represents the time required to eliminate 63.2% of the drug and has unit of time. Its value depends on the route of administration and it takes into account all the process that decides the fate of a drug in the body.

### 1.9.1 INFLUENCE OF PHYSIOLOGICAL STATES ON CLINICAL PHARMACOKINETICS:

Many physiological factors exert their influence on drug action and interaction by affecting the drug metabolizing enzymes. The metabolism of a drug is a biochemical reaction. In starvation, there is a lack of nutrients including amino acids and consequently there is a reduction of enzyme proteins. Thus, a person in a poor nutritional state might be expected to be extra-sensitive to drug action because the relative lack of drug metabolizing enzymes results in depressed drug metabolism. Similarly, a lack of substances essential to enzymatic activity,

such as ascorbic acid, may increase the sensitivity to drugs (Buns and Conney, 1974).

Such physiological states that influence the clinical pharmacokinetic of a drug include age, pregnancy, nutrition and the activity of individual.

AGE:

The newborn has a relatively lower glomeruler filtration rate and renal plasma flow than adults and are also seriously deficient in drug metabolizing enzymes for at least the first month after birth. These deficiencies are enhanced in premature babies; neonates may fail to metabolize effectively vitamin K analogues sulphonomides, chloramphenicol, barbiturates, and morphine – (Griffin and D'Acy, 1979)

In the neonates there is higher gastric $P^H$ hence slowing down of gastric emptying with decreased absorption of drugs like paracetamol and phenytoin (Marselli 1976). Also drugs like penicillin G and ampicillin are destroyed by such $P^H$.

There is also a reduction in protein binding, increase volume of distribution, a decrease in renal excretion, but an increase in the renal excretion of the infant (Labaune 1989).

In older age, there is decrease in renal excretion for most drugs (Labaune 1989).

NUTRITION:-

In the under-nourished, absorption of tetracycline, chloramphenicol and rifampicin is decreased, the protein binding of Phenylbutazone and doxcycline is decreased, renal excretion of tetracycline, gentamycin, penicillin G and tobramycin is decreased, and metabolism of chloramphenicol, salicylates, acetanilide and chloroquine is decreased (Labaune 1989).

PREGNANCY:-

Changes are primarily related to the distribution of the drug by poetal – placenta diffusion. There is an increase in gastric $P^H$ within the first 6 months, decrease albumin level, increase plasma volume by about 50% between $30^{th}$ to $40^{th}$ weeks.

SEX:

The relative ration of muscles mass and adipose tissue may affect volume of distribution and total body clearance. Hormone (FSH, Oestradiol) variation in pregnancy can influence pharmacokinetic behavior of drugs.

ALCOHOL:-

Consumption of alcohol affects metabolism being reduced after a single dose but enhanced in a chronic alcoholic.

TOBACCO:-

Tobacco abuse affects pharmacokinetic parameters to a great extent. Polycyclic hydrocarbons are among compounds found in cigarette smoke, which are powerful inducing agents of cytochrome P450 (JUSKO 1978).

### 1.9.2 EFFECTS OF PATHOLOGICAL STATES

Two major pathological sates are renal insufficiency and hepatic insufficiency. Renal insufficiently influences distribution by acting on a protein binding of weak acids, metabolism by modifying certain enzymes reactions, renal excretion related to decrease renal clearance and increase half life.

Hepatic insufficiency modifies protein binding, metabolism and hepatic clearance. Its effect depends on pharmacokinetic characteristics of the drug. Other pathological states include cordial insufficiency heper/hypo thyroidsm, pulmonary disease, obesity etc.

In the obese, there is increase volume of distribution half life and clearance (Laboune, 1989)

### 1.9.3 CHRONIC ADMINISTRATION:-

Chronic administration of a drug should ensure that:

a. Therapeutic effectiveness is attained as rapidly as possible.
b. An active plasma concentration is continuously monitored.
c. Any accumulation leading to the appearance of undesirable effect is avoided.

The relationship between the pharmacological effect of a drug and its pharmacokinetic property is much more closely associated with the plasma concentration of the drug than with the amount present in the body.

The steady state depends on the

- Administered dose - fraction absorbed
- The dose interval - the half life
- Volume of distribution.

### 1.9.4 CONCEPT OF A HEALTHY VOLUNTEER:

In clinical studies, bioavailability of a drug is commonly determined in healthy volunteers. The drug is intended for a patient whose disease can play a prominent role in the pharmacokinetics of the drug. Consequently, the extrapolation of these parameters from the healthy individual to the patient is not always appropriate; but of clinical importance to the patient is a full knowledge of the pharmacokinetic properties of the drug including possible existence of a non-linear response or entero-hepatic circulation.

# CHAPTER TWO

## LITERATURE REVIEW

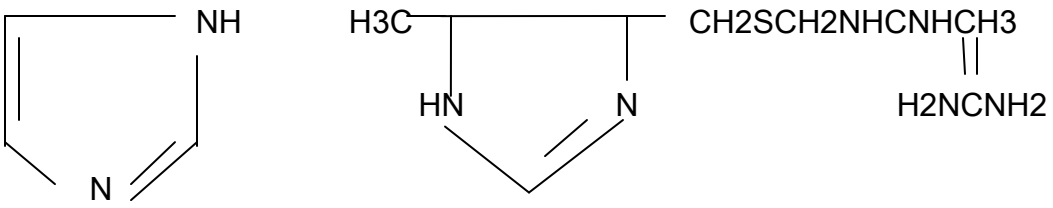
### 2.1 CIMETIDINE

#### 2.1.1 INTRODUCTION AND HISTORY:

Cimetidine is one of the drugs which have specific antagonistic activity on histamine $H_2$ – receptors. Its principal action is on parietal cell histamine $H_2$ – receptors. Cimetidine is the first histamine $H_2$ – receptor antagonist. With its safety profile, cimetidine has become extensively used in the treatment of ulcer disease and acid related disorders. The drug was introduced into market in 1976, became available in the United Kingdom (UK) in November 1976 and in the United States of America (USA) in August 1977, and by the end of 1978, it was available for clinic use in more than 90 countries (Duncan and Parsons, 1980) its popular brand name is tagamet from Glaxowellcome.

#### 2.1.2 CHEMISTRY

Chemically, Cimetidine is a substituted imidazole compound with a chemical nomenclature – 2 – cyna – methyl 3 – [2 –(5 – methyllimidazole – 4 – ylmethylthio) ethyl] guanide (B. P. 1993), and a graphic structural formula below.




Imidazole Ring Cimetidine

Fig 1.7 Chemical structure of Imidazole and Cimetidine

Cimetidine is a weak base with a high degree of water solubility. These properties affect many of the drugs pharmacokinetic characteristics. The solubility of cimetidine in water is greatly increased with the addition of dilute acid which protonates the imidazole ring

2.1.3 PHYSICAL PROPERTIES

1. Appearance - White to off-white crystalline powder
2. Odour - Odourless or with a faint odour.
3. $P^H$ $P^H$ of 5.0mg/ml in carbon dioxide
   Free water is 8.0-9.5 (Basic)
4. Solubility - Slightly soluble in water, very soluble in Methanol and practically insoluble in dichloromethane and ether.

5. Stability - stable for 48 hours at room Temperature when added to commonly Used i.v solutions.

2.1.4 CHEMICAL PROPERTIES

1. Mol formula - $C_{1O}H_{16}N_6$**S**

2. Mol weight - 252.34

3. Melting point - 141°C – 143°C

4. Loss on drying - when dried to constant weight at 100°C – 105°C, loses not more than 0.5% of its weight.

2.1.5 PHARMACOKINETICS:-

Cimetidine is rapidly absorbed from the gastrointestinal tract (GIT) and is approximately 60 – 70% bioavailable after oral administration. When Cimetidine

is administered orally in tablet or in liquid form in the fasting state, the blood/plasma concentration – time profile is discontinuous, 2 “peak” are observed, the first at about I hour and the second after about 3 hours (Somogyi and Gugler, 1983).

Cimetidine distributes widely and extensively throughout the majority of body fluids, organs and tissue in man. There is extensive uptake of Cimetidine into selected organs e.g. (kidney and lung) and tissues (Schentag et al 1981). However, the amount distributed depends upon the skeletal muscle uptakes of Cimetidine.

Cimetidine distributes into the cerebrospinal fluid (C.S.F) at a ratio of 0.1 to 0.2 compared with plasma. Higher rations have been observed in patients with liver disease (Schentage et al, 1981). The mean saliva to plasma ration is 0.2 (Somogyi and Gugler, 1983).

Cimetidine is eliminated from the body by renal, metabolic and billiary process. However, the principal, route is by renal elimination (Taylor et al, 1978; Grahnen et al1979; Walkenteins et al 1978). Between 50% and 80% of the dose administered i.v is recovered in urine as unchanged Cimetidine. This fraction is

less after oral administration, but is independent of the amount of the dose (Somogyi and Gugler, 1983). In ulcer patients, 40% is recovered unchanged in urine after oral administration. The high urinary excretion of Cimetidine coupled with low plasma concentrations results in a high renal clearance of the drug (Somogyi and Gugler 1983). Billiary excretion of Cimetidine accounts for only 2% of the dose (Gugler et al, 1981). Thus, the elimination of Cimetidine into bile is negligible and of no clinical significance.

Cimetidine is metabolized to 3 known products namely – Cimetidine sulphoxide, hydroxymethyl Cimetidine and guanylurea Cimetidine, although the later may be formed non – enzymatically and may form an in-vivo degradation product (Taylor et al (1978).

Elimination of Cimetidine is accelerated by an average of 15% in the presence of phenobarbitone, due to induction of its metabolism (Somogyi et al 1981). Elimination half life of Cimetidine is approximately 2 hours in healthy adults with normal kidney and hepatic function (Somogyi and Gugler, 1983). It increases in renal impairments, hepatic impairments and in the elderly. Cimetidine is not significantly removed by haemodialysis or peritoneal dialysis (Drug facts and comparisons, 1989b).

### 2.1.6 MECHANISM OF ACTION:-

Cimetidine competitively and selectively inhibits the action of the histamine H2 – receptor of the parietal cells. Thus it inhibits the secretion of gastric acid stimulated by histamine, pentagastrin, acetylcholine, insulin, caffeine, food and other secretagues substances.

### 2.1.7 USES

Cimetidine is used in conditions where inhibition of gastric acid may be beneficial such as in the following:-

- Short term treatment of active duodenal ulcer
- Maintenance therapy for duodenal ulcer patients at reduced dosage after healing of active ulcer.
- Pathological hypersecretory conditions such as in Zollinger – Ellison syndrome, systematic mastosytosis multiple endocrines.
- Unlabelled uses: - Oral or I.V Cimetidine, 60 – 90 minutes before anesthesia has been used to prevent aspirations pneumonitis.
- Cimetidine has been used in the prophylaxis of stress – induced ulcers and of acute upper gastrointestinal bleeding, in gastro esophageal reflux, tinea capitis, herpes virus infection and hirsute women (Drug facts and comparisons 1989b).

### 2.1.8 ADMINISTRATION AND DOSAGE

Cimetidine is available for oral use as tablets containing 200mg, 400mg or 800 mg and as a liquid containing 200 mg /5ml.

For treatment of active duodenal or benign gastric ulcers, pathological hyper secretary conditions, dosage is 800mg at bed time or 400mg twice daily.

A dose of 400mg may be given at bedtime for prevention of recurrence of duodenal ulcers. For hospitalized patients with pathological hyper secretary conditions or intractable ulcers, or patients unable to take oral medication, parenteral form may be used. Usual dose is 300mg I.M or I.V every 6 to 8 hours. Dosage may be increased if necessary but not exceeding 2400mg 1 day.

### 2.1.9 ADVERSE EFFECT OF CIMETIDINE

Cimetidine is among the safest drugs currently available. Most adverse effects of Cimetidine are of minor nature and are usually promptly reversible upon slopping treatment.

Side effects of Cimetidine include altered bowel habit, intestinal nephritis, acute pancreatic, tiredness and hypersensitivity. Reversible liver damage and hematological disorders are reported. Cardiac arrhythmias and arrest following

I.V bolus may occur. Gynaecomastia is also an occasional problem with Cimetidine and reversible impotence has also been reported.

CNS adverse effects associated with Cimetidine include dizziness, headache, confusional states, hallucinations and delirium. The apparent causes of Cimetidine included CNS toxicity appear to be due to the prescribing of large doses of Cimetidine in patients who have a reduced ability to eliminate the drug (Somogyi and Gugler, 1983).

### 2.2.0 CIMETIDINE DRUG INTERACTION

Interactions with Cimetidine occur primarily through 3 different mechanisms:-

The ability of Cimetidine to raise gastric $P^H$ may have influence on oral drug bioavailability. Change in $P^H$ may also increase the stability and presumably the oral bioavailability of acid-labile drugs (Mayersohn, 1979).

Cimetidine, like other substituted imidazoles inhibits various microsomal drug metabolizing enzymes in animals as human liver (Wilkinson et al, 1974). Thus in man Cimetidine interacts with various clinically important drugs (Somogyi and Gugler, 1982; Klotz and Reiman 1984) which are extensively metabolized in the liver.

Due to the ability of Cimetidine to undergo renal tubular secretion via the renal cationic transport system, competition with other basic compounds renally

secreted may occur as in the case of triamtene (Somogyi et al, 1989) Chlopropamide (MOcda et al 1994) Zidovudine (Fletcher et al 1995) and creatinine (Zeimniok et al 1986).

### 2.2.1 EFFECTS OF CIMETIDINE ON ABSORPTION OF OTHER DRUGS:

In 1978, Fairfax et al concluded that increased absorption of acid – labile drugs can occur in some patients taking Cimetidine. Cole et al 1980 concluded that chronic treatment with Cimetidine reduced the absorption of tetracycline from a capsule formulation, but had no effect when tetracycline is given in solution form; this is measured by urinary excretion.

Cimetidine has been shown to slightly increase serum salicylates concentrations and bioavailability following administration of enteric – coated aspirin (Paton et al 1983, Willoughby et al 1983).

In a study by Rogers et al, 1980 where six healthy subjects received 400mg of Cimetidine every 6 hours, and to the 6$^{th}$ subject, 500mg ampicillin given and assessed by the peak day plasma concentration (Cmax), the time of its occurrence (Tmax), the AUC and the terminal half life, Cimetidine induced no alterations in ampicillin disposition. In the same study with Cotrimaxazole – no

significant differences in the pharmacokinetics of sulphamethoxazole or trimethoprin were observed, although plasma concentration of the later tended to be higher under Cimetidine treatment.

When 400mg of Cimetidine was given 2 hours prior to administration of ketoconazole, the AUC of ketoconazole was reduced by 65% over the control, but was increased by 52% when ketoconazole was given in an acid solution, again 2 hours after Cimetidine (Vander meer et al, 1980).

Cimetidine the urinary excretion Zidovudine decreased and the fraction of Zidovudine converted to metabolites increased. It was concluded that Cimetidine presumably inhibits the renal clearance of Zidovudine by competing for renal tubular secretion.

Pharmacokinetics studies have consistently shown that Cimetidine reduces theophylline plasma clearance, increase theophylline half life and increase plasma theophyline levels (hanstern and horn (1989d).

Ahmad et al 1992 reported the effect of Cimetidine on the $LD_{50}$ of paracetamol in mice. The $LD_{50}$ of paracetamol was increased by the administration of

Cimetidine. Thus Cimetidine protects liver injury induced by paracetamol and could be used clinically in patients intoxicated with paracetamol.

### 2.2.2 CLINICAL SIGNIFICANCE OF CIMETIDINE DRUG INTERACTION.

Drug interaction caused by Cimetidine has stimulated the interest of clinicians and pharmacologist due to the large number of drugs affected. However, much more has been made of this than is probably justified, given that most such interactions are of purely pharmacokinetic interest (Howden, 1993). Before the effect of Cimetidine interaction can be regarded as significant, it is suggested that the change caused by the interaction should be between 20 – 25% (Upton et al 1982).

Certainly some of the effects of Cimetidine interactions are not significant at clinical level. However, many of those which are potentially harmful only occur in a small proportion of patients. Thus, long lists of drugs with which Cimetidine has been shown to interact with are likely to have served the commercial objectives of rival pharmaceutical companies than to have usefully informed prescribers (Howden 1993).

Clinically important interactions do occur between Cimetidine and certain other drugs which are extensively metabolized in the liver and have a narrow therapeutic index. Example a decrease in elimination of benzodiazepines during Cimetidine administration may not necessitate dosage changes in most patients, since benzodiazepine have a wide therapeutic concentration range. Patients who are at increased risk of Cimetidine-drug interactions include the elderly and those with impaired renal or liver function.

PRECAUTIONS

Reduce dose in renal and hepatic impairment, avoid I.V injection in high dosage and in cardiovascular impairment, pregnancy, breast feeding.

### 2.2.3 PROPANTHELINE BROMIDE

2.24 DESCRIPTION

The chemical name is di-isoprophyl methyl (2-xantheneayl carboxyloxyl ethyl) ammonium bromide. It is quarternary ammonium anti-muscarinic agent with peripheral side effects.

2.2.5 STRUCTURE

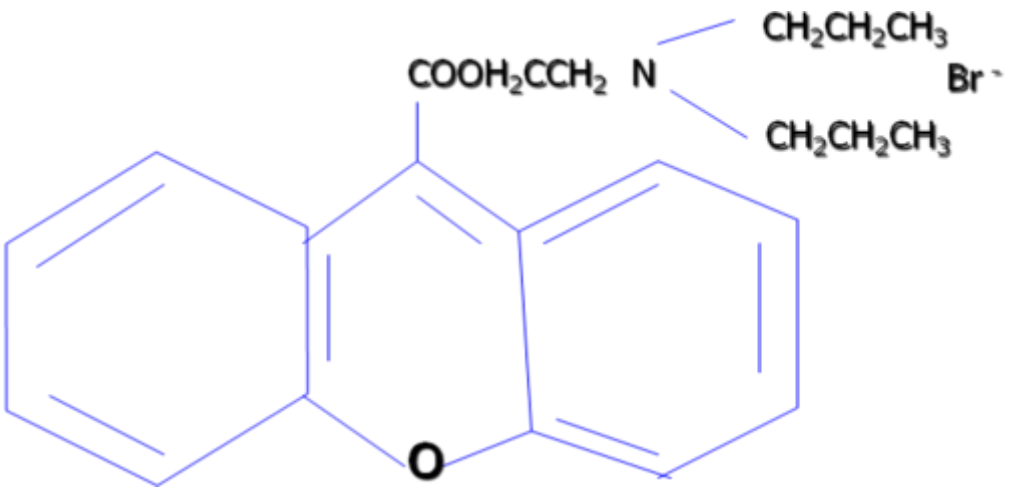



Fig1.8 Chemical structure of propanthelene

Molecular formula:- $C_{23}H_{30}BrNO_3$

Molecular weight: - 448.4

Name: - Propantheline Bromide

2.2.6 PHYSICAL PROPERTY

1. Appearance - White to yellowish white
2. Odour - odourless or almost odourless
3. Texture - Slightly hygroscopic powder or crystal
4. Solubility - Very soluble in water, alcohol (96% ethanol) and chloroform. Practically insoluble in ether.

### 2.2.7 PHARMACOKINETICS

It is incompletely absorbed from the gastro intestinal tract (GIT). It is eliminated mainly in urine as metabolites and unchanged drugs. Its duration of action lasts for 6 hours. Absorption in the GIT is decreased by food.

### 2.2.8 MECHANISM OF ACTION

It competitively blocks acetylcholine, which decreases GI motility and inhibits gastric acid secretion. Hence it is a parasympathetic agent.

### 2.2.9 PHARMACOLOGICAL ACTION:

Quaternary ammonium antimuscarinics like prophantheline bromide exhibit a greater degree of antinicotinic potency. Peripheral action includes increase heart rate, decrease production of saliva, sweat, branchial, nasal, gastric and intestine secretion, decrease intestinal motility. Ocular effects of propantheline include dilation of pupil, paralysis of ocular accommodation and photophobia.

### 2.3.0 USES AND DOSAGES

It is use as adjunct in the treatment of peptic ulcer. Used in the management of spasm of the GIT. It is also used in the treatment of Parkinsonism, treatment of excessive salivation and secretion of the respiratory tract. Initial dose is 15mg

(tid) before meals and 30mg at bedtime. Doses up to 120mg per day may be needed in some patients.

It is also used in the treatment of enuresis and hyperhydrosis. Prophantheline is highly effective in preventing neurocardiogenic syncope (Yu and Sung 1977).

### 2.3.1 SIDE EFFECTS

Toxic doses may produce non-depolarizing neuromuscular effect with paralysis of voluntarily muscles. It may slow the passage of other drugs through the intestine with variable effect of absorption.

Other side effects include dry mouth, difficulty in swallowing, dilatation of pupils (mydriasis), loss of accommodation (cycloplegia), and decrease bronchial secretions, transient bradaycardia followed by tachycardia, constipation, and difficulty in micturition. There is bromide intoxication due to propantheline bromide (Herkerling and Ammar, 1996).

### 2.3.2 DRUG INTERACTIONS

Food reduces the oral bioavailability of propantheline bromide in health subjects (Moses et al, 1983). Propantheline enhances the absorption of digoxin and

nitrofurantoin but reduce and retard that of paracetamol. In a study on the effect of delay gastric emptying and absorption on the pharmacokinetics parameters of lithium, propantheline prolongs the plateau time of lithium by 27% (Belibas et al 1995).

Vose et al 1950 showed a tentative evidence of a qualitative relationship between the oral dose administered, plasma concentration and the effect of propantheline bromide on salivary secretion. Propantheline is a satisfactory alternative when glucogon is contraindicated or not available (Merlo et al 1978).

Fournet et al 1983 demonstrated that peristaltic function of the human oesophageal smooth muscle is greatly dependent on muscarinic transmission. This is a study of motor activity of normal oesophagus. In a study of oral anticholinergic and gastric emptying, clidinium bromide 5mg delays gastric emptying to the same extent as 15mg propantheline bromide without the marked suppression of salivary secretion by the later. (Hurwitz et al 1982). Salivary suppression was noted about 4 hours after ingestion of 30mg prolong acting propantheline (Gibaldi and Grunhofer 1975). Propanthaline bromide does not affect basal growth hormones, cortisol and prolactin levels (Davies et al 1983).

Propantheline is an anticholinergic that cause xeroestomia by the decreasing salivation (Ahmed et al 1993). In a study of the effects of nifidipine, propantheline bromide and the combination of esophageal motor function in normal volunteer by Hungo et al 1984, showed that:-

a. Nifedipine has a greater effect than propantheline on the lower esophageal sphincter.
b. Propantheline bromide has a greater effect than Nifedipine on esophageal contraction amplitude.

The combination of Nifedipine and propantheline bromide is as efficacious as 400mg Cimetidine in inducing healing of uncomplicated duodenal ulcers with similar side effects (Agrawal et al 1993)

### 2.3.3 PARACETAMOL:-

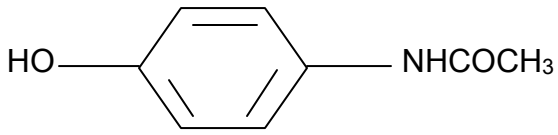
### 2.3.4 INTRODUCTION:-

Paracetamol (acetaminophen) was first used in medicine by Von Mering in 1893. However, it has gained popularity in 1949, after it was recognized as the major metabolite of acetanilide and phenacetin (Goodman and Gilman, 1990).

2.3.5 DESCRIPTION:-

Paracetamol is a Para-aminophenol derivative with the chemical name: 4 – hydroxiacetamide, N (4 – hydroxyphenyl) acetamide; N – aminophenol.

2.3.6 Chemistry




Paracetamol

Fig 1.9 Chemical structure of paracetamol

2.3.7 PHYSICOCHEMICAL PROPERTIES

1. Molecular formula : $C_8H_9NO_2$
2. Molecular weight : 151.2
3. Melting point : 169 – 172$^0$C
4. $P^H$ : 6
5. PKa : 9.5 (weak acid)
6. Colour : white
7. Odour : odourless
8. Taste : Bitter

9. Form : crystalline powder

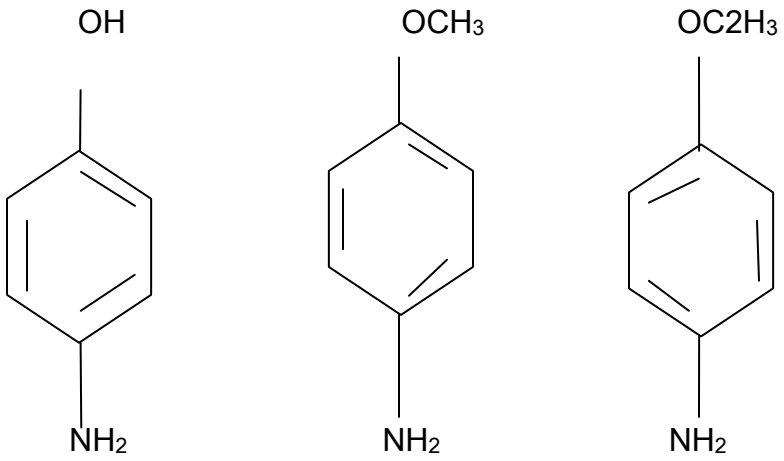
10. Solubility : insoluble in benzene, very sparingly
Soluble in chloroform and sparingly
Soluble in water, ether,
and in 96% ethanol (1:10).

### 2.3.8 STRUCTURAL ACTIVITY RELATIONSHIP (SAR)

The SAR among the P – aminophenol derivatives is as follows – the parent compounds possess a strong antipyretic and analgesic action. However, it is too toxic to serve as a drug (Welliette 1982).

In general any type of substitution in the amino group that reduces its basicity results also in a lowering of its physiological activity. Acetylation is one type of substitution that accomplishes this effect.

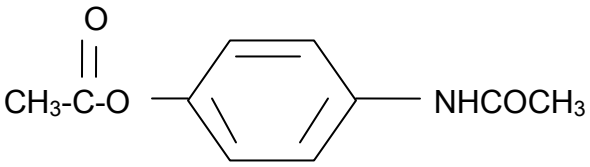
Etherification of the phenolic – OH group produces stronger analgesics but too toxic to used due to the free amino group, example include anisidine and phenetidine which are the methyl and ethyl esters respectively (Willeette, 1982).




P-aminophenol Anisidine Phenitidine

Fig 2.0 Chemical structures of aminophenol, anisidine and phenitidine.

Esterification of the OH – group with an acetyl moety produced analgesic which has the same activity and disadvantages as the free phenol.




*P-ACETOXYACETANILIDE*

Fig 2.1 Chemical structure of acetoxyacetanilide

However, the salicylic ester exhibits a diminished toxicity and an increased antipyretic activity.

Acetylation of the amino groups with free OH – group produced the best P-aminophenol analgesic e.g. paracetamol (Williette, 1982)

Among the alkyl esthers of the N-acetyl-P-aminophenol derivatives, the ethyl ether was found to be the best and is now the official phenacetin. The methyl and propyl homologue were undesirable from the stand point of causing emesis, salivation, dieresis and other reactions (Willette, 1982).

### 2.3.9 PHARMACOKINETICS:-

Paracetamol is administered orally or parenterally. It is rapidly and almost completely absorbed from the gastro-intestinal tract when administered orally. After oral administration, plasma levels of the drug reach their peak readily. The time required for maximum drug concentration in the plasma varies between 30 – 90 minutes but may be decreased significantly by the administration of a buffer solution.

Paracetamol is relatively well distributed throughout the body fluid (Flower et al, 1985). Binding of the drug to plasma proteins is variable. In humans, plasma protein binding is negligible with plasma concentrations which correspond to the therapeutic doses. Paracetamol is metabolized via a variety of path ways, it is

metabolized predominantly in the liver and secreted in the urine as the glucurinide and sulphate conjugates. Less than 50% is secreted unchanged.

Elimination half life of paracetamol is from 1 – 3 hours. Peak plasma concentration occurs within 30 – 90 minutes, and absorption is mainly from the small intestine.

Paracetamol is excreted in the urine primarily as inactive glucuronate and sulphate conjugates.

### 2.4.0 MECHANISM OF ACTION:-

Paracetamol acts by inhibiting prostaglandin synthesis in the CNS and peripherally by blocking pain impulse generation. Its antipyretic action is by acting centrally on the hypothalamus (temperature regulating center) to produce peripheral vasodilatation resulting in increase blood flow through the skin.

### 2.4.1 USES AND DOSAGES

Paracetamol is equivalent to aspirin as an effective analgesic and antipyretic agent. It is given orally or rectally for mild to moderate pain and for pyrexia. The

usual adult dose is 0.5 – 1g every 4 – 6 hours to a maximum of 4g daily. For long term use, daily dose should not exceed 2.6g.

Children less than 3 months – 10mg/kg body weight, 3 month – 1 year: 60 - 120mg daily

1 year – 5 year: - 20 – 250mg

6year – 12 year: - 250mg 3 – 4 times/day

### 2.4.2 PRECAUTIONS AND CONTRAINDICATION:-

Paracetamol should be taken with care inpatient with impaired kidney or liver and contraindicated in hypersensitive patient.

### 2.4.3 ADVERSE EFFECT:-

When used as directed, paracetamol rarely causes severe toxicity. Side effects associated with paracetamol may include hypoglycemia, jaundice and hematological disorders like neutropenia, leucopenia and pancytopenia. Allergic reactions such as skin eruptions, urticarial skin reactions, fever may also occur.

In overdose, pallor, nausea, vomiting, anorexia and abdominal pain occurs within the first 24 hours. Liver damage may become apparent 12 – 48 hours after ingestion. In severe poisoning, hepatic failure may progress to encephalopathy,

coma and death. Acute renal failure could also result. Cardiac arrhythmias may also be noticed. Treatment of over dosage is with fluid and electrolyte therapy IV glucose to prevent hypoglycemia.

### 2.4.4 PARACETAMOL – DRUG INTERACTION:-

Paracetamol absorption was reported to be considerably slower in the presence of propantheline than its absence. (Nimmo,1973). Other agents with anticholinergic activity also probably delay paracetamol absorption (Heading et al 1973).

Food, especially if high in carbohydrates, has been shown to delay paracetamol absorption, an effect associated to delayed entry of the drug into the intestine or to delay in tablet dissolution or disintegration (McGiveray and Mattok, 1972). Similarly, activated charcoal in large oral doses (5 – 10g) and oral Cholestyramine were reported to reduce the GIT absorption of paracetamol.

In the determination of paracetamol and phenacetin in plasma by high pressure liquid chromatography, (Gotelli et al, 1977) showed that of the 36 other drugs tested, only theophyline interfered with the determination of paracetamol. Caffeine enhances the analgesic of paracetamol; substantial evidence indicates

that chronic alcohol ingestion increases the toxicity of overdoses of paracetamol. Oral contraceptives may increase the hepatic metabolism of paracetamol, decreasing the elimination half life by 20 – 30% (Drugs facts and comparisons, 1989a). The magnitude of this effect is probably sufficient to inhibit the effect of paracetamol, in at least some patients (Hansten and Horn, 1989c).

### 2.4.5 AIMS AND OBJECTIVES OF THE PRESENT STUDY:-

In Nigeria today, there are millions of peptic ulcer patients including many with endoscopically proven cases of peptic ulcer as personal investigation revealed (Garba 1992). The histamine H2 – receptors antagonist are among the most widely prescribed drugs. H2 – receptors antagonist are being widely available as an over the counter medication for the treatment of heartburn and excess acidity hence increase incidence of self-medication and poly pharmacy by prescribers. It is imperative to note that clinically important drug interaction will require the affected drug to have a narrow therapeutic index and should produce greater than 20 – 25% change in absorption, distribution or disposition. This degree of change is necessary to overcome the normal intra-patient variation in drug disposition (Upton, 1982). In man, cimetidine interacts with various clinically important drugs (Somogyi and Gugler, 1983; Klotz and Reiman, 1984) which are extensively metabolized in the liver. On the other hand, in studies on drug

interactions with Cimetidine related to drug absorption, it appears that some are contradictory or inadequately designed (Somogyi and Gugler, 1982).

Also of importance is the fact that because the stomach is not an important site of drug absorption even for weakly acidic drugs, gastric emptying time, and intestinal transit rate determines to a great extent the rate of absorption of drugs.

Paracetamol is widely used in the treatment of mild to moderate pains of different etiology. Most often it is prescribed as an analgesic adjunct to ulcer patients who are on Cimetidine. It is evidently clear that other analgesics (NSAID) are to be avoided in ulcer conditions (Howden and Hott, 1991). Furthermore, since paracetamol is well tolerated and can be obtained without prescription, many patients on Cimetidine take paracetamol for analgesia and other complaints without being prescribed for them. Therefore a great potential exists, and needs to be thoroughly investigated, for interaction to occur between cimetidine and paracetamol since the two drugs are commonly used in combination.

The proposed study therefore tends to investigate and compare the effect of increase intestinal $P^H$ and decrease gut motility of Cimetidine and delayed gastric emptying and intestinal transit of Propantheline on the pharmacokinetic

parameters of paracetamol with a view of assessing whether Cimetidine has similar drug – drug metabolism/excretion as $H_2$-receptor antagonist.

On the whole, the study is expected to address the following objectives:-

1) To determine the salivary pharmacokinetic profile of paracetamol in Healthy volunteers

2) To determine the effects of Cimetidine on the pharmacokinetic parameters of paracetamol.

3) To determine the effect of Propanthaline on the pharmacokinetic parameters of paracetamol.

4) To evaluate the effect of Cimetidine and Propanthaline on the bioavailability of paracetamol.

# CHAPTER THREE

# MATERIALS AND METHODS

## 3.1 MATERIALS

### 3.1.1 GLASSWARES

- Extraction tubes (Glasfirn,W. Germany).
- Pipettes 0.02ml, 0.2ml, 1ml, 2ml, 3ml, 5ml, and 10ml.
- Test tubes:- 10ml and 20mml, pyrex England.
- Measuring cylinders: - 5ml, 10ml, 50ml and 100ml.
- Volumetric flasks:- 25ml, 50ml, 250ml, 500ml.
- Crucible
- Conical flask:- 25ml, 50ml and 250ml pyrex England
- Beakers 50ml, 100ml, and 250ml pyrex England
- Round bottom flask, pyrex England
- Syringe and needle, 2ml, 5ml, 10ml.
- Glass funnel and filter papers (whatman)
- Stirring rod
- Sample bottles 10ml, 20ml

### 3.1.2 EQUIPMENT

- Vortex mixer (Kanke and Kunke Germany)
- Centrifuge; gallenkamp, England

- Flask shaker – Gallenkamp, England
- Hot air oven – Gallenkamp, England
- Electric balance
- Double beam UV spectrophotometer
- Refrigerator
- Disintegration rate study apparatus, Eureka, Germany
- Dissolution rate study apparatus, Eureka, Germany
- Friability test study apparatus (Eureka, England)
- Melting point study apparatus (Eureka, England)

### 3.1.3 REAGENTS

- Methanol (BDH Chemical England)
- Ethylacette (May and Baker England)
- Filtered distilled water
- Acetone, May and Baker England
- Potassium dichromate (May and Baker England)
- Sodium hydroxide (May and Baker England)
- Paracetamol powder
- Potassium hydroxide, May and Baker England

3.1.4 DRUGS

| | | | |
|---|---|---|---|
| Chemical Name: - | Cimetidine | Paracetamol | Propantheline |
| Propreitary Name: - | Tagamet® | Panadol® | Pontine® |
| Manufacturer: - | SKB | SKB | Generic |
| Batch Number: - | B01736 | 05K | 04130 |
| Expiry Date: - | 01-2010 | 07-2011 | 08-2010 |
| Manufacturing Date:- | 01-2007 | 07-2008 | 08-2007 |
| Strength:- | 400mg | 500mg | 15mg |

## 3.2.0 METHODOLOGY

3.2.1 IN-VITRO TESTS

3.2.2 Identification test for paracetamol BP (2002)

A powder of paracetamol containing 0.5g paracetamol was extracted with 20ml of acetone. It was filtered, evaporated using boiling water, to dryness and dried at $105^0$C, 1ml of hydrochloric acid was added to 0.1g of residue 10ml of distilled water was added and then cooled.

3.2.3 ASSAY OF PARACETAMOL

Twenty tablets of paracetamol were weighed and powdered. 0.176g of the product containing 0.15g of paracetamol was added to 5mls of 0.1m sodium

hydroxide solution. It was diluted with 100mls of water was shaken for 15 minutes. Sufficient water was added to make 200ml and was mixed using stirrer and filtered. 10ml of the filtrate was diluted to 100ml with water. Again 10ml of the resulting solution was added to 10ml of 0.1m sodium hydroxide. It was diluted to 100ml with water and the absorbance measured at 257nm.

### 3.2.4 DISINTEGRATION TEST BP 2002

A Eureka disintegration test apparatus was employed. One tablet was placed in the tube of the basket and a disk was added to each tube. The set was suspended in a beaker containing distilled water and maintained at $37^0C \pm 0.5^0C$ and the set was operated for 15 minutes. This procedure was carried out for 5 tablets.

### 3.2.5 DISSOLUTION TEST BP 2002

Rotary basket method was used. 1000ml of 0.1N hydrochloric acid was placed in the vessel of dissolution apparatus. It was immersed in constant temperature water both maintained at $37^0C \pm 0.5^0C$, it was allowed to equilibrate. A tablet was placed in the basket which was immersed into the vessel and rotated at 100rpm for 45 minutes.

10ml of the sample was withdrawn from a point half-way between the surface of the dissolution media and the top of the rotating basket. Absorbance was measured at 262nm with a UV spectrophotometer.

### 3.2.6 FRIABILITY TEST BP 2002

Ten (10) tablets were taken and weighed. They were subjected to an abrasion test in a friabilator operated at 25rpm for 4 minutes. The tablets were dusted and reweighed. The difference in their weight was determined and percentage friability was calculated using the formula

$$\frac{W1 - W2}{W1} \times 100\%$$

### 3.2.7 ASSAY OF PROPANTHELINE

A tablet was crushed and finely powdered and was placed in a 100ml volumetric flask. Methanol was added to volume and it was mixed and filtered. The first portion of the filtrate was discarded. 5ml of the filtrate was taken and diluted to 10ml with methanol to give a solution of 75ug/ml. the absorbance was measured at 282nm using methanol as a blank.

### 3.3.0 IN-VIVO STUDIES

Having got a satisfactory invitro results that are within the BP2002 specifications, this initiate the start of the in vivo studies.

### 3.3.1 Analytical method

The analytical method used was adopted and modified from Garba M, 1992, and absorbance was measured at 275 nm.

### 3.3.2 CALIBRATION CURVE

A calibration curve of the concentration of paracetamol in human saliva was constructed. Sufficient quantity of the blank sample was collected and 2ml each was placed in 14 x 20ml centrifuge tube using a pipette. The two were kept as blanks and the remaining were spiked with different concentration of paracetamol in methanol from the stock solution using a micrometer syringe. Each concentration was spiked in duplicates. The stock solution contains 0.1g of paracetamol powder in 100mg/ml of methanol. 1, 2, 3. 4, 5. 6,and 7,ml of the solution were spiked in duplicates. 5ml of ethyl acetate was added to each of the samples and extracted. The absorbance of the blank in ethyl acetate was measured and the calibration curve drawn.

### 3.3.3 VALIDATION OF THE CALIBRATION CURVE

A set of 7 x 2ml blanks saliva were randomly spiked with different known concentration of paracetamol. It was extracted with 5ml of ethyl acetate and the absorbance measured. The concentration obtained was compared with that of the calibration curve and the “r” value for the calibration curve was calculated.

### 3.3.4 EXTRACTION

2ml of saliva samples were placed in 20ml centrifuge using an auto pipette. 5ml of ethyl acetate was added and the tube was stoppered with plastic screw caps and shaken vigorously with a rota-mixer for 1 minute. It was centrifuged for 5 minutes at 300rpm. The ethyl acetate layer was removed with a pipette and put into the curvette. The absorbance of the blank was measured and the machine was set to zero absorbance reading. The absorbance of the ethylacetate layer was measured at 262nm.

### 3.3.5 Protocol

Healthy volunteers with age range between 25 – 35 years and average weight of 52kg were employed for the study. They had normal laboratory values being free from liver and kidney disease. They were non-smokers and they all do not take alcohol. It was a cross over study and the protocol involved 5 – phases.

Phase I:- This involves the administration of two 500mg tablets Of paracetamol with a glass of water after an Overnight fasting. The mouth was rinsed immediately with water. saliva samples were taken at 0, 0.25, 0.5, 1, 2, 3, 4 and 5 hours thereafter. The saliva samples taken were kept at $-4^0$C, until analysis. That was followed by a Washout period of two weeks.

Phase II: - Involves the administration of 500mg paracetamol Tablets with one tablet of 400mg Cimetidine tablet concurrently. The procedure for the saliva collection was repeated as in phase I.

Phase III:- In this phase 1g of paracetamol was given an hour After 400mg of Cimetidine. The procedure for the saliva collection was carried out as in phase I.

Phase IV: - This involves the concurrent administration of 2 x 500mg paracetamol tablets with 15mg of propantheline. The procedure for the saliva collection and storage was repeated again.

Phase V: - 2 x 500mg of paracetamol tablets was administered An hour after the administration of 15mg

Propanteline tablet. The saliva samples were collected and stored as done in all the phases.

### 3.3.6 Sample collection

Samples were collected and refrigerated at -4$^{o}$C before analysis

.

### 3.3.7 DATA HANDLING

Various concentrations of paracetamol in individual saliva sample were used. Semi-log graph was used to determine the T½, abs, Kabs, T½eli, Keli. The AUC was calculated using the trapezoidal method. Other parameters were calculated as follows:

$$AUC_{5 - infinity} = \frac{Concn}{Keli}$$

$$AUC_{0\text{-}Infinity} = AUC_{0\text{-}5} + AUC_{5\text{-}Infinity}$$

$$TBC = \frac{Dose \times f}{AUC_{0\text{-}Infinity}}$$

Assuming a bioavailability of 100%

$$Vd = \frac{cl}{K\beta}$$

Using student t-test, paired was employed with;

1. $P < 0.05$ and $P < 0.01$ as statistically significant
2. $P > 0.05$ and $P > 0.01$ as statistically insignificant

# CHAPTER FOUR

## 4.0 RESULTS

## 4.1 IN-VITRO STUDIES

### 4.1.1 IDENTIFICATION

a) A violet colour developed slowly, and did not turn red (BP 2002).

### 4.1.2 ASSAY

The range between 95% - 105% is the accepted range by the BP of 2002.

Tab 4.1: Summary of the contents of the six tablets

| *NO* | *% CONTENTS* | *COMMENT* |
|---|---|---|
| 1 | 100.15 | Satisfactory |
| 2 | 100.05 | √ |
| 3 | 99.5 | √ |
| 4 | 100.00 | √ |
| 5 | 104.51 | √ |
| 6 | 99.56 | √ |

Mean ± Sem 100.76 ± 0.899

### 4.1.3 DISSOLUTION TEST

The table below shows the mean dissolution profile for 6 paracetamol tablets in compliance with the official specification.

Table 4.2 Mean dissolution profile for four brands of six paracetamol tablets (BP 2002).

| *Table NO* | *TIME(MIN) RELEASED* | *% RELEASED* | | | |
|---|---|---|---|---|---|
| | | I | II | III | IV |
| 1 | 45 | 97 | 98 | 99 | 98 |
| 2 | 45 | 90 | 94 | 90 | 94 |
| 3 | 45 | 87 | 88 | 89 | 88 |
| 4 | 45 | 98 | 99 | 96 | 93 |
| 5 | 45 | 88 | 94 | 86 | 91 |
| 6 | 45 | 92 | 89 | 94 | 88 |

4.1.4 The time limit allowed by BP 2002 for paracetamol disintegration is 5 minutes.

Table 4.3 RESULT OF DISINTEGRATION TEST

| *TABLET NO.* | *DISINTEGRATION TIME (MINS)* | *COMMENT* |
|---|---|---|
| 1 | 3.8 | Satisfactory |
| 2 | 4.0 | ,, |
| 3 | 4.5 | ,, |
| 4 | 3.2 | ,, |
| 5 | 3.6 | ,, |

Mean 3.82 Sem 0.482

4.1.5 FRIABILITY TEST

The BP of 2002 recommended that the percentage friability of paracetamol should not exceed 1%.

Table 4.4 PERCENTAGE FRIABILITY OF TEN PARACETAMOL TABLETS

| NO OF TABLETS | WEIGHT BEFORE FIBRILATION | WEIGHT AFTER FIBRILATION | PERCENTAGE LOSS |
|---|---|---|---|
| 10 | 6,038mg | 5,983 | 0.91% |

Table 4.1.6 ASSAY OF PROPANTHELINE BROMIDE

The following result was obtained after light absorption at 262nm using UV spectrophotometer.

Table 4.5 Percentage contents of five (5) propantheline bromide tablets

| TABS. NO | % CONTENT |
|---|---|
| 1 | 100.00 |
| 2 | 97.68 |
| 3 | 102.32 |
| 4 | 102.30 |
| 5 | 98.60 |

### 4.2.0 IN-VIVO RESULTS

### 4.2.1 CALIBRATION CURVE FOR PARACETAMOL IN ug/ml ± SD

Tab 4.6 Mean absorbance of paracetamol for calibration curve

| S/NO | concentration of drug/ml of saliva (mg/ml) | Mean absorbance | Standard deviation |
|---|---|---|---|
| 1 | 10 | 0.567 | 0.0128 |
| 2 | 20 | 0.651 | 0.0105 |
| 3 | 30 | 0.927 | 0.0019 |
| 4 | 40 | 1.012 | 0.0016 |
| 5 | 50 | 1.120 | 0.0021 |
| 6 | 60 | 1.309 | 0.0023 |
| 7 | 70 | 1.522 | 0.0195 |

CALIBRATION CURVE FOR PARACETAMOL

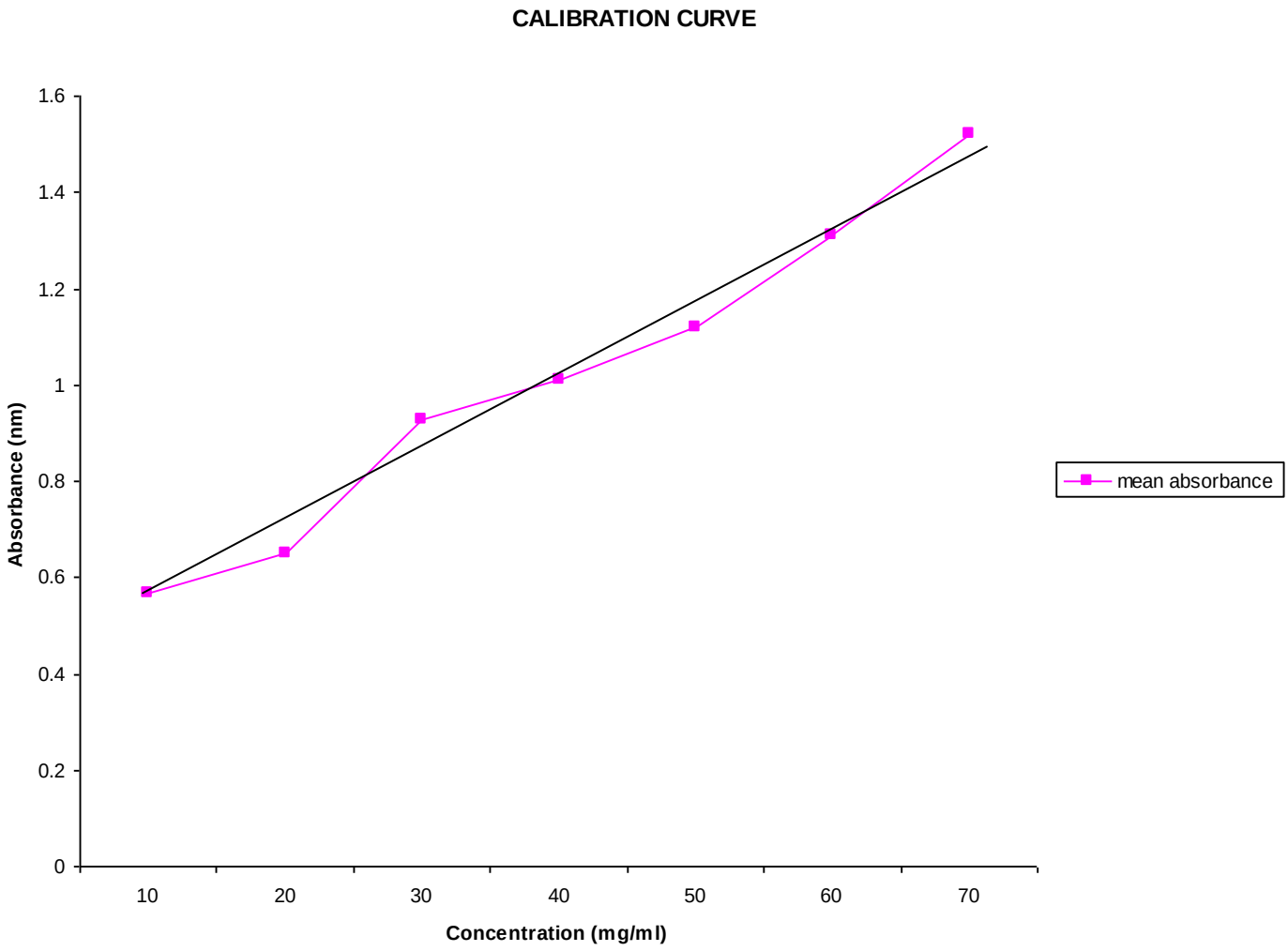



Fig 2.2 CALIBRATION CURVE FOR PARACETAMOL

Tab 4.7 The mean saliva paracetamol concentrations for the five phases (ug/ml)

| Time(hrs) | PCM alone (ug/ml) | PCM+CMT (ug/ml) ( c ) | PCM+CMT (ug/ml) ( D ) | PCM+PPT (ug/ml) ( C ) | PCM+PPT (ug/ml) ( D ) |
|---|---|---|---|---|---|
| 0.25 | 11.25 | 12.00 | 9.13 | 11.05 | 1.85 |
| 0.50 | 18.85 | 22.06 | 16.88 | 17.67 | 6.56 |
| 1.00 | 36.75 | 30.81 | 22.75 | 32.04 | 10.06 |
| 2.00 | 27.75 | 24.81 | 18.69 | 23.44 | 15.74 |
| 3.00 | 22.56 | 18.94 | 12.44 | 13.88 | 20.07 |
| 4.00 | 15.25 | 11.81 | 8.19 | 10.54 | 13.25 |
| 5.00 | 11.75 | 7.38 | 5.69 | 7.94 | 8.94 |

Fig 2.3: Curves for the pcm salivary concentration in the five phases

TAB 4.8 MEAN PHARMACOKINETIC PARAMETERS FOLLOWING ADMINISTRATION OF PARACETAMOL, CIMETIDINE AND PROPANTHELENE IN FIVE PHASES

| s/n | Parameter | PCM Alone | PCM+CMT (Conc) | PCM+CMT (Delay) | PCM + PPT (Conc) | PCM+PPT (delay) |
|---|---|---|---|---|---|---|
| 1 | Tmax (hr) | 1 | 1 | 1 | 1 | 2 |
| 2 | Cmax (ug/ml) | 36.75 | 30.81 | 22.50 | 32.50 | 20.01 |
| 3 | T1/2 ab (hr) | 0.295 | 0.302 | 0.630 | 0.30 | 0.95 |
| 4 | Kab ($hr^{-1}$) | 2.54 | 2.77 | 1.98 | 2.31 | 1.73 |
| 5 | T ½ el (hr) | 1.355 | 1.328 | 1.689 | 1.70 | 1.81 |
| 6 | Kel ($hr^{-1}$) | 0.860 | 0.77 | 0.49 | 0.73 | 0.40 |
| 7 | Log Time (hr) | 0.09 | 0.10 | 0.15 | 0.15 | 0.10 |
| 8 | Vd (L) | 12.90 | 12.58 | 25.69 | 14.35 | 20.22 |
| 9 | Cl (ml/min) | 10.833 | 9.68 | 12.59 | 11.05 | 14.20 |
| 10 | AUC ug/ml/hr | 128.45 | 103.20 | 79.45 | 90.49 | 70.42 |

## COMPARISON OF PHARMACOKINETIC PARAMETERS OF PARACETAMOL FOLLOWING ADMINISTRATION WITH CIMETIDINE AND/OR PROPANTHELENE.

**Table 4.9: Comparism of mean pharmacokinetics parameters of phase I and II values ±SEM**

| S/N | Pharmacokinetics parameters | Phase I PCM Alone | Phase II PCM+CMT (Concur) | o/o change | P-values |
|---|---|---|---|---|---|
| 1 | **tmax** (hr) | 1 | 1 | 0.00 | P>0.05 |
| 2 | **Cmax** (ug/ml) | 36.75 | 30.81 | -16.16 | P> ” |
| 3 | **t½ab** (hr) | 0.295 | 0.302 | 2.37 | P> ” |
| 4 | **Kab** ($hr^{-1}$) | 2.54 | 2.77 | 9.05 | P> ” |
| 5 | **$t_{½el}$** (hr) | 1.355 | 1.328 | 1.99 | P> ” |
| 6 | **$K_{el}$** ($hr^{-1}$) | 0.860 | 0.77 | 10.46 | P> ” |
| 7 | **Lag time** (hr) | 0.09 | 0.10 | 11.11 | P> ” |
| 8 | **Vd** (L) | 12.90 | 12.59 | -2.48 | P> ” |
| 9 | **Cl** (ml/min) | 10.833 | 9.68 | 10.60 | P> ” |
| 10 | **AUC** $_{0-5}$ (ug/hr/ml) | 128.45 | 103.2 | 19.6 | p> ” |

**Table 5.0: Comparism of mean pharmacokinetics parameters of phase I and III values ±SEM**

| S/N | Pharmacokinetics parameters | Phase I PCM Alone | Phase III PCM+CMT (Delayed) | o/o change | P-values |
|---|---|---|---|---|---|
| 1 | **tmax** (hr) | 1 | 1 | 0.00 | P>0.05 |
| 2 | **Cmax** (ug/ml) | 36.75 | 22.50 | -38.77 | P> ” |
| 3 | **t½ab** (hr) | 0.295 | 0.630 | 113.56 | P> ” |
| 4 | **Kab** ($hr^{-1}$) | 2.54 | 1.98 | -22.05 | P> ” |
| 5 | **$t_{½el}$** (hr) | 1.355 | 1.689 | 24.37 | P> ” |
| 6 | **$K_{el}$** ($hr^{-1}$) | 0.860 | 0.49 | -43.02 | P> ” |
| 7 | **Lag time** (hr) | 0.09 | 0.15 | 66.66 | P> ” |
| 8 | **Vd** (L) | 12.90 | 25.69 | 99.14 | P> ” |
| 9 | **Cl** (ml/min) | 10.833 | 12.59 | -38.15 | P> ” |
| 10 | **AUC** $_{0-5}$ (ug/hr/ml) | 128.45 | 79.45 | 1.10 | p> ” |

**Table 5.1: Comparism of mean pharmacokinetics parameters of phase I and IV values ±SEM**

| S/N | Pharmacokinetics parameters | Phase I PCM Alone | Phase IV PCM+PPT (Concur) | o/o change | P-values |
|---|---|---|---|---|---|
| 1 | **tmax** (hr) | 1 | 1 | 0.00 | P>0.05 |
| 2 | **Cmax** (ug/ml) | 36.75 | 32.50 | -11.56 | P> ” |
| 3 | **t½ab** (hr) | 0.295 | 0.30 | 01.69 | P> ” |
| 4 | **Kab** ($hr^{-1}$) | 2.54 | 2.31 | -9.055 | P> ” |
| 5 | **$t_{½el}$** (hr) | 1.355 | 1.70 | 25.46 | P> ” |
| 6 | **$K_{el}$** ($hr^{-1}$) | 0.860 | 0.713 | -17.09 | P> ” |
| 7 | **Lag time** (hr) | 0.09 | 1.5 | 66.66 | P> ” |
| 8 | **Vd** (L) | 12.90 | 14.35 | 11.24 | P> ” |
| 9 | **Cl** (ml/min) | 10.833 | 11.05 | 2.003 | P> ” |
| 10 | **AUC** $_{0-5}$ (ug/hr/ml) | 128.45 | 90.49 | -29.50 | p> ” |

**Table 5.2: Comparism of mean pharmacokinetics parameters of phase I and V values ±SEM**

| S/N | Pharmacokinetics parameters | Phase I PCM Alone | Phase V PCM+PPT (Delayed) | o/o change | P-values |
|---|---|---|---|---|---|
| 1 | **tmax** (hr) | 1 | 1 | 0.00 | P>0.05 |
| 2 | **Cmax** (ug/ml) | 36.75 | 20.01 | -45.55 | P> ” |
| 3 | **t½ab** (hr) | 0.295 | 0.95 | 222.03 | P> ” |
| 4 | **Kab** ($hr^{-1}$) | 2.54 | 1.73 | -33.89 | P> ” |
| 5 | **$t_{½el}$** (hr) | 1.355 | 1.81 | 33.58 | P> ” |
| 6 | **$K_{el}$** ($hr^{-1}$) | 0.860 | 0.40 | -53.49 | P> ” |
| 7 | **Lag time** (hr) | 0.09 | 0.10 | 11.11 | P> ” |
| 8 | **Vd** (L) | 12.90 | 20.22 | 56.74 | P> ” |
| 9 | **Cl** (ml/min) | 10.833 | 14.20 | 31.08 | P> ” |
| 10 | **AUC** $_{0-5}$ (ug/hr/ml) | 128.45 | 70.42 | -45.192 | p> ” |

# CHAPTER FIVE

## DISCUSSION OF RESULT

Non-invasive method can be used to estimate the levels of drug in plasma and can be used to determine the pharmacokinetics of paracetamol.

The measurement of saliva concentration of a drug is of most value in studies on compounds that are low ionized at physiological $P^H$ values like neutral drugs, phenytoin and weakly basic drugs e.g. carbamazepine and antipyrine where good parallelism is shown between saliva and plasma drug concentration Graham, 1982).

A correlation between saliva and plasma level of paracetamol allowed the estimation of some simple pharmacokinetic parameters from their salivary concentration (Ahmed and Enever, 1981). Salivary level of paracetamol demonstrates a good correlation to their plasma levels. This was confirmed by Graham, 1982 and the objective of this single dose study is to observe the profile of interaction without any disturbance by the multiple drug regimens which will mask the pharmacokinetic interaction profile (Garba et al 1998).

Since the Tmax of paracetamol is 30 – 90 minutes (Reynold 1993) while that of propantheline is 2 – 3 hours (Vase 1980) and that of cimetidine is 3 hours (Somogyi and Gugler 1983), therefore it is necessary to administer cimetidine and propantheline during the administration of paracetamol as an optimal study condition to determine possible interaction as these drugs must reach the systemic concentration before exerting their effects (Khoury et al, 1979).

Saliva samples were taken for up to 6 hours to allow for 3 half lives in order to have full absorption phases completed, (Garba et al, 1988).

The use of ACH antagonist might be thought to affect the result. However, the anti salivary secretion of ACH antagonist is dose dependent. ACH antagonist in general decreases salivary secretion but it is important to note that this has dose – dependent relationship. This was further proved by Gibaldi and Grunhfer, 1975, who reported that on the administration of 30mg propantheline bromide, decrease in salivary secretion was noted only 4 hours after ingestion while in some patients it was not observed, hence the use of 15mg propantheline for the study to reduce the anti salivary secretion effect propantheline.

Also, since peak plasma levels of paracetamol occurs within 30 – 90 minutes (Reynolds, 1993) and the concentration of paracetamol is high enough, the half life is short enough to allow for fairly good characterization of the course of the drug. It is also worthy to note that major metabolites of paracetamol, some commonly used drugs or phenolic substrates that may be present in parts with renal failure or liver disease do not interfere with the calorimetric and liquid chromatographic determination of paracetamol (Price et al, 1983). Paracetamol elimination half life can be estimated with reasonable precision using a two point blood sampling (Scavone et al, 1980).

During the study, the volunteers employed were male, healthy and free of liver and kidney disease, non – smokers and non – alcoholic and their consent was sought for the study. This is to ensure good compliance.

The pharmacokinetic parameters considered in this study are those related to the rate and extent of absorption like $K\alpha$, $t_{max}$, $C_{max}$, lag time and those indicative of metabolism and/or excretion like $t_{1/2\beta}$, $K_{\beta}$, Cl, Vd. The inter–individual variations in the kinetic data obtained, was observed. Drug interaction may be of major clinical or no-clinical significance at all (Regiman et al 1971).

It can be seen that on comparism between those parameters of phase I and phase II there are no significant changes in the pharmacokinetic parameters of the two phases. This simply leads to a suggestion that there is no significant inhibition of paracetamol absorption. Reynolds, 1993, reported that paracetamol reaches its Tmax between 30 – 90 minutes; cimetidine is maximally absorbed between 1 – 2 hours. Based on this finding paracetamol will reach its peak an hour before cimetidine hence there is insignificant inhibition by cimetidine. On comparison of phase I with phase III, it can be seen that there are changes when paracetamol administration was delayed by 1 hour after cimetidine. Cmax dropped to 30.81 with percentage change of 30.7%. Likewise an increase of T1/2ab, T1/2el, volume of distribution and clearance were also observed. This also observed. This also supports the suggestion that there is a significant inhibition of paracetamol absorption in this phase, resulting to a decrease in the concentration of paracetamol in the saliva as already seen.

## 5.2 SINGLE DOSE SALIVARY PHARMACOKINETICS OF PARACETAMOL

The salivary pharmacokinetics profile of paracetamol alone was studied in 8 healthy volunteers in fasting state.

Lag time for the control was 0.09 hours. Grab et al reported 0.15 hours (1977). Ameer et al (1983) reported 3.4 minutes. A Tmax of 1 hour was obtained. Ameer

et al (1983) reported 0.75 hours for tablets, Hong et al (1984) 1.48 hours, Joel (1985) 7.1 hours.

A $T_{1/2}$ab of 0.295 hours was reported for the study and a Kab of 2.54 was reported. Garba et al reported Kab of 2.1 ug/ml/hr, in plasma concentration. Cmax for my study was 36.75 ug/ml.

Sambo et al reported a Cmax of 34.88 ug/ml and AUC of 128.45 were obtained. Sambo et al (2002) reported an AUC of 140.14 ug/ml/hr.

T1/2 el for this study 1.355 and the value of distribution was 12.90L and the total body clearance was 10.833 ml/min. the difference between the parameters obtained and that of the literature might be due to inter subject variation in paracetamol absorption. The pharmacokinetics of the paracetamol determined is within the range of values reported in established literature.

Lag time for the control was 0.09 hours. Garba et al reported 0.15 hours (1997) Ameer et al (1983) reported 3.4 minutes. A Tmax of 1 hour was obtained. Ameer et al (1983) reported 0.75 hours for tablets, Hong et al (1984) 1.48 hours, Joel (1985) 7.1 hours.

A T1/2ab of 0.295 hours was reported for the study and a Kab of 2.54 was reported. Garba et al reported Kab in plasma concentration of 2.1 ug/ml/hr. Cmax for my study was 36.75ug/ml.

Sambo et al reported a Cmax of 34.88 ug/ml AUC of 128.45 was obtained. Sambo et al (2002) reported an AUC of 140.14 ug/ml/hr. T1/2 el for this study 1.355 at the value of distribution was 12.90L and the total body clearance was 10.833 ml/min. the difference between the parameters obtained and that of the literature might due to inter subject variation in paracetamol absorption. The pharmacokinetics of the paracetemol determined is within the range of values reported in established literature

Propanthaline is said to have caused delay in gastric emptying just like Cimetidine, so it is expected that such delay may affect the absorption of paracetamol. The pharmacokinetic parameters observed when paracetamol was administered concurrently with propantheline look synonymous to those figures obtained when paracetamol was taking together with cimetidine.

On comparison, all the pharmacokinetics parameters were in the same range. The percentage changes observed were all insignificant. The maximum concentration of paracetamol found in phase I was almost the same compared

with that when propantheline was administered concurrently. Since Tmax of paracetamol is 30 – 90 minutes (Reynold, 1993) and that of propantheline 2 hours (Vase, 1980) it is thus safe to administer paracetamol concurrently with propantheline due to significant variation in their Tmax. It is therefore expected that the absorption of paracetamol may not be affected putting into consideration that paracetamol must have been absorbed maximally before a considerable portion of propantheline gets into the system. This was further proven by Gibaldin and Grunhofer (1975) who reported that on the administration of 30mg of propantheline bromide decrease in salivary concentration was noted only 4 hours after ingestion, while in some patients it was not observed.

As it has been earlier mentioned that there is a remarkable decrease in the concentration of paracetamol when later was administered an hour after cimetidine, some features were observed when paracetamol was taken an hour after propantheline. This lead to a suggestion that both cimetidine and propantheline affect the absorption of paracetamol when either of the two is given after an hour interval.

For a deayed administration of 1g paracetamol an hour after both cimetidine and propantheline, it was observed that there is an increase in Tmax, decrease in Cmax, increase in T1/2ab, an increase in lag time and a decrease in Ka. All

these parameters lead to a suggestion that there is interference in the absorption of paracetamol. A delayed lag time also suggest an effect on the gut smooth muscle, also since peak plasma levels of paracetamol occurs within 30 – 90 minutes (Reynold 1993) and the concentration of paracetamol is high enough, the half life is short enough to allow for fairly good characterization of the course of the drug.

Considering that the major metabolites of paracetamol, some commonly used drugs or phenolic substances that may be present in patients with renal failure or liver disease do not interfere with the calorimetric and liquid chromatography determination of paracetamol (Price et al 1983) paracetamol elimination half life can be estimated with reasonable precision using a two point blood sampling (scavove et al 1990).

In a delayed administration, papantheline affects the absorption of paracetamol more than cimetidine. This can be attributed to the fact that paropantheline an Ach antagonist is known to delay gastric emptying (Nimmo, 1981), hence slowing down the rate of absorption of paracetamol. Propantheline is known to decrease intestinal transit time in all segment of the intestinal tract by about 50% in rats (Haruna et al, 1998), hence a decrease in absorption.

## Summary/ Conclusion/ Recommendation

Tablet of paracetamol and propantheline bromide were assayed for identification, disintegration, dissolution, friability and all the results obtained complied with official specifications (B.P. 2002).

An evidence of drug-drug absorption interaction between cimetidine and paracetamol was observed which indicates marginal changes. However, the result does not indicate a toxicological or metabolic/excretion drug interaction between cimetidine and paracetamol. There was also pronounced alteration of the absorption kinetics of paracetamol by propantheline but are not of any clinical significance.

From the findings it can be concluded that Cimetidine has no effect in the pharmacokinetics of paracetamol when the two drugs were administered together. However, Cimetidine impaired the absorption and inhibited the metabolism of paracetamol when given in a delay time which might be due to the modification of gastric emptying caused by Cimetidine. The impairment of absorption and inhibition of metabolism have been significant and this might have some important clinical implication in situations where the two drugs are used

together. From this study and other studies conducted an attempt has been made to show and probe the various mechanisms of Cimetidine drug interactions.

Also the pharmacokinetics changes obtained either increase or decrease might be due to the modification of the study design previously reported. The effect of Cimetidine and drug absorption is only evident when the $H_2$ antagonist is given 1 hour before the test drug.

The recommendation to be drawn from this study is that whenever a combination of paracetamol and Cimetidine is to be given, the two drugs should be administered concurrently.

The exact mechanism involves in the drug interaction needs to be thoroughly evaluated, to allow usage of the drugs combinations.

From the complexity of the mechanism of Cimetidine drug interactions effort should be made to look at the structure activity relationship of $H_2$ - receptor antagonist in order to elucidate the full meanings of these complex interactions

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