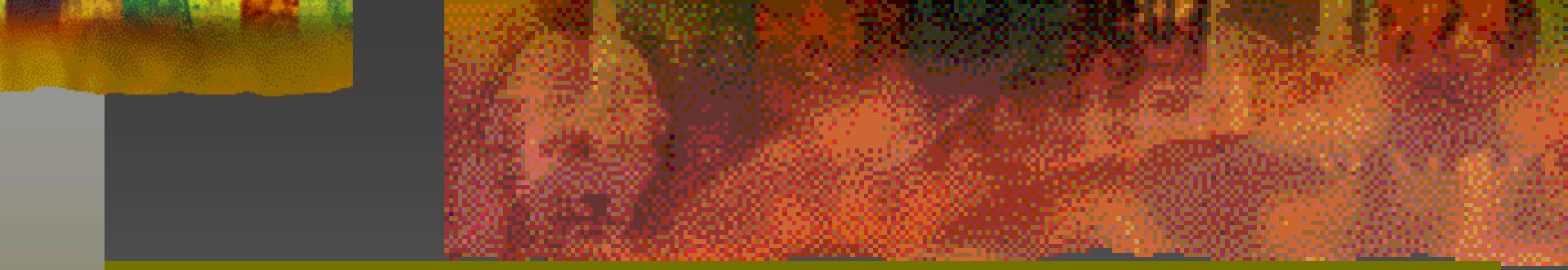


INTRODUCTION to CLINICAL PHARMACOKINETICS

CLINICAL PHARMACOKINETICS

- How to adjust the dosage regimen to suit the patient's ADME characteristics & concentration vs time profile following the therapeutic planning.

- The service known as Therapeutic Drug Monitoring (TDM) or Clinical Pharmacokinetic Services

CLINICAL PHARMACOKINETICS

- Success of drug therapy dependent on dosage regimen.
- A properly designed dosage regimen - to achieve an optimum concentration of drug at receptor site to produce an optimal therapeutic response with minimum adverse effects.
- Sometimes individual variation in pharmacokinetics – makes dosage regimen design is very difficult.

CLINICAL PHARMACOKINETICS

- During drug development process, large numbers of patients are tested to determine optimum dosing regimens & recommended by manufacturer to produce desired pharmacologic response.

- But intra & inter-individual variations will results in either a sub-therapeutic (drug concentration below the MEC) or toxic response (drug concentrations above minimum toxic concentration, MTC), which may require adjustment to dosing regimen.

CLINICAL PHARMACOKINETICS

- So an application of pharmacokinetics comes in to the clinical setting - whereas **pharmacokinetic parameters of drugs are used to develop therapeutic model** which can be used to individualize drug regimen & provide most effective drug therapy with **safest manner.**
- **Clinical pharmacokinetics** - is application of **pharmacokinetic methods** to drug therapy
- **Pharmacokinetics** is also applied to therapeutic drug monitoring (TDM)

CLINICAL PHARMACOKINETICS

- Pharmacokinetics also applied to TDM for potent drugs with a narrow therapeutic range, in order to optimize efficacy & prevent adverse toxicity

- For these drugs, it is necessary to monitor patient, either by monitoring plasma drug concentrations (eg.theophylline) or pharmacodynamic endpoint such as prothrombin clotting time (eg. warfarin).

CLINICAL PHARMACOKINETICS

- So Pharmacokinetic analysis & drug analysis necessary for safe drug monitoring are provided by clinical pharmacokinetic service (CPKS).

- Some drugs are frequently monitored ex. Amino glcosides & anticonvulsants. other drugs are closely monitored. Ex. Cancer chemotherapy, in order to minimize adverse side effects.

CLINICAL PHARMACOKINETICS

- So clinical pharmacokinetics is the application of pharmacokinetics methods to design drug therapy and it's depends on patient disease state & patient specific consideration.

or

- Application of pharmacokinetics to the safe effective therapeutic management of individual patient.

CLINICAL PHARMACOKINETICS

This involves…….

- Design of a drug
- Design of a dosage regimen including dose, dosing interval & route of administration based on serial monitoring of drug concentration in plasma/fluids.

CLINICAL PHARMACOKINETICS

- Age, gender, genetic & ethnic differences can also results in pharmacokinetic variations may affect outcome of drug therapy.

- So study of pharmacokinetic difference of drugs in various population group is termed as "Population Pharmacokinetics".

CLINICAL PHARMACOKINETICS

- So measurement of drug concentration (monitoring drug conc in blood, plasma/serum, tissue, urine/feces & saliva) --- it allows for adjustment of drug dosage to individual & optimize good TE.

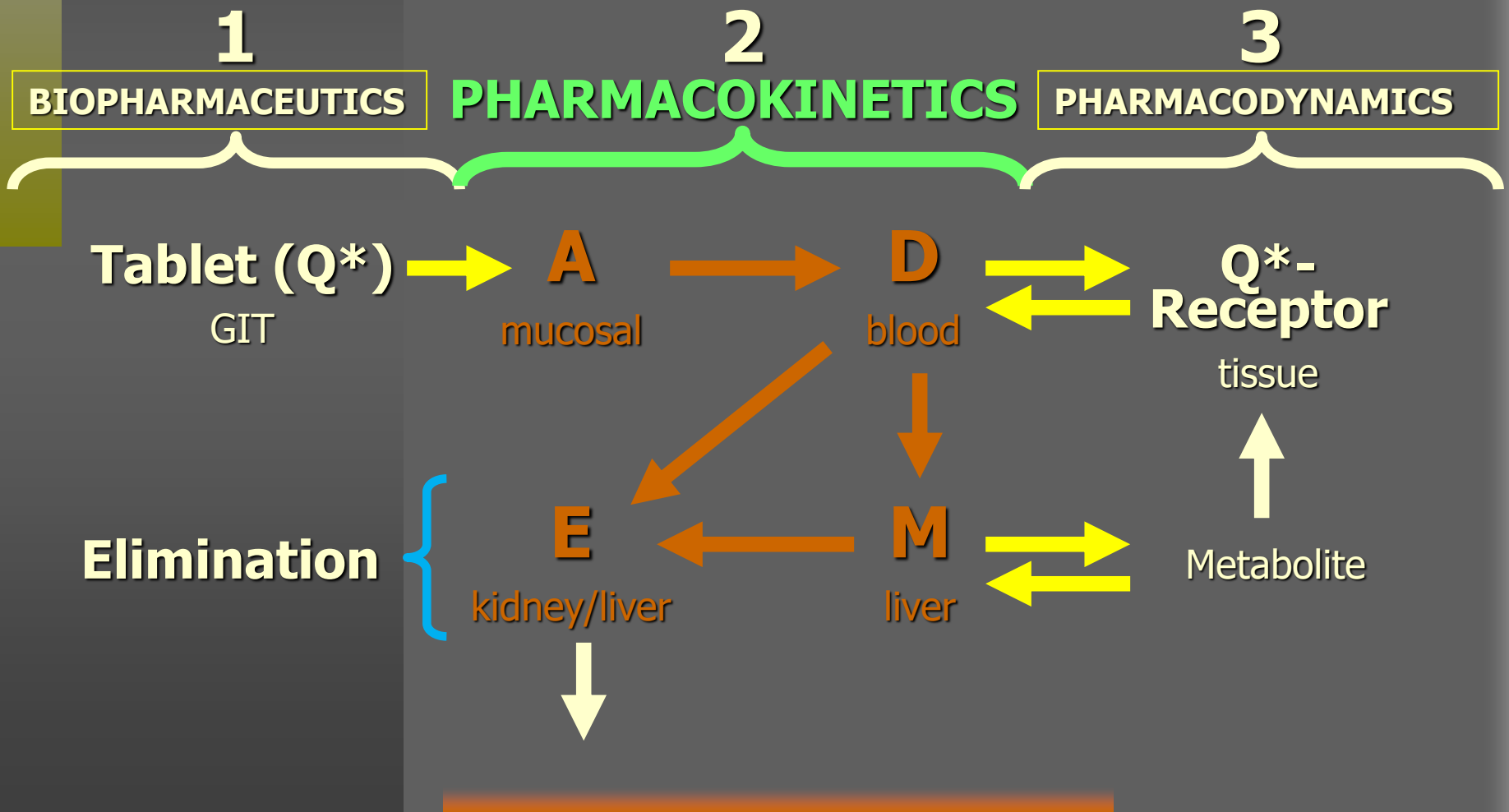
- Because drug concentration relationship to drug response / not response due to genetic difference in receptor response.

CLINICAL PHARMACOKINETICS

- Ex. Some patients – responds to drug treatment at low doses & some are higher doses of drug.

- So monitoring drug concentration be safe to patients.

THE PHASES


1
BIOPHARMACEUTICS
2
PHARMACOKINETICS
3
PHARMACODYNAMICS
Tablet (Q*)
GIT
A
mucosal
D
blood
Q*-
Receptor
tissue
Elimination
E
kidney/liver
M
liver
Metabolite

CONCENTRATION VS TIME PROFILE

Pharmacokinetic Parameters - (AUC, C_{max}, t_{max})

Area under curve (AUC)

Total integrated area under plasma level time – total amt of drug comes into systemic circulation & expressed in mcg/ml.

Peak plasma concentration (Cmax)

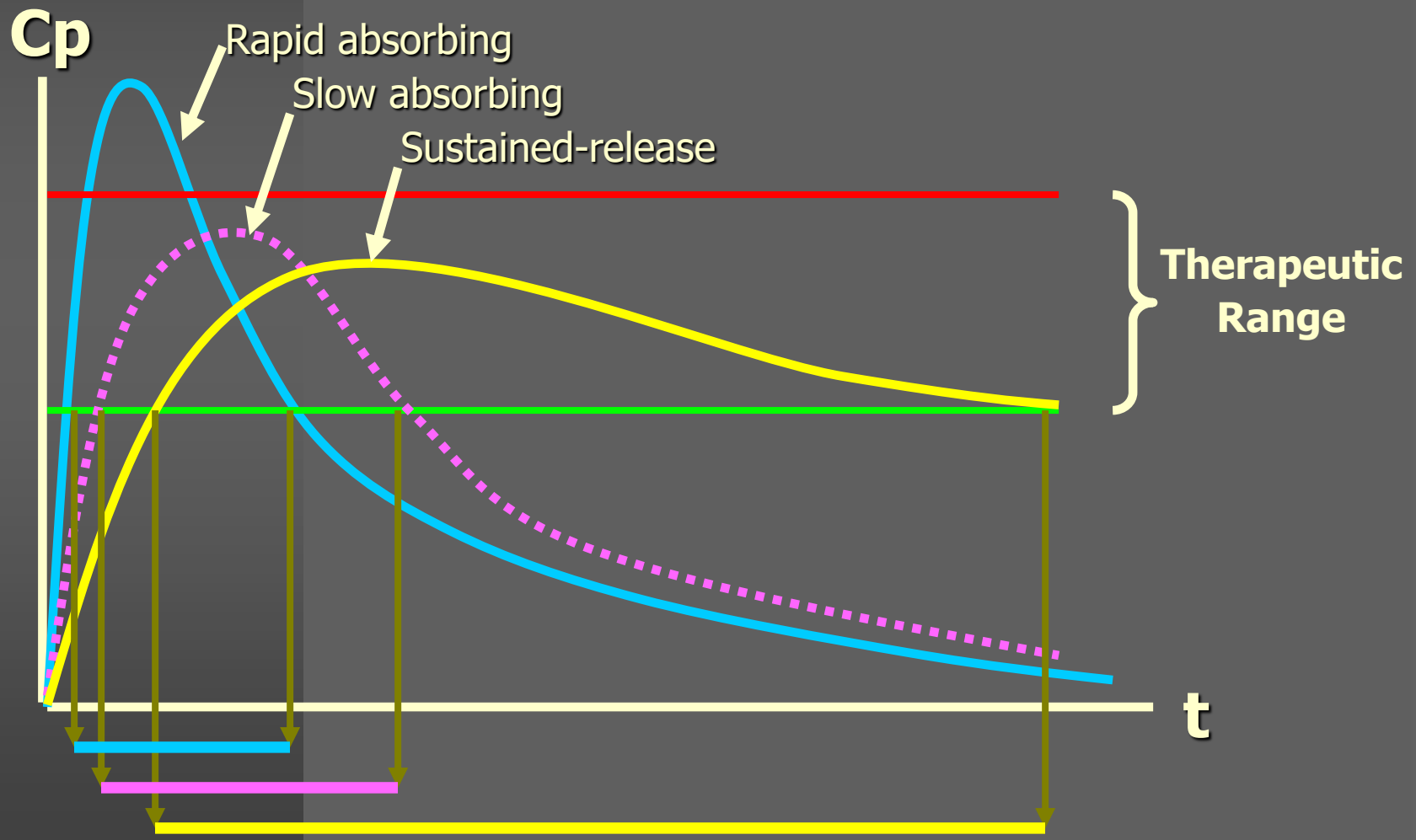
The point of max conc of drug in plasma (called peak height conc & expressed as mcg/ml).

Time of peak concentration (Tmax)

The time for drug to reach peak conc in plasma (after extravascular adm & expressed in hr).

CONCENTRATION VS TIME PROFILE

(Formulation, onset, duration of action)



Rate of reaction

To consider processes of ADME - they can be characterized by two basic Rate of reaction.

Rate of reaction is defined as velocity at which it proceeds & described as either zero-order or first-order

i.e., ADME predicted by……..

✓Zero order reaction

✓First order reaction

Rate of reaction

✓Zero order reaction

Consider rate of elimination of drug A from body.

If amount of drug is decreasing at a constant rate, then the rate of elimination of drug A can be described as

$$\frac{dA}{dt} = -k^*$$

Where k* is zero-order rate constant

The reaction proceeds at a constant rate & independent of concentration of A present in body. Ex. Elimination of alcohol.

Rate of reaction

✓First order reaction

If amount of drug A is decreasing at a rate i.e., proportional to A, the amount of drug A remaining in the body, then the rate of elimination of drug A can be described as:

$$\frac{dA}{dt} = -kA$$

Where k is first-order rate constant

The reaction proceeds at a rate is dependent on the concentration of A present in the body.

It is assumed that the processes of ADME follow first-order reactions and most drugs are eliminated in this manner.

Application of clinical pharmacokinetics

✓**Compartment model**

If tissue drug concentrations & binding are known, physiologic pharmacokinetic models, which are based on actual tissues and their respective blood flow, describe the data realistically.

Physiologic pharmacokinetic models are frequently used in describing drug distribution in animals, because tissue samples are easily available for assay.

Application of clinical pharmacokinetics

✓Compartment model contd…..

On other hand, tissue samples are not available for human subjects, so most physiological models assume an average set of blood flow for individual subjects.

In contrast, because of the vast complexity of the body, drug kinetics in body are frequently simplified to be represented by one or more tanks, or compartments, that communicate reversibly with each other

A compartment is not a real physiologic or anatomic region but is considered as a tissue or group of tissues that have similar blood flow and drug affinity.

Application of clinical pharmacokinetics

✓Compartment model contd…..

Within each compartment - drug is uniformly distributed. so concentration of drug represents an average concentration & each drug molecule has an equal probability of leaving the compartment.

Rate constants are represent overall rate processes of drug entry into & exit from compartment.

The model is an open system because drug can be eliminated from system. Compartment models are based on linear assumptions using linear differential equations.

Application of clinical pharmacokinetics

✓Mamillary model

A compartmental model provides a simple way of grouping all the tissues into one or more compartments where drugs move to and from central/plasma compartment.

The mammillary model is a strongly connected system & most common model used in pharmacokinetics, because one can estimate the amount of drug in any compartment of system after drug is introduced into a given compartment.

Application of clinical pharmacokinetics

✓One Compartment Model

Following drug administration, the body is depicted as a kinetically homogeneous unit. This assumes that the drug achieves instantaneous distribution throughout body & drug equilibrates instantaneously between tissues.

Thus the drug concentration–time profile shows a monophasic response (i.e. it is monoexponential; It is important to note that this does not imply that the drug concentration in plasma (Cp) is equal to the drug concentration in the tissues.

However, changes in plasma concentration quantitatively reflect changes in tissues.

The relationship can be plotted on a log Cp vs time graph and will then show a linear relation; this represents a one-compartment model

Application of clinical pharmacokinetics

✓Two Compartment Model

Central compartment comprises tissues that are highly perfused such as heart, lungs, kidneys, liver & brain.
Peripheral compartment comprises less well-perfused tissues such as muscle, fat and skin.

A two-compartment model assumes that, following drug administration into central compartment, drug distributes between compartment & peripheral compartment.

However, drug does not achieve instantaneous distribution, i.e. equilibration between two compartments.

Application of clinical pharmacokinetics

- ✓ **Multi Compartment Model**

In this model drug distributes into more than one compartment & concentration–time profile shows more than one exponential.

Each exponential on the concentration–time profile describes a compartment.

Ex. gentamycin can be described by a three-compartment model following a single IV dose

Application of clinical pharmacokinetics

✓ Caternary Model

Mammillary model distinguished from another type of compartmental model called catenary model - consists of compartments joined to one another like the compartments of a train.

Catenary model are directly connected to the plasma, it is not used as often as the mammillary model.

Overall Pharmacokinetics Parameters play an important roles……

- ✓Volume of distribution
- ✓Elimination rate constant
- ✓Half life
- ✓clearance