Lecturer Dr. shaimaa saleh **Lec. 2**

Therapeutic Drug Monitoring (TDM)

Clinical Pharmacokinetic and Pharmacodynamic Concepts

Pharmacokinetics: is the study of the absorption, distribution, metabolism, and excretion (ADME) of drugs.

Pharmacodynamics: is the relationship between drug concentration and pharmacological response.

Clinical pharmacokinetics: is the application of pharmacokinetic concepts and principles in humans in order to design individualized dosage regimens which optimize the therapeutic response and minimize the adverse drug reaction.

Therapeutic drug monitoring (TDM)

is the measurement of the serum level of the drug and the coordination of this serum level with the therapeutic range .

Criteria of drugs suitable for TDM:

1- A good relationship exists between plasma concentrations and clinical effects. This relationship allows to predict pharmacologic effects with changing plasma drug concentrations.

2- The drug should have a narrow therapeutic range

3- At any given dose, there is large interindividual variability in plasma concentration of the drug and/or its metabolites.

4- The therapeutic effect cannot be readily assessed by the observation of the clinical parameters i.c. a precise clinical end point is not available (e g. anticonvulsants, anti-arythmics antidepressants etc.).

5- An appropriate cost-effective analytical test must be available for the analysis of drug and/or its active metabolites.

Indications for TDM include:

1-Assess medication compliance
2-Avoid toxicity
3-Increase therapeutic response

Sources of Errors in TDM

Common potential sources of error are:

1. Administration times not recorded accurately.
2. Dose administration error.
3. Blood drawn at incorrect time.
4. Blood drawn before steady-state.
5. Blood drawn from wrong site.
6. Lab assay error.

Linear versus non-linear pharmacokinetics:

• If a plot of steady state concentration versus dose yields a straight line, the drug is said to follow linear pharmacokinetics . In this situation, steady-state serum concentrations increase or decrease proportionally with dose (e.g., a 50% increase in dose yields a 50% increase in steady-state concentration) .

• Most drugs follow linear pharmacokinetics

• When steady-state concentrations change in a disproportionate fashion after the dose is altered, a plot of steady-state concentration versus dose is not a straight line and the drug is said to follow non-linear pharmacokinetics.

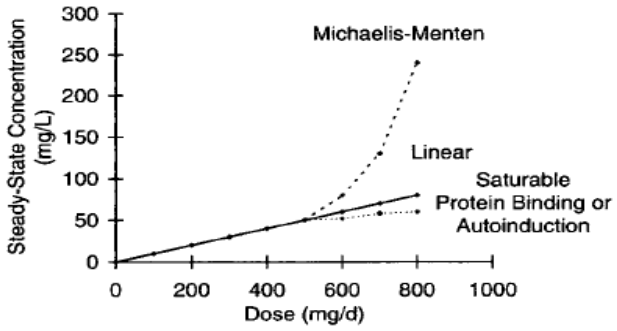

Figure2. Linear ph.k (solid line). Michalis-Menten ph.k(upper dashed line). Saturable plasma protein binding or autoinduction(lower dashed line).

• When steady-state concentrations increase more than expected after a dosage increase , the most likely explanation is that the metabolism of the drug has become saturated. This phenomenon is known as saturable or Michaelis-Menten pharmacokinetics.Both phenytoin and salicylic acid follow Michaelis-Menten pharmacokinetics.

•When steady-state concentrations increase less than expected after a dosage increase , there are two typical explanations

1- Some drugs, such as valproic acid, saturate plasma protein binding sites so that as the dosage is increased steady-state serum concentrations increase less than expected.

2- Other drugs, such as carbamazepine, increase their own rate of metabolism from the body as dose is increased so steady-state serum concentrations increase less than expected. This process is known as autoinduction of drug metabolism.

• Drugs that exhibit non-linear pharmacokinetics are often very difficult to dose correctly.

Basic pharmacokinetic concepts

Clearance:

Clearance (Cl) is the volume of serum or blood completely cleared of the drug per unit time. Thus, the dimension of clearance is volume per unit time, such as L/h or mL/min.

• The liver is most often the organ responsible for drug metabolism while in most cases the kidney is responsible for drug elimination.

• The gastrointestinal wall, lung, and kidney can also metabolize some drugs, and some medications are eliminated unchanged in the bile.

• Clearance is the most important pharmacokinetic parameter because it determines the maintenance dose (MD) that is required to obtain a given steady-state serum concentration (Css):

$$MD = Css.\ C1$$

Volume of distribution:

•Volume of distribution (V) is an important pharmacokinetic parameter because it determines the loading dose (LD) that is required to achieve a particular steady state drug concentration immediately after the dose is administered:

$$LD = C_{ss}\ .V$$

•The volume of distribution is a hypothetical volume that relates drug serum concentrations to the amount of drug in the body. Thus, the dimension of volume of distribution is in volume units, such as L or mL.

•At any given time after drug has been absorbed from extravascular sites and the serum and tissue drug concentrations are in equilibrium, the serum concentration for a drug (C) is equal to the quotient of the amount of drug in the body (AB) and the volume of distribution:

$$C = A_B/V$$

The volume of distribution can be very small if the drug is primarily contained in the blood (warfarin V = 5-7 L), or very large if the drug distributes widely in the body and is mostly bound to body tissues (digoxin V = 500 L).

• The physiologic determinates of volume of distribution are the actual volume of blood (V_B) and size (measured as a volume) of the various tissues and organs of the body (V_T). Therefore, a larger person, such as a 160-kg football player, would be expected to have a larger volume of distribution for a drug than a smaller person, such as a 40-kg grandmother.

• How the drug binds in the blood or serum compared to the binding in tissues is also an important determinate of the volume of distribution for a drug.

• For example, the reason warfarin has such a small volume of distribution is that it is highly bound to serum albumin so that the free fraction of drug in the blood (f_b) is very small.

• Digoxin has a very large volume of distribution because it is very highly bound to tissues (primarily muscle) so that the free fraction of drug in the tissues (f_T; f_T = unbound drug concentration in the tissue/total tissue drug concentration) is very small.

•The equation that relates all of these physiologic determinates to the volume of distribution is:

$$V = V_B + \frac{f_B}{f_T} V_T$$

Half-life and elimination rate constant:

•When drugs that follow linear pharmacokinetics are given to humans, serum concentrations decline in a curvilinear fashion (Figure 3). When the same data is plotted on a semilogarithmic axis, serum concentrations decrease in a linear fashion after drug absorption and distribution phases are complete. This part of the curve is known as the elimination phase.

•The time that it takes for serum concentrations to decrease by 1/2 (one-half) in the elimination phase is a constant and is called the half-life ($t_{1/2}$). The half-life describes how quickly drug serum concentrations decrease in a patient after a medication is administered, and the dimension of half-life is time (hour, minute, day, etc..).

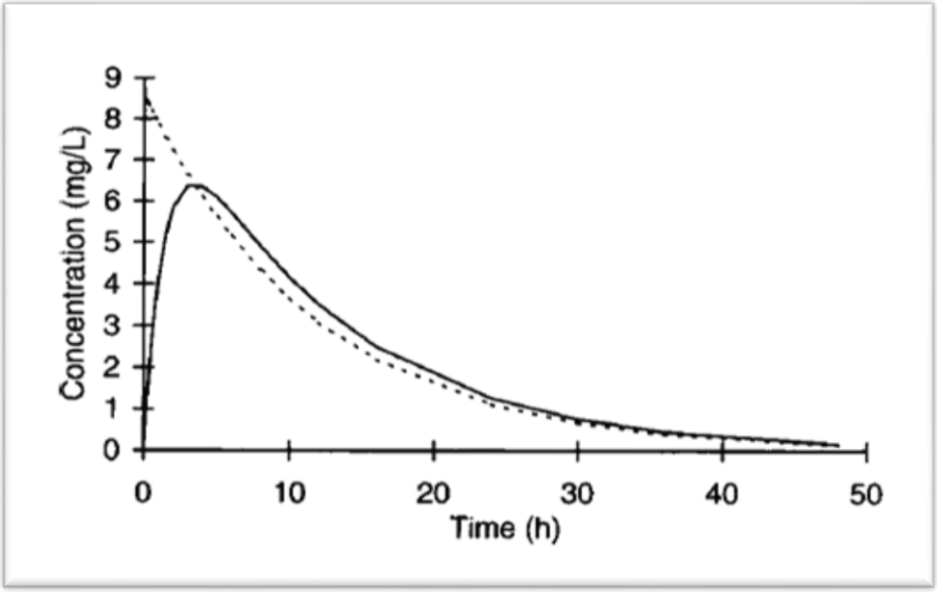

Figure 3, Serum concentration/time profile for a patient receiving a drug orally (solid line) and by intravenous bolus (dashed line). When the drug is given orally, serum concentrations initially increase while the drug is being

absorbed and decline after drug absorption is complete.

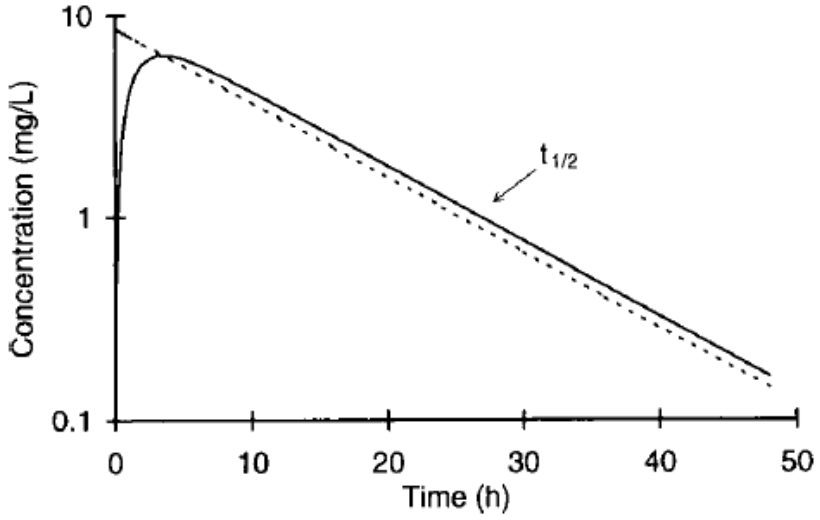

Figure 4. Data from Figure 3 plotted on semilogarithmic axes. Serum concentrations decline in a straight line in both cases.

The half-life and elimination rate constant are related to each other by the following equation, so it is easy to compute one once the other is known:

$$T_{1/2}=0.693/ke$$

The elimination rate constant can also be measured graphically by computing the slope of the log concentration versus time graph during the elimination phase:

$$K_e = - (\text{In } C1 - \text{In } C2) /(t_1 – t_2)$$

Half-life is important because it determines the time required to reach steady state and the dosage interval. It takes approximately 3 to 5 half-lives to reach steady-state concentrations during continuous dosing.

Half-life is also used to determine the dosage interval for a drug. For example, it may be desirable to maintain maximum steady-state concentrations at 20 mg/L and minimum steady-state concentrations at 10 mg/L. In this case, it would be necessary to administer the drug every half-life because the minimum desirable concentration is one-half the maximum desirable concentration.

•The half-life and elimination rate constant are known as dependent parameters because their values depend on the clearance (Cl) and volume of distribution (V) of the agent:

$T_{1/2}$= (0.693 · V)/CI

ke = CI/V

•The half-life and elimination rate constant for a drug can change either because of a change in clearance or a change in the volume of distribution.

Because the values for clearance and volume of distribution depend only on physiological parameters and can vary independently of each other, they are known as independent parameters.

Michaelis-Menten or saturable pharmacokinetics:

•Drugs that are metabolized by the cytochrome P-450 enzymes and other enzyme systems may undergo Michaelis-Menten or saturable pharmacokinetics. This is the type of nonlinear pharmacokinetics that occurs when the number of drug molecules overwhelms or saturates the enzyme's ability to metabolize the drug.

When this occurs, steady-state drug serum concentrations increase in a disproportionate way after a dosage increase .

In this case the rate of drug removal is described by the classic Michaelis-Menten relationship that is used for all enzyme systems:

$$\text{rate of metabolism} = (V_{max}. C)/(K_m + C)$$

where Vmax is the maximum rate of metabolism, C is the substrate concentration, and Km is the substrate concentration where the rate of metabolism = $V_{max}/2$.

The clinical implication of Michaelis-Menten pharmacokinetics is that the clearance of a drug is not a constant but is concentration- or dose-dependent. As the dose or concentration increases, the clearance rate (Cl) decreases as the enzyme approaches saturable conditions:

$Cl = V_{max}(Km + C)$

This is the reason concentrations increase disproportionately after a dosage increase. There is so much interpatient variability in Michaelis-Menten pharmacokinetic parameters for a drug (typically V_{max} = 100-1000 mg⁄d and K_m = 1-10 mg/L for phenytoin) that dosing drugs which follow saturable metabolism is extremely difficult.

The volume of distribution (V) is unaffected by saturable metabolism and is still determined by the physiological volume of blood (V_B) and tissues (V_T) and the unbound concentration of drug in the blood (f_B) and tissues (f_T)

$$V = VB + (f_B/f_T)VT$$

Also, half-life ($t_{1/2}$) is still related to clearance and volume of distribution using the same equation as for linear pharmacokinetics: $t1/2 = (0.693\ V)/CI$. However, since clearance is dose- or concentration-dependent, half-life also changes with dosage or concentration changes. As doses or concentrations increase for a drug that follows Michaelis-Menten pharmacokinetics, clearance decreases, and half-life becomes longer for the drug: ↑t 1⁄2 =(0.693 . V)/ ↓CI.

•The clinical implication of this finding is that the time to steady state (3-5 t1⁄2) is longer as the dose or concentration is increased for a drug that follows saturable pharmacokinetics.

•Under steady-state conditions the rate of drug administration equals the rate of drug removal. Therefore, for a drug that is only removed by metabolism by one enzyme system, the Michaelis-Menten equation can be used to compute the maintenance dose (MD) required to achieve a target steady-state serum concentration (Css)

$$MD = \frac{V_{max} \cdot Css}{Km + Css}$$

When the therapeutic range for a drug is far below the Km value for the enzymes that metabolize the drug, this equation simplifies to:

$$MD = (Vmax/Km) .Css$$

or, since Vmax/Km is a constant،

$$MD = Cl \cdot Css$$

Therefore, in this case, drugs that are metabolized follow Iinear pharmacokinetics. First order pharmacokinetics is another name for linear pharmacokinetics. When the therapeutic range for a drug is far above the Km value for the enzyme system that metabolizes the drug, the rate of metabolism becomes a constant equal to V_{max}. Under these conditions only a fixed amount

of drug is metabolized because the enzyme system is completely saturated and cannot increase its metabolic capacity. This situation is also known as zero-order pharmacokinetics.

• For example, the average Km for phenytoin is about 4 mg/L and The therapeutic range for phenytoin is 10 to 20 mg/L. Therefore, most patients experience Michaelis-Menten kinetics while taking phenytoin.

• Based on these facts.it can be seen that any drug that is metabolized by enzymes undergoes Michaelis-Menten pharmacokinetics. But, the therapeutic ranges of most drugs are far below the Km for the enzymes that metabolize the agent. Because of this, most medications that are metabolized follow linear pharmacokinetics. However, even in these cases saturable drug metabolism can occur in drug overdose cases where the drug concentration far exceeds the therapeutic range for the medication.

Bioavailability:

When a drug is administered extravascularly, the entire dose may not enter the systemic circulation. The fraction of the administered dose that is delivered to the systemic circulation is known as the bioavailability for the drug and dosage form.

For drugs that follow linear pharmacokinetics, bioavailability is measured by comparing the total area under the serum concentration time curve (AUC) for the extravascular and intravenous doses .

If the extravascular and intravenous doses are the same, the bioavailability for a drug can be calculated by dividing the AUC after oral administration (AUC_{PO}) by the AUC after intravenous administration (AUC_{iv}) :

$$F=AUC_{PO}/AUC_{iv}$$

•If it is not possible to administer the same dose intravenously and extravascularly, the bioavailability calculation can be corrected to allow for different size doses for the different routes of administration:

$F=(AUC_{PO}/AUC_{IV})(D_{iv}/D_{po})$

where D_{iv} is the intravenous dose and D_{po} is the oral dose.

Bioequivalence:

•Bioequivalence is achieved when the serum concentration/time curve for the generic and brand name drug dosage forms (or two different dosage forms of

the same drug) are considered superimposable and identical using statistical tests.

•Concentration/time curves are superimposable when the area under the total serum concentration/time curve (AUC), maximum concentration (Cmax), and time that the maximum concentration occurs (Tmax) are identical within statistical limits .

• The ratio of the area under the serum concentration/time curves for the generic($AUC_{generic}$) and brand name (AUC_{brand}) drug dosage forms is known as the relative bioavailability ($F_{relative}$) since the reference AUC is derived from the brand name drug dosage form:

$$F_{relative} = AUC_{generic}/AUC_{brand}$$