□ Introduction:

- The role of population pharmacokinetic modeling is to store experience with drug behavior. The behavior of the model is then correlated with the clinical behavior of the patients studied, permitting selection of a specific serum level therapeutic goal that is based on each individual patient's need for the drug and on the risk of adverse reactions, both of which must be considered.
- A dosage regimen is then computed to achieve that goal with maximum precision. The patient should not run a greater risk of toxicity than is justified, and should obtain the maximum possible benefit within the acceptable risk. The regimen is given and the patient monitored.

• The use of population pharmacokinetic models is to store experiences about drugs in patients and to apply that experience to the care of new patients. Population models are the Bayesian prior. For truly individualized therapy, it is necessary first to select a specific target goal, such as a desired serum or peripheral compartment concentration, and then to develop the dosage regimen individualized to best hit that target in that patient.

• One must monitor the behavior of the drug by measuring serum concentrations or other responses, hopefully obtained at optimally chosen times, not only to see the raw results, but to also make an individualized (Bayesian posterior) model of how the drug is behaving in that patient. Only

then can one see the relationship between the dose and the absorption, distribution effect and elimination of the drug and the patient's clinical sensitivity to it; one must always look at the patient - only by looking at both the patient and the model can it be judged whether the target goal was correct or needs to be changed. The adjusted dosage regimen is again developed to hit that target most precisely starting with the very next dose, not just for some future steady state.

. The adaptive model for dosage regimen calculation uses patient variables such as weight, age, sex, body surface area, and known patient pathophysiology, such as renal disease, as well as the known population average pharmacokinetic parameters of the drug.

• In this case, calculation of the dosage regimen takes into consideration any changing pathophysiology of the patient and attempts to adapt or modify the dosage regimen according to the needs of the patient.

• The adaptive model generally assumes that pharmacokinetic parameters such as drug clearance do not change from one dose to the next.

• However, some adaptive models allow for continuously adaptive change with time in order to simulate more closely the changing process of drug disposition in the patient, especially during a disease state.

• In dosing drugs with narrow therapeutic ratios, an initial dose is calculated based on mean population pharmacokinetic parameters.

• After dosing, plasma drug concentrations are obtained from the patient. As more blood samples are drawn from the patient, the calculated individualized patient pharmacokinetic parameters become increasingly more reliable.

• This type of approach has been referred to as adaptive or Bayesian adaptive method with feedback when a special extended least-squares algorithm is used.

• Many ordinary least-squares computer software packages are available to clinical practice for parameter and dosage calculation.

• Some software packages record medical history and provide adjustments for weight, age and in some cases, disease factors. A common approach is to estimate the clearance and volume of distribution from intermittent infusion.

- Abbottbase Pharmacokinetic Systems (1986 and 1992) is an example of patient-oriented software that records patient information and dosing history based on 24-hour clock time.
- An adaptive-type algorithm is used to estimate pharmacokinetic parameters. The average population clearance and volume of distribution of drugs are used for initial estimates and the program computes patient-specific Cl and V_D as serum drug concentrations are entered.
- The program accounts for renal dysfunction based on creatinine clearance, which is estimated from serum creatinine concentration using the Cockroft-Gault equation.
- The software package allows specific parameter estimation for digoxin, theophylline and aminoglycosides, although other

drugs can also be analyzed manually.

- Many least-squares (LS) and weighted-least squares (WLS) algorithms are available for estimating patient pharmacokinetic parameters.
- Their common objective involves estimating the parameters with minimum bias and good prediction, often as evaluated by mean predictive error.
- The advantage of the Bayesian method is the ability to input known information into the program, so that the search for the real pharmacokinetic parameter is more efficient and, perhaps, more precise.
- For example, a drug is administered by intravenous infusion at a rate, R, to a patient. The drug is infused over t hours (t may be 0.5 to 2 hours for a typical infusion). The patient's clearance Cl_T, may be estimated from plasma drug

concentration taken at a known time according to a one compartment-model equation.

Sheiner and Beal (1982) simulated a set of theophylline data and estimated parameters from the data using one and two serum concentrations, assuming different variabilities.

These investigators tested the method with a Bayesian approach and with an ordinary least-squares method, OBJ_{OLS}

$$C_i = f(P, t_i) + \varepsilon_i$$

$$OBJ_{OLS} = \sum_{i=1}^{n} \frac{(C_i - \hat{C}_i)^2}{\sigma_i^2}$$

P = pharmacokinetic parameter

C_i = set of plasma drug concentration data

ε = measurement error, intra-individual error

t_i = drug is infused over t hours

f = fraction of bioavailable dose