Clinical Pharmacokinetics in a Patient Care Setting

By

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One of the more dramatic demonstrations of the role of pharmaceutical science in pharmacy practice has been the successful implementation of clinical pharmacokinetics service by pharmacists in a patient care setting. Pharmaceutical scientists in pharmaceutical industry and academia have been at the forefront of the modern development of pharmacokinetics and biopharmaceutics. Since the 1950's they have measured the biologic half-lives of drugs, studied their absorption-distribution-metabolism-excretion characteristics, and have designed various drug dosage forms including sustained release forms, based upon a knowledge of pharmacokinetic principles. But until recently, there has been very little input by pharmacists in selection of drug doses and modification of dosage regimens based upon unique and special needs of some of the patients who require therapy. A service, education and demonstration program now functioning at the University of Kentucky Medical Center is illustrating just how valuable the pharmacist can be in this role. This presentation describes the basis for pharmacist involvement in this activity, out-lines the organization and function of a clinical pharmacokinetics service in an academic medical center, provides examples of patient care benefits to be derived, and considers the potential for application in settings other than an academic medical center.

Rationale for Pharmacist Involvement

For many important drugs there is a relatively narrow range between minimum blood levels required to produce a desired response and levels which give rise to toxic manifestations. Optimization of drug dosage regimens for individual patients is often necessary as a result of individual patient differences in drug absorption or disposition rates.

For a number of drugs, there is now sufficient understanding of the interrelation between drug response and drug blood levels so that an effective approach to optimization of drug therapy is the establishment of a regimen which will produce the desired time course of drug levels in body fluids and tissues. These levels may be based upon maintaining a steady-state drug level which is above that necessary to produce a desired therapeutic response, but below a level recognized as producing an undesired response or toxicity. In other instances, optimum therapy may require a non-steady-state time course of drug in blood.

Until the development in recent years of methodology to permit rapid measurement of drug blood levels at therapeutic doses, dosage adjustment had to be based on development in the patient of overt toxicity or non-responsiveness. It is now possible to monitor drug levels in blood, or in other body fluids, and to adjust dosage to maintain desired levels of drug in the body without awaiting development of toxicity or lack of response to drug therapy. Much has been learned of factors which influence absorption, distribution, metabolism and excretion of critical drugs such as the cardiac glycosides, aminoglycoside antibiotics and anticonvulsants—all of which may require careful individualization of dose, particularly in seriously ill patients.

Modern pharmaceutical education for professional practice includes course work in biopharmaceutics and pharmacokinetics, with extensive consideration of dosage regimen determination and adjustment. An important component of professional pharmacy education is the clinical clerkship, which provides the student with the confidence which can only be acquired through actual experience in applying scientific principles in the patient care setting. In conjunction with the physician's clinical evaluation of patient progress, the modern pharmacist should be capable of utilizing his unique educational background to contribute to improved patient care by assuming a major responsibility for development of drug dosing regimens and, for drugs which merit it, of utilizing patient drug level data to verify suitability of the selected regimen.

Organization and Function of a Clinical Pharmacokinetics Service

The essential components of a clinical pharmacokinetics service program are: (1) the availability of patient data for concentration of drug in biological fluids; (2) development of dosing recommendations based on pharmacokinetic interpretation of data and evaluation of the clinical status of the patient; and (3) implementation and follow-up of dosing recommendations.

In recent years there has been a proliferation of laboratory services devoted to determination of drug concentrations in biological fluids of patients. The utility of such data, however, depends upon their appropriate application in the patient care setting. There is no standardized mechanism for such utilization of data. It is our opinion that it is the **application**, rather than the generation, of such information that offers the greatest opportunity and challenge to pharmacists. At the University of Kentucky we have placed our emphasis on development of the role of the pharmacist as the interface between the clinical laboratory and the patient care setting.

The organizational structure through which pharmacy services are provided at the University of Kentucky Medical Center has provided an excellent opportunity for the development of this function of the pharmacist. The University of Kentucky College of Pharmacy manages the pharmacy service provided at University Hospital through a contractual arrangement between the College

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and the Hospital. The University is a 400-bed teaching hospital which serves as a referral center for a large portion of the state of Kentucky. Nineteen staff pharmacists are employed in this hospital, and ten of them hold faculty appointments in the College of Pharmacy. Five of these faculty members function in the patient care areas, where they are involved in service, teaching and research. Each hospital pharmacist-faculty member has associated with him one to three pharmacy residents, who share with him the responsibility for patient care. The fact that College of Pharmacy faculty members function side-by-side with physicians and other health care professionals has been a significant factor in the development of our clinical pharmacokinetics program.

The delineation of responsibilities and the integration of resources in implementing the clinical pharmacokinetics service is illustrated in the following brief discussion of each of the three components of the service.

1. Generation of Laboratory Data

In our institution a laboratory which is supported by the College of Pharmacy provides analytical support necessary for research on analytical methods development and generation of pharmacokinetic data on drugs being considered for inclusion in a monitoring program. This laboratory also provides its services without charge to the patient when demonstration programs are undertaken to determine whether routine monitoring of a specific drug is of sufficient benefit to justify the cost of such a service.

If a demonstration program proves to be of sufficient patient benefit, the responsibility for routine assay service is transferred to the hospital clinical laboratory. A close liaison is maintained between the hospital clinical laboratory and the College of Pharmacy laboratory personnel to assure efficient transfer of responsibility. In addition to methods development and analytical services associated with the introduction of a new drug to the clinical pharmacokinetics program, the College of Pharmacy laboratory also monitors the quality control of assays and assists with trouble shooting when an assay becomes a routine service function and is transferred to the hospital clinical laboratory.

2. Pharmacokinetic Interpretation of Data and Dosing Recommendation

The pharmacokinetic interpretation of drug levels is provided through a daily conference, which is chaired by a faculty member designated as the clinical pharmacokinetics coordinator. This conference is attended by all pharmacy staff members having responsibility for patients for whom drug levels were determined that day. The clinical pharmacokinetics coordinator is skilled in pharmacokinetics, and it is through a combination to pharmacokinetic interpretation of data and the pharmacists' knowledge of each patient's current clinical status that a dosing recommendation is determined during discussion. It is necessary that the pharmacist bring to the conference information relative to therapeutic objectives, patient clinical status, past and current drug history and any additional information that might assist in the determination of an appropriate dosing regimen.

3. Implementation

The final determination of action to be taken relative to dosing regimen changes occurs as a result of pharmacist-physician discussion of the dosing recommendations. The extent to which the pharmacist and the physician, respectively, influence the final decision generally reflects the extent to which judgements can be based on dosing to achieve a specific blood level of drug or on dosing in response to clinical status of the patient. For drugs such as phenytoin and aminoglycoside antibiotics, the pharmacist assumes the major responsibility for determination of dosage. For drugs such as digoxin, where the clinical status of the patient is a more important determinant of dosing need than is blood level, the physician has a greater input. In either case, it is becoming a common practice for physicians to prescribe some drugs in terms of the average steady-state blood level desired in a particular patient, rather than to specify the dose of the drug. It is then the responsibility of the pharmacist to determine a suitable loading and maintenance dose, to determine when drug levels should be monitored, and to determine what adjustments should be made in the dosing regimen. The responsibility for developing specific dosing needs based upon factors such as patient size, age and sex, route of administration, rate and extent of drug availability from a dosage form, individual variables such as rate of drug absorption, metabolism and renal function falls principally to the pharmacist.

Examples of Dosage Adjustment

Two examples will be described to illustrate how pharmacy involvement in dosing regimen adjustment can be of great importance in patient management. The first example concerns the adjustment of kanamycin dosage in patients with compromised renal function. These data are taken from the first experience undertaken in dosage adjustment at Kentucky in 1970 (F. Shainfeld and P. Stull, unpublished). A second example illustrates pharmacy involvement in the development of a parenteral dosing regimen for phenytoin in severely ill patients [H. B. Kostenbauder, **et al**, Clin. Pharmacol. Ther., **18**, 449 (1975); D. G. Perrier, **et al**, Annals Int. Med., in press].

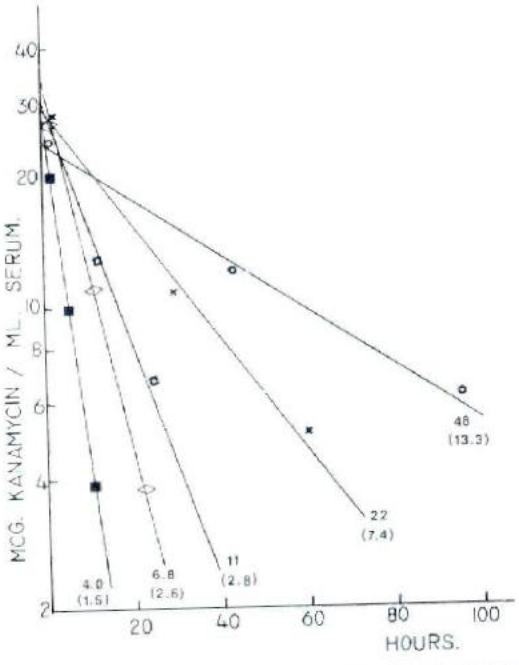
Kanamycin

Kanamycin is an antibiotic which is eliminated from the body principally through glomerular filtration and elimination of intact drug in urine. Rate of drug elimination therefore is dependent upon kidney function and may be markedly decreased in severe renal failure. Overdosage with kanamycin, or administration of normal dosage to patients with renal insufficiency, can result in serum levels of kanamycin which produce permanent hearing loss.

Slide 1 This slide shows serum levels in normal subjects after intra-muscular administration of 500 mg or 2 gm of kanamycin. Two hours after the intramuscular injection the plot of logarithm of kanamycin concentration in serum versus time is a straight line. Disappearance of kanamycin follows a first order process, and the elimination data can be treated according to a one compartment open model.

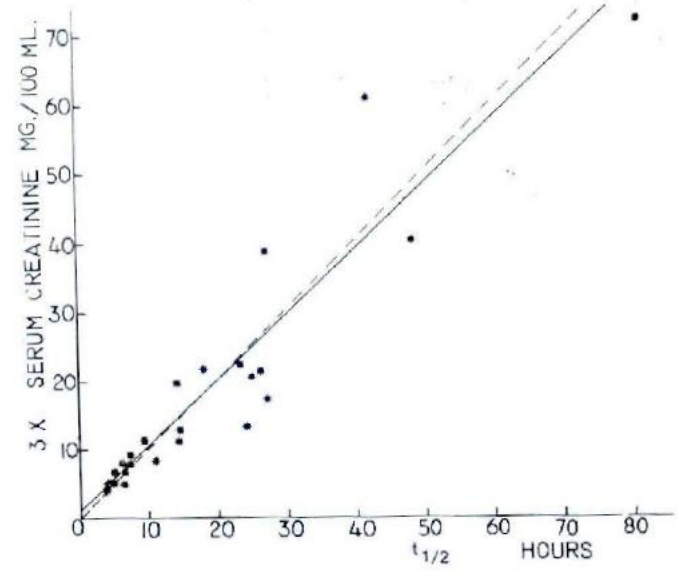
Slide 8 They observed that:
kanamycin $t_{\frac{1}{2}}$ (Hrs) 3. (Creatinine) serum (mg%).

Slide 9 We ran similar studies in our faculty on several patients and seemed to substantiate this observation. The $t_{\frac{1}{2}}$ is noted beside each plot, and the serum creatinine in parentheses.



Slide 9 -- Differences in rate of kanamycin elimination in patients with varying degree of renal failure. Number beside each plot is kanamycin half life, with serum creatinine indicated in parentheses (Shainfeld, et al., unpublished).

Slide 10 This slide shows similar measurements in 33 patients with serum creatinine up to 24 mg% and $t_{\frac{1}{2}}$ 80 hours. (Serum creatinine levels do not correlate as well as creatinine clearance— but they are reasonably close.)



Slide 10 -- Relationship between kanamycin half-life and serum creatinine in 33 patients (Shainfeld, et al., unpublished).

Slide 11 It has been suggested that the desired dose regimen for kanamycin in normal subjects is 7.5 mg/Kg administered I.M. every third half life. In normal subjects this would mean repeating the dose every 8 hours.

This dose regimen is expected to produce peak serum levels between 20 and 30 ug/ml., but avoid the potentially toxic levels of over 35 ug/ml. This regimen will produce a marked peak and valley effect, but it is not necessary and perhaps not desirable to maintain a constant serum level of the antibiotic.

We wished to have our pharmacists use this method for dosing kanamycin to patients with impaired renal function to avoid overdosing them and producing ototoxicity. We wanted, however, to have further evidence of the efficacy of such prediction of dosing regimen. So we had the pharmacist determine the patient's dose based on his renal function, but we also obtained blood samples periodically and determined kanamycin serum levels to see how good the predictions were in practice.

Kanamycin Dose 7.5 mg/Kg

Repeat every three half-lives

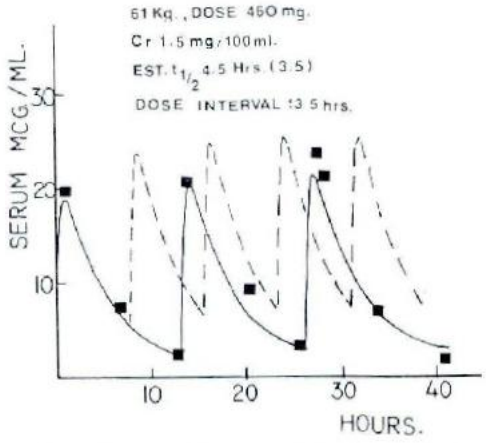
Normal dosing interval 8 hours

Slide 11 -- A typical dosing regimen for kanamycin.

Slide 12 The first slide shows data for a patient exhibiting serum creatinine of 1.5 mg%— essentially within normal limits, but the prediction on which we are working says the $t_{\frac{1}{2}}$ should be 4.5 hrs. and that the dose interval should be 3x this $t_{\frac{1}{2}}$ or 13.5 hrs. So it was dosed in this manner, 460 mg I.M. every 13.5 hrs., and blood samples were taken one and two hours after each dose, at the midpoint of the dosing interval, and just before administration of the next dose.

The black points show the actual levels achieved, and the value in parenthesis indicated that the experimental $t_{\frac{1}{2}}$ appeared to be about 3.5 hrs.

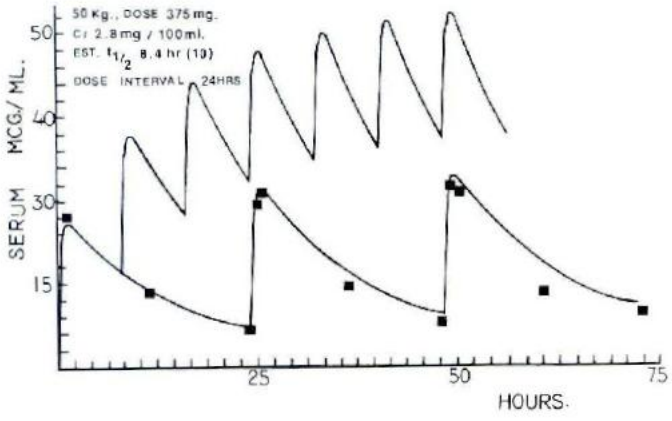
The dosing prediction kept the levels in the right range, but in this case the adjustment was not of great importance. The dotted lines show what levels would have been achieved had the usual 8-hour dose interval been used, and in this case that would have presented no problem.



Slide 12 -- Comparison of anticipated kanamycin serum levels (solid line) and actual levels (points) in a patient for whom dose was adjusted on basis of serum creatinine. Broken line indicates levels which would have been achieved with normal dosing regimen.

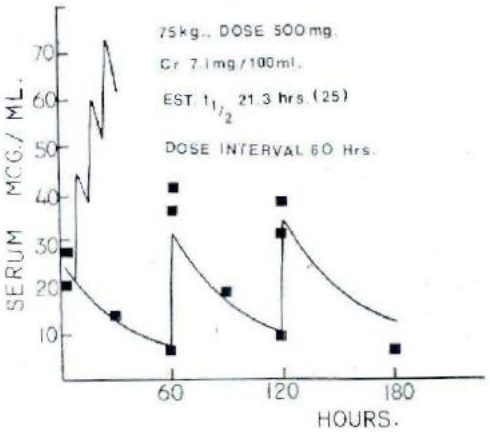
Slide 13 The next example involves a patient with serum creatinine of 2.8 mg%. The estimated $t_{\frac{1}{2}}$ would be 3x the serum creatinine or 8.4 hr, and the dosing interval would therefore be once every 24 hours. A 375 mg dose was administered every 24 hours and the points represent the serum levels of kanamycin. The levels are within the desired range and the experimental $t_{\frac{1}{2}}$ appears to be about 10 hours (compared with the predicted 8.4 hr.)

The upper curve is the level which would have been achieved had the drug been dosed in the usual manner—repeating the dose every 8-hours. Obviously the patient would have had serum levels which have been known to produce hearing loss, and note that the 8-hr dosing would **maintain** the kanamycin levels in this toxic range throughout the course of treatment.



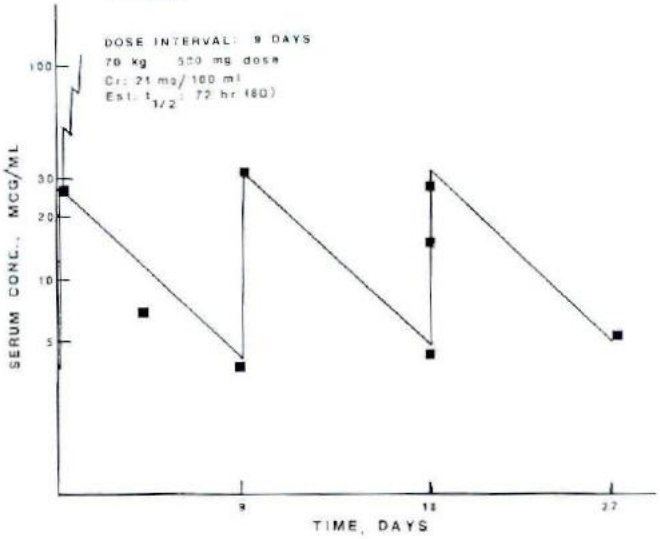
Slide 13 -- Comparison of anticipated kanamycin serum levels (solid line) and actual levels (points) in a patient for whom dose was adjusted on basis of serum creatinine. Upper line indicates levels which would have been achieved with normal dosing regimen.

Slide 14 The next patient had more severe renal failure—a serum creatinine of 7.1mg%, therefore a predicted $t_{\frac{1}{2}}$ of 21.3 hrs, and a dosing interval of 60 hours. The solid lower line is the predicted serum kanamycin levels and the points the actual values. Again the kanamycin levels were within an acceptable range. The rapidly ascending line shows what would have happened if the usual 8-hour dosing interval had been used for this patient.



Slide 14 -- Comparison of anticipated kanamycin serum levels (solid line) and actual levels (points) in a patient for whom dose was adjusted on basis of serum creatinine. Upper line indicates levels which would have been achieved with normal dosing regimen.

Slide 15 This slide shows data on a patient exhibiting a serum creatinine level of 24 mg%, for whom the predicted kanamycin half-life would be 72 hours, and the dosing interval would be once every **9 days.** These data for kanamycin represent an example of dosage regimen adjustment whereby the dose was held constant and the dosing interval was varied. The pronounced "peak" and "trough" effect was not considered inappropriate in this case, but if desired, a more constant plasma concentration could be achieved by varying the size of the dose. The following example of phenytoin dose adjustment illustrates such a case.



Slide 15 -- Comparison of anticipated kanamycin serum levels (solid line) and actual levels (points) in a patient for whom dose was adjusted on basis of serum creatinine. Upper line indicates levels which would have been achieved with normal dosing regimen.

Phenytoin

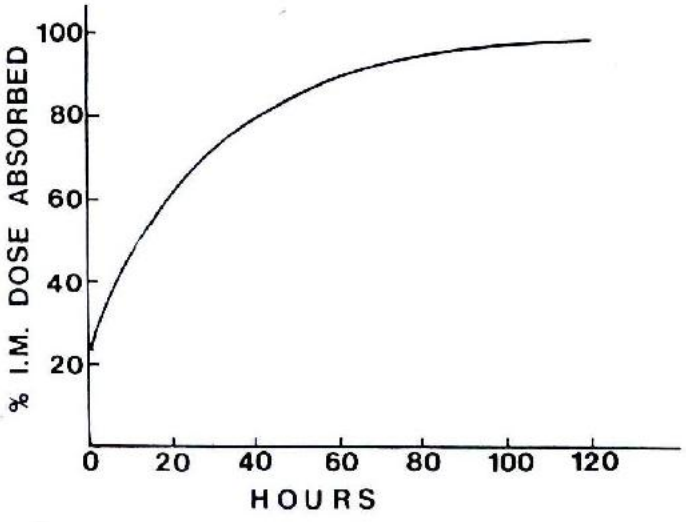
Phenytoin is routinely administered to prevent epileptic seizures in acutely head-injured patients. Parenteral administration of the drug is usually a necessity. Repeated intravenous administration of phenytoin is rather impractical because of the necessity to infuse large doses at a rate of not more than 25 mg/min. Intramuscular administration of phenytoin is therefore a common route of administration in these patients. Because early seizures following head trauma are hazardous, it is essential that plasma phenytoin levels be maintained within a range usually specified as 10-20 mcg/ml of plasma. Pharmacists attempting to dose patients with I. M. phenytoin to meet these criteria face two problems:

(a) Phenytoin administered intramuscularly is slowly absorbed over a period of five days, as shown in **slide 16**.

(b) Phenytoin exhibits non-linear (Michaelis-Menten) kinetics which makes dosage adjustment very critical near the upper region of the therapeutic range. The non-linear characteristics of phenytoin elimination is illustrated in **slide 17**. This slide shows the transition from zero order to first order kinetics in a patient who had received a phenytoin overdose.

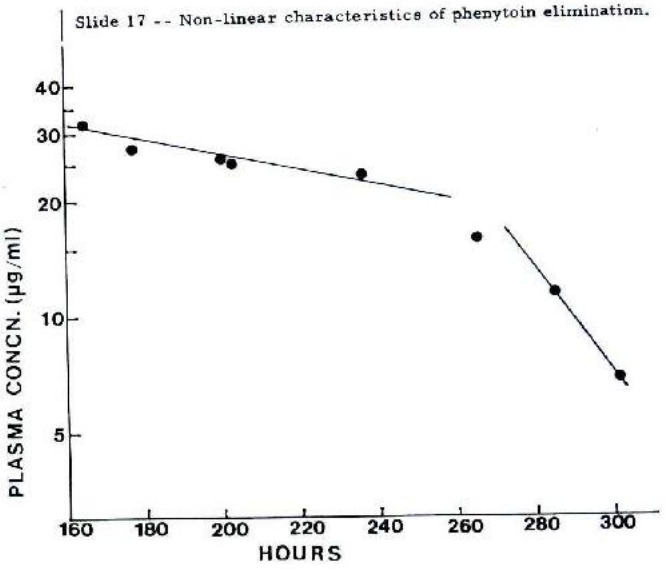
The first requirement for establishing a rational dosage regimen was the performance of studies to determine phenytoin pharmacokinetics after I.V. and I.M. administration. From such a study it was possible to show that phenytoin was totally available following I.M. administration, and that the slow absorption was consistent with a mathematical model depicting precipitation of drug at the I.M. injection site, followed by slow dissolution and absorption (**slide 18**).

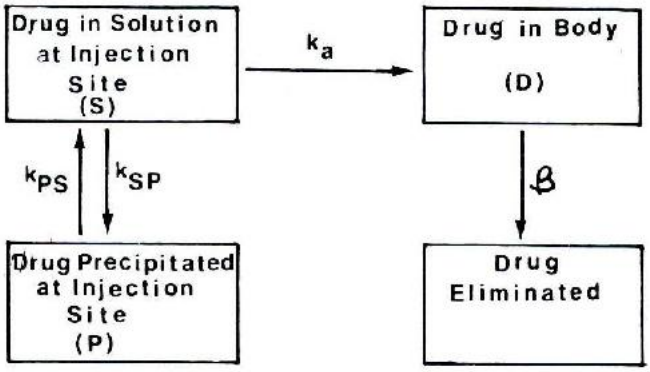
A dosing regimen was designed which consisted of a combination of an I.V. and I.M. loading dose, followed by a single I.M. maintenance dose each day. **Slide 19** illustrates the anticipated phenytoin blood levels from the I. V. dose, the slowly absorbed I.M. dose, and the sum of both routes of administration.



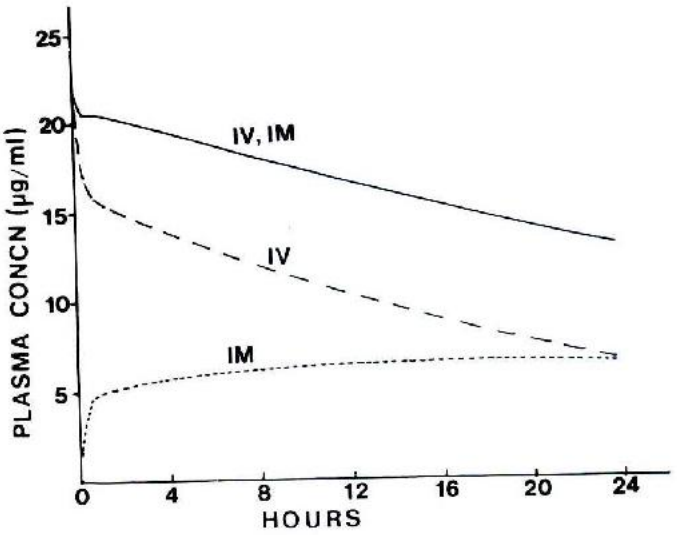
Slide 16 -- Slow absorption of intramuscular phenytoin [Kostenbauder, et al., Clin. Pharmacol. Ther., 19, 449 (1975)].

Slide 17 -- Non-linear characteristics of phenytoin elimination.





Slide 18 -- Model for phenytoin absorption following intramuscular administration [Kostenbauder, et al., Clin. Pharmacol. Ther., 19, 449 (1975)].



Slide 19 -- Plasma phenytoin concentrations achieved from intravenous administration (dashed line), intramuscular administration (dotted line) or simultaneous IV and IM (solid line). (Perrier, et al., Ann. Int. Med., in press).

Because of marked inter-individual differences in rate of phenytoin disposition, and the non-linear kinetics associated with this drug, an average dosing regimen is not suited to every patient. Consequently, plasma phenytoin levels must be monitored, and the I.M. maintedance dose adjusted. **Slide 20** illustrates plasma level data on 98 patients who received phenytoin via this dosing regimen. Open symbols represent plasma phenytoin concentrations in patients receiving an average daily I.M. maintenance dose of 8.8 mg/Kg; solid symbols are plasma levels in patients for whom an adjustment in dose was made.

Potential for Application of Clinical Pharmacokinetics in Settings Other Than an Academic Medical Center

While at present it is a fact that determinations of drug levels in patients is a service being provided in relatively few settings, to an infinitesimally small percentage of the total patient population, it should not be assumed that this condition will always prevail. Analytical methodology amenable to automated analysis is being developed for an increasing number of drugs. It can be anticipated that in the foreseeable future drug level determinations can be as readily available to health care practitioners as blood glucose levels are today. The potential offered for pharmacist involvement in improved drug therapy through utilization of drug level data is immense.

In a recent survey of an outpatient population attending a chest clinic, it was found that only 1 of 55 patients for whom the drug theophylline had been prescribed exhibited plasma theophylline levels within the therapeutic range. While patient compliance was a major factor in this situation, the principal reasons for non-compliance were that the patients discontinued their medication because either the doses prescribed were inadequate to elicit any improvement in their condition, or the prescribed doses elicited undesired side effects. It is anticipated that knowledge of drug dosage required for individual patients, combined with pharmacist counselling of patients, can result in a profound improvement in situations such as this.

It is our opinion that the development and application of the science of clinical pharmacokinetics offers the pharmacy practitioner a most significant opportunity for professional service to patients.

Slide 20 -- Phenytoin plasma concentrations achieved in 98 patients who received phenytoin via an IV and IM loading dose and once a day maintenance dose. Solid points represent plasma levels on patients following a dosage adjustment. Dotted lines indicate the desired range of 10 to 20 mcg/ml (Perrier, et al., Ann. Int. Med., in press).