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Pharmacokinetics and Pharmacodynamics for Medical Students: A Proposed Course Outline

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Keywords

pharmacokinetics, pharmacodynamics, drug interactions, medical

The discipline of pharmacokinetics (PK) applies mathematical models to describe and predict the time course of drug concentrations and drug amounts in body fluids.[1–3] Pharmacodynamics (PD) applies similar models to understand the time course of drug actions on the body. Clinicians are most concerned with pharmacodynamics—they want to know how drug dosage, route of administration, and frequency of administration can be chosen to maximize the probability of therapeutic success while minimizing the likelihood of unwanted drug effects. However the path to pharmacodynamics comes via pharmacokinetics. Because drug effects are related to drug concentrations, understanding and predicting the time course of concentrations can be used to help optimize therapy.

The link of drug dosage to drug effect involves a sequence of events (Figure 1). Even when a drug is administered directly into the vascular system, the drug diffuses to both its pharmacologic target receptor and to other peripheral distribution sites where it does not have the desired activity but may exert toxic effects. Simultaneously, the drug undergoes clearance by metabolism and excretion. After oral administration, the situation is more complex, since the drug must undergo dissolution and absorption, then survive first-pass metabolism in the liver, before reaching the systemic circulation. Pharmacokinetics provides a rational mathematical framework for understanding these concurrent processes, and facilitates achieving optimal clinical pharmacodynamic effects more efficiently than trial and error alone.

The following 3 clinical vignettes illustrate how familiarity with principles of pharmacokinetics and pharmacodynamics can facilitate optimal understanding and prediction of drug effects in human subjects and patients.

Clinical Vignettes

Case 1

A 30-year-old man has been extensively evaluated for recurrent supraventricular tachycardia (SVT), which is associated with palpitations and dizziness. No identifiable cardiac disease is evident, and other medical diseases have been excluded.

The treating physician elects to start therapy with digitoxin, 0.1 mg daily. One week later the patient is seen again, and states that episodes of SVT are reduced in number. The plasma digitoxin level is 8 ng/mL (usual therapeutic range, 10–20 ng/mL). The dose is increased to 0.2 mg/day. At a follow-up visit 7 days later, the patient claims that symptoms attributable to SVT have disappeared completely. The plasma digitoxin level is 17.4 ng/mL. The patient continues on 0.2 mg/day of digitoxin.

One month later the patient sees the physician on an urgent basis. He has diminished appetite and waves

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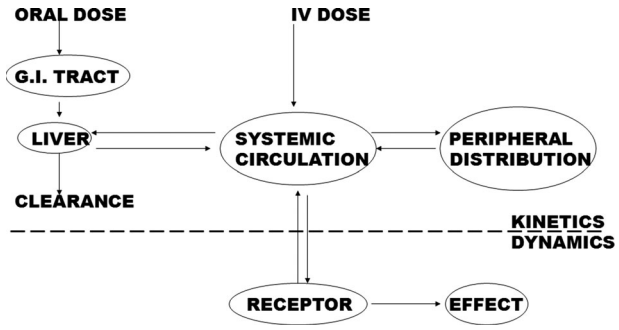

Figure 1. Sequence of events between intravenous or oral administration of a drug and the drug's interaction with the target receptor mediating pharmacologic action. This type of schematic diagram has been attributed to Dr. Leslie Z. Benet. The segment above the dashed line is the pharmacokinetic component—"what the body does to the drug." Below the dashed line is the pharmacodynamic component—"what the drug does to the body" (from reference 2, with permission).

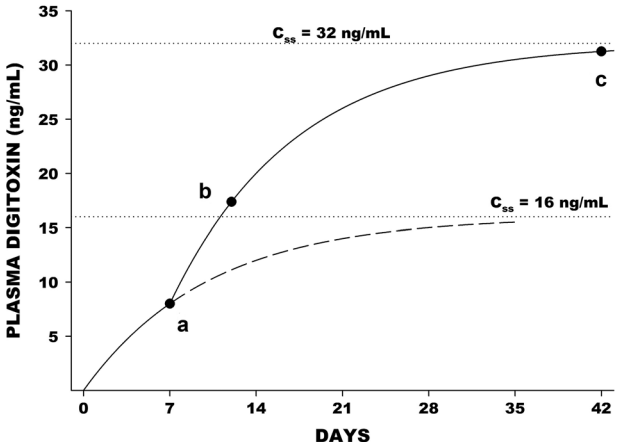

Figure 2. Hypothetical mean plasma concentrations of digitoxin, corresponding to case 1 in the text. Digitoxin is initially given at a dosage of 0.1 mg per day for 1 week, after which the plasma concentration is 8 ng/mL (point *a*). The treating physician wants to increase the plasma concentration to a value within the usual therapeutic range (10–20 ng/mL). If the physician stayed with the 0.1-mg-per-day dosage, the eventual steady-state concentration would have been 16 ng/mL (dashed line)—within the desired therapeutic range. Instead, the dosage is increased to 0.2 mg per day on day 7. The next measured plasma concentration is 17.4 ng/mL 1 week later (point *b*), but 1 month later it has reached 31.3 ng/mL (point *c*), close to the eventual steady-state value of 32 ng/mL. This is well above the therapeutic range and may be associated with toxicity.

of nausea. The electrocardiogram shows T-wave abnormalities, and the plasma digitoxin level is 31.3 ng/mL.

Discussion—Case 1

Digitoxin is seldom used in contemporary therapeutics, but case 1 nonetheless illustrates 2 important principles: dose proportionality, and attainment of steady-state. The rate of attainment of the steady-state condition after initiation of multiple-dose treatment is dependent on the half-life of the particular drug. In the case of digitoxin, the half-life is about 7 days, implying that 3–4 weeks of continuous treatment (without a loading dose) is necessary for steady-state to be reached.[4] In the example given, the increase in dosage from 0.1 to 0.2 mg/day is anticipated to proportionally increase the steady-state concentration (Figure 2). At the daily dosage of 0.1 mg (without a loading dose) and a half-life of 7 days, the plasma digitoxin concentration of 8 ng/mL after 7 days of treatment represents 50% of the eventual steady-state concentration of 16 ng/mL. If the physician had stayed with the 0.1 mg/day dosage, that steady-state concentration—attained after several weeks of treatment (4 to 5 times the half-life)—would have been in the therapeutic range. However the dosage was increased to 0.2 mg/day, yielding a corresponding steady-state concentration of 32 ng/mL, exceeding the therapeutic range and producing adverse effects (Figure 2).

Case 2

A 56-year-old man has a history of grand mal seizures, which have been completely suppressed for the last 12 years by phenytoin, 300 mg daily. His plasma phenytoin level consistently falls in the range of 12–16 μg/mL. The patient is able to lead a normal life, and is an excellent tennis player. During a particularly competitive tennis match, the patient injures his shoulder. That night he experiences severe pain, tenderness, and limitation of motion. He contacts his physician. An x-ray is negative. The physician prescribes rest, topical heat, and aspirin, 650 mg 4 times daily.

At a return visit to the physician 2 days later, the patient is greatly improved. The physician uses that opportunity to do a routine check of the plasma phenytoin level, which is reported as 5 μg/mL. There is no evidence of recurrent seizure activity, and the patient insists that he is continuing to take phenytoin as directed (300 mg/day). The physician increases the dose to 500 mg/day.

One week later the patient returns complaining of difficulty with balance and with fixing his eyes on objects. The plasma phenytoin level is 14 μg/mL.

Discussion—Case 2

In case 2, plasma protein binding of phenytoin is reduced by coadministration of aspirin because of displacement of phenytoin from plasma-binding sites by salicylate.[5–7] This is evident as an increase in the free fraction (Table 1). However, the clearance of unbound (free) drug, and the steady-state concentration of unbound drug, are unchanged.[8,9] As such, no change in clinical effect would be anticipated, and the correct clinical course would have been to leave the daily dosage at 300 mg/day. Because salicylate reduces plasma protein binding of phenytoin (higher free fraction in plasma), this has the effect of reducing total (free +

Table 1. Total and Free (Unbound) Plasma Phenytoin Concentrations in Case 2

Phenytoin Daily Dosage, and Cotreatment	Total Phenytoin (μg/mL)	Fraction Free	Free Phenytoin (μg/mL)
300 mg/day (no cotreatment)	12–16	0.1	1.2–1.6
300 mg/day + aspirin	5	0.3	1.5
500 mg/day + aspirin	14	0.3	4.2

bound) concentrations of phenytoin as well as the interpretation of these measured total concentrations.[5–7] Increasing the daily dosage of phenytoin to 500 mg/day increases the free (unbound) concentration to 4.2 μg/mL, which is associated with adverse effects despite the total concentration of 14 μg/mL.

A second important point is the nonlinear kinetic profile of phenytoin.[10] At daily doses in a range exceeding 300 mg/day, steady-state plasma concentrations increase disproportionately with an increase in dosage. The free phenytoin concentration is 1.5 μg/mL at 300 mg/day, but increases to 4.2 μg/mL with an increase in dosage to 500 mg/day. This property of phenytoin makes it difficult to titrate dosage at this higher dosage range.

Case 3

A fourth-year dental student is doing a clerkship in a dental surgeon's practice. A healthy 34-year-old woman is scheduled to undergo procedures estimated to last approximately 2 hours. Following instillation of local anesthesia and prior to the start of the procedure, the surgeon notices that the patient still is extremely agitated and fearful. The surgeon administers 0.5 mg/kg of propofol intravenously over a 2-minute period. The patient becomes calm, relaxed, and falls into a light sleep from which she is easily roused. The surgical procedure is initiated and proceeds without incident for about 45 minutes. At this time, the patient becomes alert, and again is fearful and agitated. The surgeon administers another 0.5 mg/kg of propofol intravenously, the patient again becomes calm, and the surgical procedure proceeds to completion without incident.

The student is confused. He/she asks the surgeon, "Why did the patient wake up after only 45 minutes? The half-life of propofol usually is at least 8 hours."

Discussion—Case 3

Case 3 is an example of how the pharmacodynamic effects of lipophilic psychotropic drugs after single intravenous doses are dependent more on the rapid process of peripheral distribution than on clearance or elimination. The pharmacokinetics of propofol are described by a 2- or 3-compartment model, in which the initial "distribution" phase represents rapid distribution from systemic circulation to peripheral tissues, followed by the terminal "elimination" phase which mainly reflects clearance.[11–14] Although the propofol has not been eliminated from the body, its distribution from systemic circulation into peripheral tissue results in lower concentrations in plasma and brain, which is highly vascular and rapidly equilibrates with systemic circulation (Figure 3). As such, the patient becomes more alert, and a second dose is required.

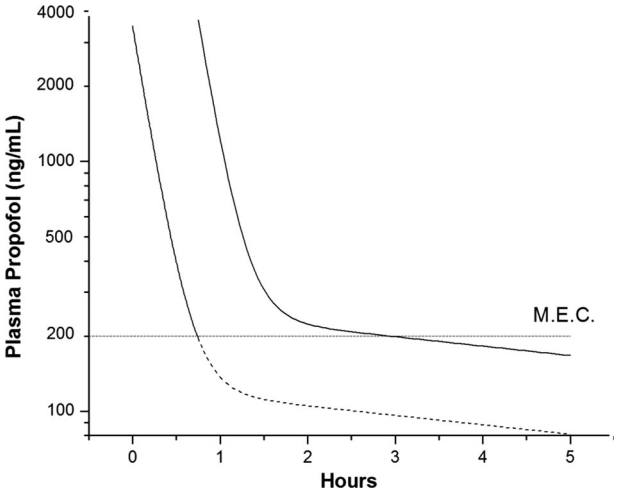

Figure 3. Hypothetical plasma concentrations of propofol corresponding to case 3 in the text. A 0.5 mg/kg intravenous dose of propofol is initially given at time zero. The plasma propofol concentration declines rapidly, falling below the hypothetical minimum effective concentration (MEC) of 200 ng/mL at 0.75 hours, at which time the patient emerges from the sedated condition. The rate of drug disappearance in the postdistributive phase would be slower (dashed line), but an additional 0.5 mg/kg dose of propofol is required at the 0.75-hour time to maintain plasma concentrations above the MEC and maintain the patient in a sedated condition for the remainder of the procedure.

Components of Medical Education in Pharmacokinetics and Pharmacodynamics

An outline of key elements of content for the teaching of clinical pharmacokinetics and pharmacodynamics to first- or second-year medical students, along with pertinent literature references,[15–54] are presented in Table 2. The same or similar content can be applied to the teaching of graduate students at both the PhD and masters levels, or to postdoctoral education programs for house staff or practicing physicians. The material can be reasonably presented in 3 or 4 total lecture contact hours. The didactic presentations should be reinforced through problem sets and review sessions

aimed at supporting conceptual understanding, as well as ensuring proficiency with pharmacokinetic calculations and construction of graphics.

Individual instructors can adapt the outline and accompanying graphics as needed, to construct specific lecture content consistent with their own style and institutional needs. An ongoing point of discussion is the extent to which formulas, equations, and mathematics are needed for the teaching of pharmacokinetics. Student backgrounds in mathematics and their comfort with quantitative content vary widely. Some dislike and resist the mathematical content, whereas others welcome it. "Equation-free" pharmacokinetics is not realistic, but the density of equations can be managed such that the mathematical framework enhances conceptual understanding. The outline in Table 2 has that objective. The need for memorization of formulas and equations is minimal.

Table 3 lists biomedical journals that have a focus on clinical pharmacokinetics and pharmacodynamics. Students are encouraged to consult original research sources when seeking information on pharmacokinetic/pharmacodynamic properties or drug interactions involving specific drugs or drug classes. Review articles and secondary sources do have a role in the educational process, in that large amounts of data are collated and summarized. However, secondary sources are inevitably "filtered" and interpreted by their authors. Students need to consider the benefits and drawbacks of available information sources.

Table 2. Course Outline: Pharmacokinetics and Pharmacodynamics for a Medical School Curriculum

Section 1. Definition and scope
- A. Pharmacokinetics: concentration versus time
- B. Pharmacodynamics: effect versus time
- C. Kinetic-dynamic modeling: effect versus concentration

Section 2. Value of pharmacokinetic principles in medical science[15–19]
- A. Choice of loading and maintenance dose
- B. Choice of frequency and route of administration
- C. Predicting the rate and extent of drug accumulation
- D. Predicting the effect of dose changes
- E. Identifying and anticipating drug interactions
- F. Identifying patient and disease factors that could alter clinical response
- G. Interpreting drug concentrations in serum or plasma[19]

Section 3. Fundamental assumptions
- A. Proportionality cascade (Figure 4):
  - –Intravascular free drug
  - –Extracellular water
  - –Receptor occupancy
  - –Quantitative pharmacodynamic effect
- B. Concentration ranges
  - –Subtherapeutic
  - –Therapeutic
  - –Potentially toxic

Section 4. Body compartments and volumes of distribution[15–17,20–22]
- A. Definition of a compartment
- B. Calculation of volume of distribution derived from definition of concentration:

$$\text{Concentration} = \frac{\text{Amount}}{\text{Volume}}$$

$$\text{Volume of distribution } V_d = \frac{\text{Amount of drug in body}}{\text{Concentration in reference compartment}}$$

- C. The value and ambiguity of compartment models (hydraulic analogues)
  1. One-compartment model: V_d is unique
  2. Two-compartment model: V_d is not unique[23]
- D. Anatomic correlates of volume of distribution
- E. Physiochemical correlates of volume of distribution[24]

Section 5. Exponential behavior and the meaning of half-life
- A. First-order processes:
  1. *Rate* is proportional to concentration

$$\frac{dC}{dt} = -kC$$

  2. *Rate* is *not* constant, even though k is called a "rate constant"
- B. Calculation of half-life

$$t_{1/2} = \frac{\ln 2}{k} = \frac{0.693}{k}$$

- C. k and $t_{1/2}$ are independent of route of administration
- D. Logarithmic versus linear graphs (Figure 5)
- E. Interpretation and implications of half-life

Time elapsed (multiples of $t_{1/2}$)	Fractional completion of process
1	0.5
2	0.75
3	0.875
4	>0.90

- F. Implications of first-order behavior
  - –$t_{1/2}$, V_d, and clearance are fixed
  - –After single doses, AUC (area under the curve from time = zero to "infinity") is proportional to dose
  - –At steady state, C_{ss} (steady-state concentration) is proportional to infusion rate (or dosing rate)

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