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Basic Science Review

Antibiotic Pharmacokinetics in Surgery

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• Pharmacokinetics is the study of variables that affect drug concentrations at the effector site. The descriptive terms *peak concentration, elimination half-life, volume of distribution,* and *bioavailability* are commonly used to express pharmacokinetic variability among drugs used in patient care. The pharmacokinetic characteristics of drugs are important for surgeons to understand because they represent differences that may assume clinical significance when selecting antibiotics for preoperative preventive indications. In addition, the changing hemodynamic pattern of the stressed and septic patient may result in changing pharmacokinetic patterns for an antibiotic, which, in turn, may require changes in the dosing regimen during the course of treatment.

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The pharmacokinetics of antibiotics (and other drugs) is commonly discussed by pharmacologists in unfamiliar descriptive terms that are poorly understood by surgeons. Because surgeons use antibiotics in many areas of their practice, a greater awareness of pharmacokinetics and its clinical significance is important.

PHARMACOKINETIC PRINCIPLES

Pharmacokinetics is the study of variables that govern the concentration of a drug at its effector site. The drug is administered and absorbed into the central pool, or serum, of the patient. Oral drugs are absorbed over variable lengths of time, while intramuscularly administered antibiotics are absorbed more rapidly and with less variability than orally administered drugs. Both oral and intramuscular administration have a sustained-release profile, which means that drug metabolism or excretion will begin prior to complete absorption of a given dose. Thus, concentrations in the central pool are influenced by both rates of drug uptake from the gut or intramuscular reservoir, and the rates of drug metabolism or excretion. With intravenous administration, drug absorption is virtually immediate so that the central pool concentration becomes a consequence of drug elimination alone.

As the drug concentration in the central pool rises, gradients for diffusion into the various tissues occur. The equilibrium state between the central pool and any tissue is governed by multiple variables. The total blood supply, the lipid content of the tissue, the lipophilic or lipophobic character of the drug, and the protein-binding characteristics of the drug will each affect the rapidity of drug delivery at the tissue site. Thus, drug concentration will rise more quickly in well-vascularized muscle as opposed to relatively avascular fat tissue. If the drug is lipophilic, fat tissue concentrations will steadily rise as long as the central pool concentration exceeds the fat tissue concentration, but will then have sustained tissue concentrations even though serum concentrations will subsequently become negligible. Highly protein-bound drugs will diffuse less rapidly into the interstitial space than non–protein bound drugs, and will largely be excluded from intracellular water. The important point of this discussion is that serum concentrations may have no correlation with the concentrations at the target site.

Peak concentration (PC) of any drug in serum after intravenous administration is illustrated at point A in Fig 1. Peak concentration is the greatest concentration of drug in serum following a single dose. Peak concentration occurs very rapidly after intravenous administration, is somewhat delayed (12 to 15 minutes) after intramuscular administration, and may not occur until much later with oral administration. Point C in Fig 1 represents the equilibrated maximum concentration of the antibiotic. This reduced concentration when compared with point A occurs as a consequence of equilibration between the tissues and the central pool.

The time required for the drug serum concentration to decline by one half is then defined as the *elimination half-life* ($t_{1/2}$). When declining drug concentrations from metabolism or excretion are recorded on a semilogarithmic plot, the rate of drug elimination becomes linear and reflects the slope of the line. The $t_{1/2}$ remains constant over a broad range of concentrations, such that the duration of drug presence in serum can be described as multiples of that $t_{1/2}$. Thus, changes in the function or perfusion of organs responsible for drug elimination will have an impact on $t_{1/2}$ and the necessary dosing interval for the antibiotic being used.

Volume of distribution (VD) represents the theoretical volume of body water necessary to dissolve a given dose of a drug, assuming no elimination. This is calculated by extrapolation of the equilibrated elimination slope to point B, or time-zero concentration on the ordinate (Fig 1). Point B is the extrapolated concentration of the drug in serum after full equilibration among all tissues, but without any elimination.

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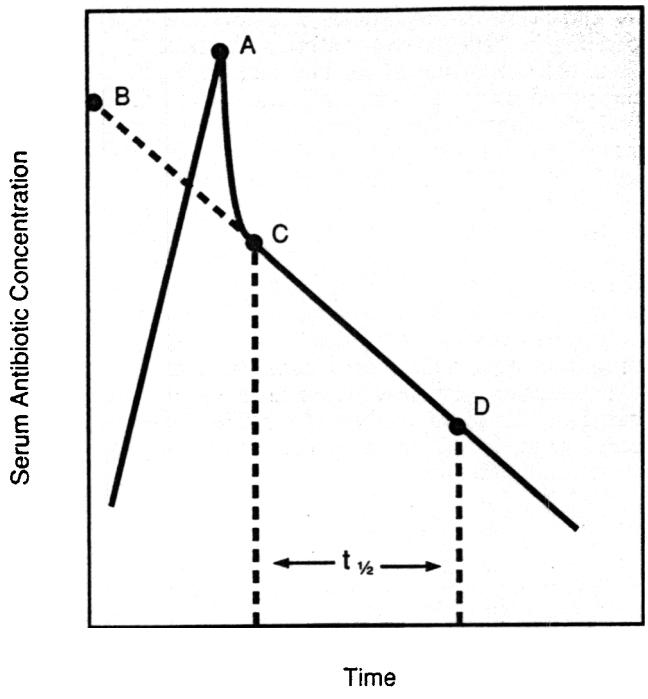

Fig 1.—The serum concentrations of a theoretical antibiotic given to a patient. Point A is the peak serum concentration; B, the extrapolated, time-zero concentration that is useful in the calculation of the volume of distribution; C, the maximum equilibrated serum concentration; and D, the concentration of the antibiotic in serum that is one half of point C and thus defines the elimination half-life ($t_{1/2}$) of the antibiotic. The area under the curve represents the bioavailability of the drug. The time interval from administration until the drug concentration dropped below the minimum acceptable therapeutic concentration represents the therapeutic availability. The plot is given a linear configuration because the drug concentrations are expressed as the logarithm of the actual values.

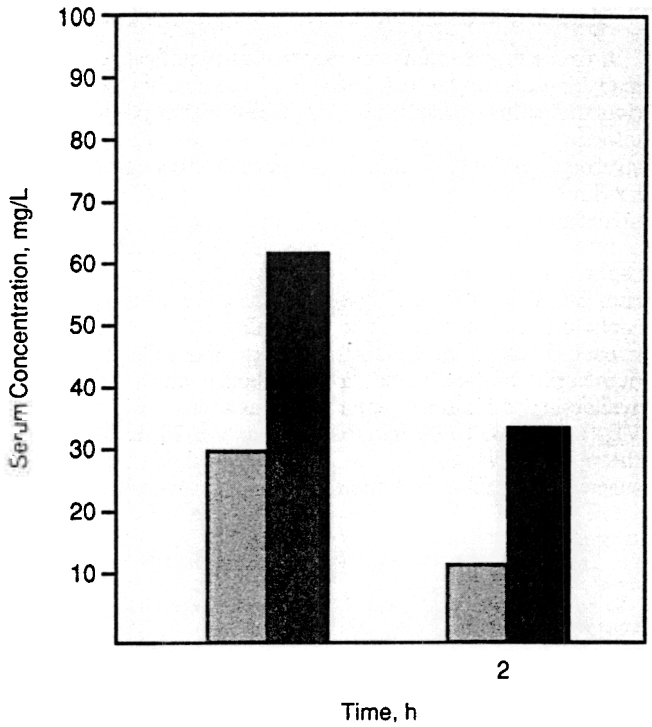

Fig 2.—The serum concentrations in milligrams per liter after preoperative administration of cephalothin (2 g given intravenously) and cefazolin (1 g given intravenously) in patients undergoing cholecystectomy. Shaded bars represent cephalothin; closed bars, cefazolin.

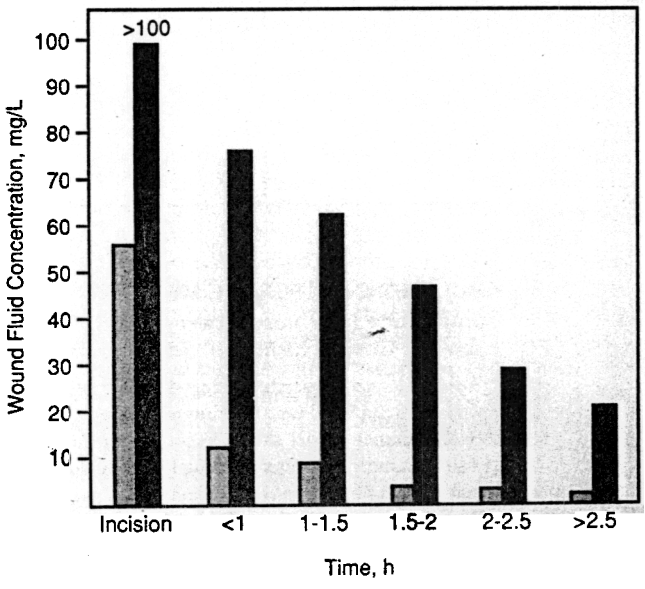

Fig 3.—The wound fluid concentrations in milligrams per liter after preoperative administration of cephalothin (2 g given intravenously) and cefazolin (1 g given intravenously) in patients undergoing cholecystectomy. Shaded bars represent cephalothin; closed bars, cefazolin.

Thus, a 1-g (1000-mg)–dose that results in an extrapolated time-zero concentration of 50 mg/L would have a VD equal to dose/time-zero concentration, or 1000 mg/(50 mg/L) = 20 L. Knowing that a patient weighing 70 kg has an extracellular water volume of 14 L means that this drug most likely penetrates the intracellular water volume to have a VD of 20 L. The determination of the VD assumes significance by virtue of dictating the maximum PC in serum for a drug with a given $t_{1/2}$.

Another common term used in pharmacokinetics is *bioavailability*. Bioavailability represents the area under the curve of the serum concentration plot. Drugs with high PC, small VD, and longer $t_{1/2}$ will have greater bioavailability than drugs with low PC, large VD, and short $t_{1/2}$. Differences in bioavailability explain why drugs with similar elimination $t_{1/2}$ may actually have different redosing intervals.

Therapeutic availability is our term, chosen because it is more clinically applicable. Therapeutic availability is the duration of time by which the antibiotic concentration exceeds the targeted therapeutic concentration that is desired for treatment objectives. Antibiotics with high PC but very short $t_{1/2}$ have a large calculated bioavailability but with a short redosing interval. The actual duration of antibiotic concentration or therapeutic availability that is greater than or equal to the minimum inhibitory concentration for the bacteria likely to be encountered is relatively short. Drugs with lower PC, but long $t_{1/2}$, may have a smaller bioavailability but a longer therapeutic availability by virtue of a longer period of time above the minimum inhibitory concentration. Because of differences in target tissue pharmacokinetics, an ideal design would be to know the therapeutic availability at the tissue site rather than in serum.

CLINICAL SIGNIFICANCE OF PHARMACOKINETICS

A first example that underscores the significance of pharmacokinetics can be seen in the use of antibiotics for preventive indications. Early studies in antibiotic prevention of infection for elective gastrointestinal resections demonstrated significant benefits from preoperative use of cephaloridine[1] or cefazolin sodium.[2] Subsequent studies using cephalothin sodium[3,4] showed no benefit, despite the similar antimicrobial spectrum of this cephalosporin compared with cephaloridine and cefazolin. However, measurement of serum (Fig 2) and tissue (Fig 3) concentrations of cefazolin and cephalothin demonstrated lower cephalothin concentrations at each time period.[5] Cefazolin has a greater PC, a lesser VD (it is highly protein bound), a $t_{1/2}$ of 2 hours, and a therapeutic availability of 4 hours. Cephalothin has a lesser PC, a greater VD, a $t_{1/2}$ of 35 to 40 minutes, and only a 75- to 90-minute therapeutic availability. The failure of cephalothin, and the success of cephaloridine and cefazolin, as preventive antibiotics emphasize the importance of therapeutic availability in covering the period of bacterial contamination.

An additional example can be identified in the use of aminoglycosides for therapeutic indications. Septic and stressed patients generally demonstrate a hyperdynamic circulation, which, in patients with normal kidney function, will result in accelerated excretion of the drug.[6,7] Pharmacokinetic dosing, while initially advocated to prevent toxic effects of aminoglycoside antibiotics, is now commonly used to ensure adequacy of drug administration. Up to five times the daily recommended dose of aminoglycosides may now be required in these patients with very elevated cardiac outputs. One can only speculate about the underdosing of other antibiotics or drugs that occur in the hyperdynamic setting.

In summary, drug pharmacokinetics has been ignored by surgeons. An understanding of pharmacokinetics is necessary if we are to optimize the clinical applications of antibiotics for the care of the surgical patient.

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ARCHIVES OF INTERNAL MEDICINE

Compliance Declines Between Clinic Visits

Joyce A. Cramer; Richard D. Scheyer, MD; Richard H. Mattson, MD

Adherence to prescribed drug dosing regimens declined substantially during th terval between clinic visits and drug level tests. Using microelectronic monitors to observe pill-taking hal 20 patients averaged 88% compliance before and 86% compliance after the visit, but this dropped to 67% ɔliance a month later. These data indica that spot drug levels rep ıg-term "steady-state" d serum concentrations *Arch Intern Me* 1990;150:1509-1510).

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