State of the Art/Review

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Rational Therapeutic Drug Monitoring

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FOR MANY drugs, the measurement of concentrations in serum or plasma has become widely available and accepted as an important component of clinical decision making. While these drug levels often do allow more objective monitoring and titration of therapy, the information also has the potential to be valueless or even misleading. Laboratories sometimes report that a serum concentration is in the "toxic" range, when the patient is doing well and has no evidence of toxic effects. Or, conversely, the drug is not detectable in serum. Such discrepancies between measured serum drug concentrations and observed clinical drug effects may occur for numerous reasons. This article will review some principles and problems associated with therapeutic drug monitoring.

RATIONALE FOR MONITORING SERUM DRUG LEVELS

For a serum drug concentration to be potentially useful for purposes of therapeutic monitoring, at least two requisites must be fulfilled.[1] First, the serum drug concentration must reflect the concentration at the receptor site; second, the intensity and duration of the pharmacodynamic effect must be temporally correlated with the receptor site drug concentration. When these two conditions are not met, as in the case of anticancer drugs showing effects long after they are gone from the serum, the likelihood of correlating serum levels with therapeutic effect is considerably reduced.

During long-term dosage with any drug, the two major determinants of its mean steady-state serum concentration are the rate at which the drug is administered (dosing rate) and the drug's total clearance in that particular patient.[2,3] The mathematical relationship is

$$\text{Mean Steady-State Concentration} = \frac{\text{Dosing Rate}}{\text{Clearance}}$$

Clearance is measured in units of volume per unit of time, and describes in quantitative terms the capacity of a given individual to biotransform or eliminate a given drug. Drug clearance is usually accomplished by hepatic biotransformation, renal excretion, or a combination of the two. Thus, under usual circumstances, the steady-state concentration of a particular drug in a given individual is directly proportional to the dosing rate (with the exception of a few drugs with saturable or nonlinear kinetics, such as salicylate, phenytoin, and alcohol). Among different individuals, however, any given dosing rate is likely to produce wide variations in steady-state concentration, attributable to large interindividual differences in clearance (Fig 1). A number of identifiable factors can alter the clearance of drugs, such as age, gender, body habitus, disease states, cigarette smoking, and drug interactions.[2-9] However, substantial unexplained individual variation in drug clearance is commonly observed even among healthy, drug-free persons of the same sex and within a narrow age range.[10] Therefore, dosage may not be a good predictor of steady-state concentration.

"Therapeutic range" and "therapeutic index" are two concepts used to quantitate the relationships of serum concentration to efficacy and safety, respectively. Some drugs have a well-defined therapeutic range. When the steady-state concentration falls within this range, the likelihood of clinically effective and nontoxic therapy is maximized. Direct measurement of the serum concentration allows appropriate upward or downward titration of dosage in the individual patient, to attain the desired level. Therapeutic ranges, however, are not absolute (Fig 2). Levels at the "low" therapeutic end have a significant likelihood of being clinically ineffective, whereas levels at the high therapeutic end have a significant likelihood of causing toxic effects.

In experimental pharmacology, "therapeutic index" is defined as the ratio of the median lethal dose to the median effective dose. In clinical medicine, however, therapeutic index is usually estimated as the ratio of the highest potentially therapeutic concentration divided by the lowest potentially therapeutic concentration (Fig 2). Some drugs (such as gentamicin, digoxin, and lithium) have a narrow therapeutic range and therefore a low therapeutic index. For such drugs, one can anticipate considerable overlap among ineffective, effective, and possibly toxic concentrations, thereby increasing the importance of serum level monitoring.

Serum drug concentrations may still be of considerable value even when a therapeutic range has not been definitely established. Consider a patient with no apparent clinical response to drug therapy despite seemingly adequate dosage. A measured steady-state concentration that appropriately reflects the dosage rate suggests that the patient may actually be a "nonresponder." If, however, the measured level is very low or undetectable, this suggests that the patient either is not taking the medication (noncompliance) or has unusually high metabolic clearance. Another example is the patient with a sign or symptom (such as loss of appetite during digitalis therapy) that could be attributable either to an adverse drug reaction or to the underlying disease itself.[11] In this case, a high serum drug level suggests that the medication might be responsible for the adverse effect; a low serum level, on the other hand, could indicate that the underlying disease, or some other factor, explains the reaction.

Drug concentrations frequently are measured for medicolegal reasons. In cases of deliberate or accidental drug overdosage, verification of the particular substances ingested, and their concentrations in serum, may have important therapeutic and forensic value. "Screening" of current and prospective employees for the presence of "illicit drugs" is becoming increasingly common, although these tests are usually done on samples of urine.[12]

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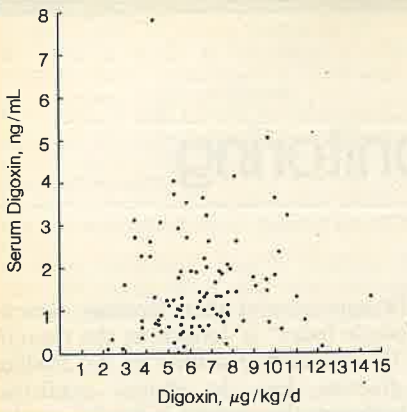


Fig 1.—Relation of steady-state serum digoxin concentration to daily dose per kilogram for 100 patients receiving long-term digoxin therapy. Correlation is poor (r=.069), indicating substantial variability in steady-state concentration that is not explained by dosage (Hermann R. Ochs, MD, unpublished data, 1979).

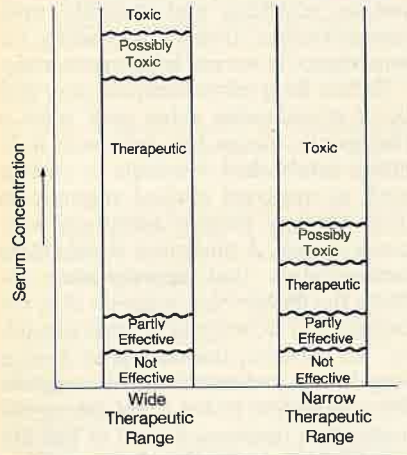


Fig 2.—Schematic relation of serum or plasma drug concentration to clinical efficacy or toxicity for hypothetical drugs having wide or narrow therapeutic ranges (from Greenblatt and Shader[2]).

Finally, the availability of methods for measurement of drug concentrations provides the impetus for clinicians to increase their expertise and understanding of pharmacologic and pharmacokinetic principles of drug therapy. Enhanced awareness of dose-concentration relationships, and factors influencing these relationships, may lead to an overall improvement in the quality of drug treatment.[13]

DRUG DISTRIBUTION AND ACCESS TO ITS RECEPTOR

When a drug is given by an extravascular route of administration (orally, intramuscularly, rectally, subcutaneously, sublingually, transdermally, etc), or even by intravenous injection, the entire administered dose does not have immediate and complete access to its receptor site mediating pharmacologic activity (Fig 3). After intravenous injection, the entire dose reaches the systemic circulation and by definition has 100% bioavailability. However, the drug is distributed not only to the tissue where it is active, but also to a number of other sites (Fig 4). Furthermore, once the drug has reached the systemic circulation, it also encounters serum or plasma proteins. Drugs are bound to proteins to varying degrees.[14,15] The principal binding proteins are albumin and α_1-acid glycoprotein. The affinity of a drug for serum protein limits its freedom to diffuse across cell membranes, hence further limiting its accessibility to the receptor site.

When a drug is administered by an extravascular route, it reaches the systemic circulation indirectly, often yielding less than 100% bioavailability.[16] Oral bioavailability of drugs in tablet and capsule form can be influenced by incomplete absorption due to incomplete dissolution, which in turn depends on packaging and drug particle size. Oral solutions overcome the dissolution problem. Other factors that can influence oral bioavailability include changes in gastrointestinal motility, gastric and intestinal pH, malabsorption syndromes, and the coadministration of foods and drugs (especially antacids, antidiarrheal agents, and chelating agents).

After absorption of the drug from the gastrointestinal tract, systemic bioavailability may be reduced because of metabolic transformation in the gut wall, or by extraction from the portal circulation during the "first pass" through the liver. This is the case for certain drugs characterized by high hepatic clearance, including propranolol, lidocaine, tricyclic antidepressants, opiate analgesics, neuroleptics, hydralazine, nitroglycerin, verapamil, and prednisone.[17]

Incomplete bioavailability after intramuscular injection is also possible. This has been attributed to poor drug solubility at physiologic pH and precipitation at the injection site after administration of chlordiazepoxide, digoxin, phenylbutazone, phenytoin, and quinidine.[18]

A number of recent studies have evaluated drug absorption after sublingual or buccal administration.[19-21] In principle, this route of administration delivers the drug directly into the systemic circulation, bypassing both the gastrointestinal tract, where some drugs are degraded or metabolized, and the portal circulation and consequent first-pass hepatic extraction. For most drugs evaluated to date, bioavailability after sublingual dosage is equivalent to or greater than that after oral administration. A similar principle holds for rectal drug administration, since approximately 50% of the hemorrhoidal circulation empties into the systemic rather than the portal venous system.[22] Finally, the transdermal[23] or pulmonary route can be used to administer some drugs.

For all these reasons, drug concentrations in blood, serum, or plasma often reflect pharmacologic action more closely than administered dosage alone.

FACTORS INFLUENCING INTERPRETATION OF SERUM DRUG CONCENTRATIONS

Total vs Free Serum Concentrations

Although only the unbound or free drug can passively cross cell membranes and interact with receptors, free drug levels nonetheless are still not routinely monitored. This is partly because their measurement is technically more difficult to perform than that of total levels. Fortunately, for most drugs, the ratio of free to total serum concentration (free fraction) usually remains relatively constant during a given patient's course of therapy, with salicylate and ibuprofen[24,25] being among notable exceptions. Therefore, a doubling of the total concentration will also lead to a doubling of the free serum drug concentration at steady state. In most clinical circumstances, variability *between* patients in free fraction may also be relatively small.[26] When within- and between-individual differences in serum protein binding are small, monitoring of total serum concentration should prove to be as useful therapeutically as monitoring of free or unbound concentration.[15,27,28] In some conditions, however, drug binding to serum protein may be substantially altered. For example, protein binding of a given drug may be reduced (increased free fraction) when another drug displaces it from its binding sites.[15,29] Such interactions in themselves are unlikely to be of direct clinical importance,[15,27,29,30] since the increased "free" concentrations will be only transient due to rapid equilibration with tissues. However, the total drug concentration will consequently fall, and may lead to a lowering of the therapeutic and toxic ranges for the total serum drug level (Fig 5).[31] Uremia and hypoalbuminemia are other clini-

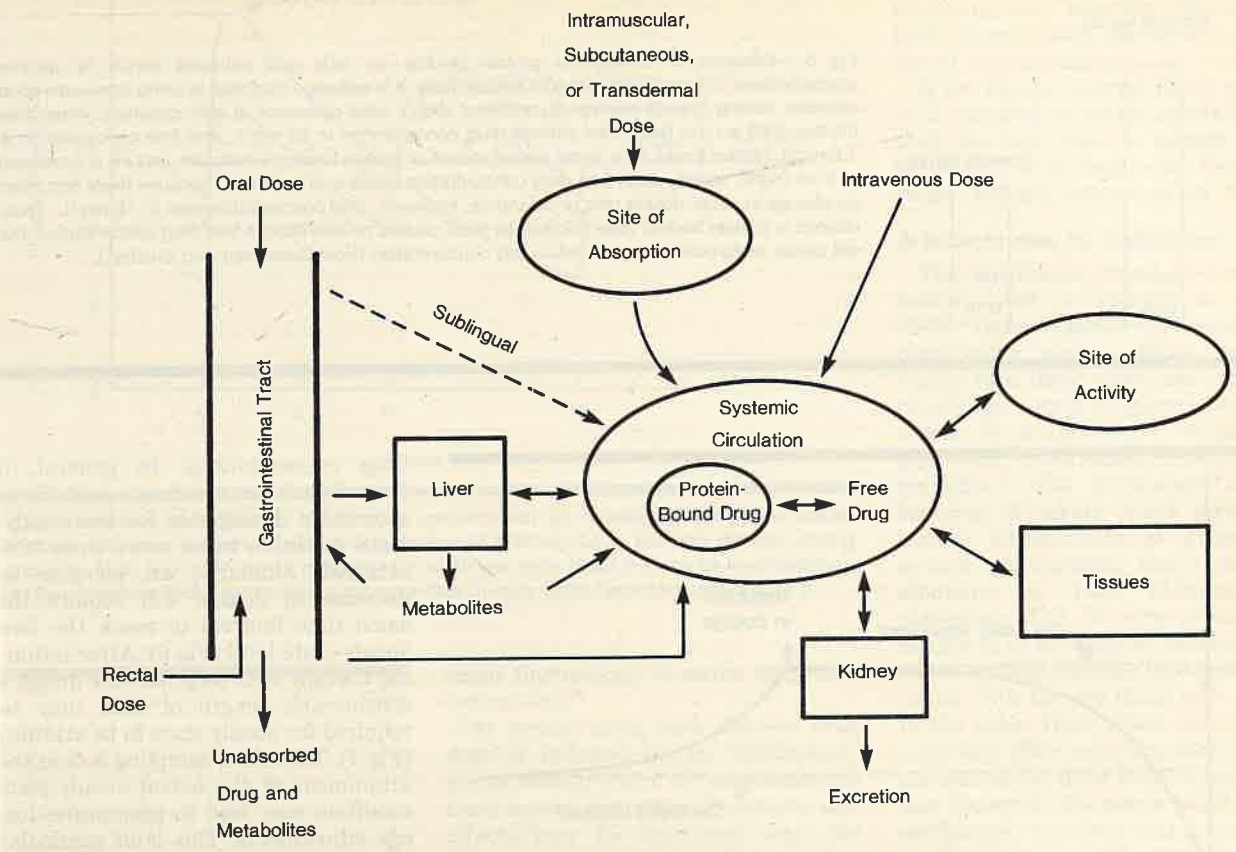


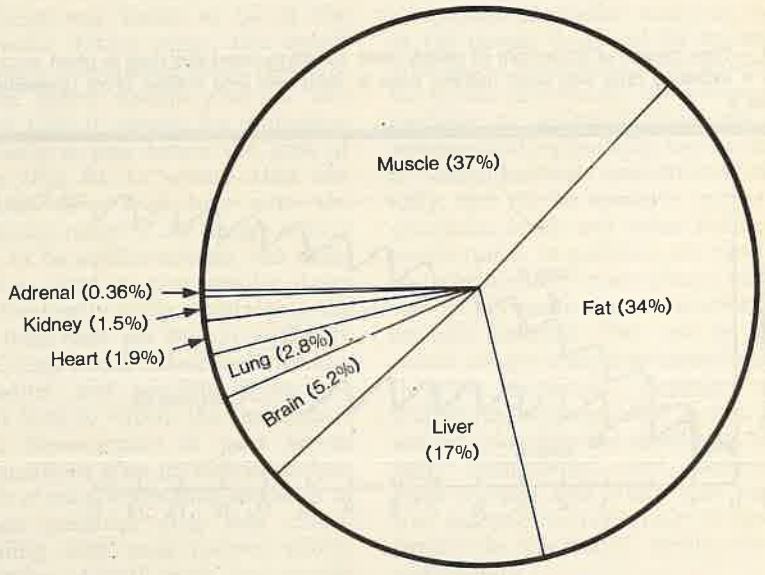
Fig 3.—Schematic diagram of pathways of drug absorption, distribution, elimination, and clearance.

cal situations in which serum protein binding of drugs is reduced, causing lowered therapeutic and toxic ranges for total drug concentration. For example, phenytoin free fraction, which usually falls between 10% and 20%, may become as high as 30% in uremics.[31] Alternatively, α_1-acid glycoprotein, an acute phase reactant, may be transiently elevated in acute myocardial infarction, shock, severe burns, injuries, or infectious processes,[32] causing *increased* binding of some basic drugs, and result in increased total serum drug levels without an enhancement of clinical effect. Examples of such drugs include lidocaine, propranolol, imipramine, phenytoin, quinidine, and disopyramide. For drugs not extensively bound to serum proteins, such as cimetidine, digoxin, and gentamicin, lithium, procainamide and acecainamide (N-acetylprocainamide), changes in protein binding are of far less consequence.

Optimal Sample Timing

Proper choice of sampling time is crucial for the interpretation of serum

Fig 4.—Estimated distribution pattern of benzodiazepine derivative nordazepam (desmethyldiazepam) in normal healthy woman (30% body fat), based on human autopsy studies.[47] Nordazepam (desmethyldiazepam) is major metabolite of diazepam (Valium) and halazepam (Paxipam), and is principal active substance present in blood during treatment with clorazepate dipotassium (Tranxene) and prazepam (Centrax).



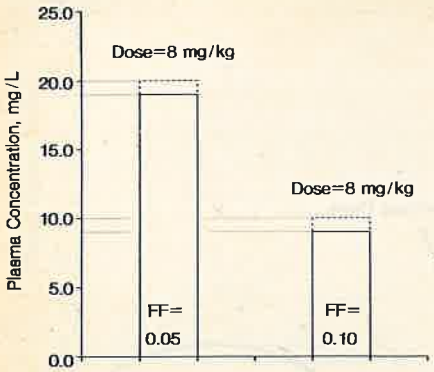


Fig 5.—Influence of change in protein binding on total and unbound serum or plasma concentrations of hypothetical drug at steady state. It is assumed that drug is being administered at constant dosing rate (8 mg/kg/d), and that drug's total clearance is also constant. When free fraction (FF) is 0.05 (left), total plasma drug concentration is 20 mg/L, and free concentration is 1.0 mg/L (dotted lines). If for some reason extent of protein binding is reduced, and FF is increased to 0.10 (right), steady-state free drug concentration remains at 1.0 mg/L because there has been no change in either dosing rate or clearance. However, *total* concentration falls to 10 mg/L. Thus, change in protein binding (free fraction) by itself causes no alteration in free drug concentration, but will cause reciprocal change in total drug concentration (from Greenblatt and Shader[2]).

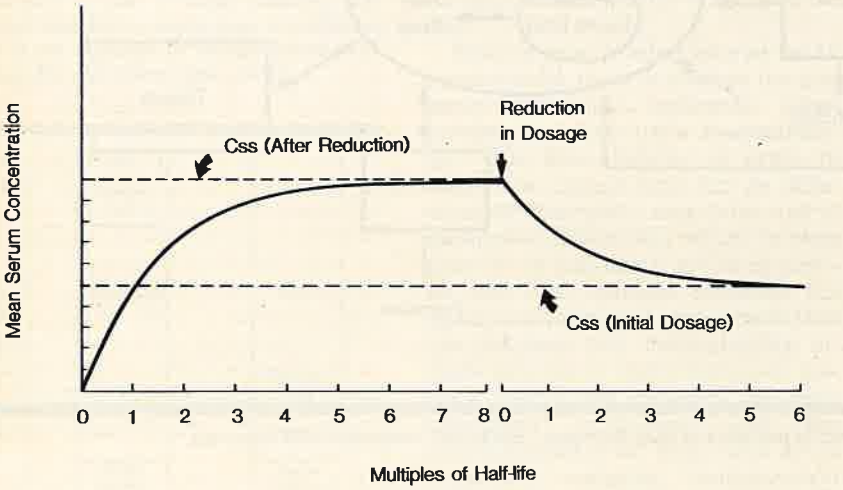
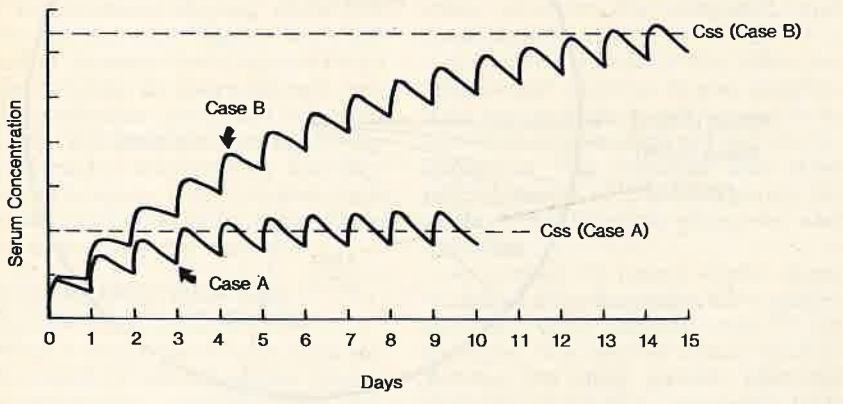


Fig 6.—Time course (in multiples of half-life) of mean serum concentration during attainment of steady-state condition after starting therapy and after reducing dosage. Css indicates mean serum concentration at steady state (from Greenblatt and Shader[2]).

Fig 7.—Time course of attainment of steady-state condition, assuming drug is given once daily. Case A indicates drug with short half-life; case B, drug with long half-life (from Greenblatt and Shader[2]).



drug concentrations. In general, it takes four times the drug's half-life at a constant dosing rate for the steady-state condition to be more than 90% attained. Similarly, an increase or decrease in dosage will require the same time interval to reach the new steady-state level (Fig 6). After initiating therapy with long half-life drugs, a considerable length of time may be required for steady state to be attained (Fig 7). Therefore, sampling before the attainment of the actual steady-state condition may lead to premature dosage adjustments. This is of particular importance for drugs such as theophylline that are administered to infants and children.

Occasionally, the need may arise to hasten the attainment of therapeutic concentrations. This can be achieved by giving an initial loading dose, the size of which has been appropriately chosen based on the desired therapeutic concentration and the pharmacokinetic characteristics of the drug.[33,34] However, even the ideally selected loading dose has potential disadvantages. The rapid attainment of therapeutic concentrations precludes gradual adaptation to therapeutic or adverse drug effects, such as sedative, hypotensive, bradycardic, or anticholinergic properties.

Once the steady-state condition has been achieved, the mean steady-state serum drug level should remain constant as long as the dosing rate and clearance are constant (as indicated in the equation in the first section of this article). However, the interdose fluctuation depends on the dosage interval. A proportional increase or decrease in both the size of each dose and the interval between doses, such that the overall dosing rate remains constant, does not change the mean steady-state concentration, but will alter the interdose fluctuation (Fig 8). More frequent

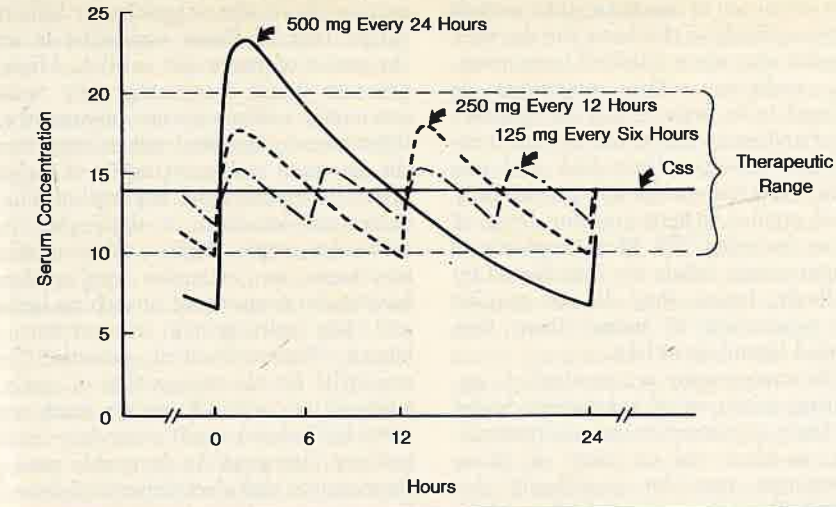


Fig 8.—Interdose fluctuation of serum drug concentration as function of dosage schedule, assuming that drug is given in overall total dosage of 500 mg/24 h, but with different dosing schedules. Note that mean serum concentration at steady state (Css) is same for each regimen, and that interdose fluctuation is largest for once-daily therapy (from Greenblatt and Shader[2]).

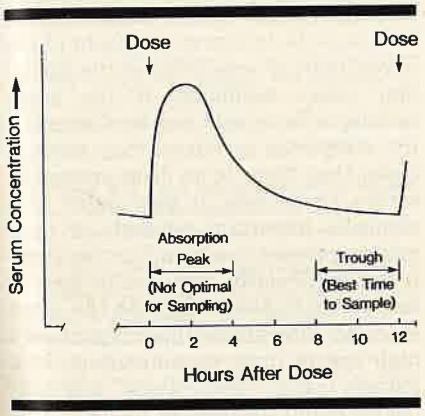


Fig 9.—Time course of serum drug concentration at steady state during oral dosage every 12 hours, with illustration of optimal sampling time (from Greenblatt and Shader[2]).

dosing is useful to minimize transient effects due to high peak levels that some people find objectionable, such as sedation and drowsiness from certain psychotropic drugs.[35] On the other hand, dosing schedules that require very frequent dosing are inconvenient, and may be associated with reduced patient compliance.

Certain sustained-release formulations of drugs have been designed to prolong drug action after each dose, thereby allowing less frequent dosing. If the rate of drug entry into the systemic circulation precisely mimics a fixed-rate infusion, then the serum drug level will not fluctuate. Although this is not an attainable ideal, some sustained-release preparations do in fact allow infrequent dosing, with only small fluctuations in serum drug concentrations.[36]

At steady state, each discrete drug dose is followed by an "absorptive" phase, during which serum concentrations exceed the mean. Transient side effects may be associated with the absorptive peak. After peak concentrations are reached, the serum level then falls as distribution and clearance predominate. Just before the next dose, levels are at a minimum during the "trough" phase. Sampling shortly after a dose, during the absorptive phase, is not recommended for evaluation of therapeutic efficacy since the measured level does not necessarily correspond to the peak. Furthermore, even if the peak level was found to be in the therapeutic dosing range, this would not ensure therapeutic levels throughout the entire dosage interval. The optimal time to sample for evaluation of efficacy is just before the time of dosing (Fig 9), to ensure that the minimum drug level falls with the therapeutic range. If the trough level is found to be subtherapeutic, the clinician may elect to give smaller doses more frequently while maintaining the same total dose per 24 hours (Fig 8). This change would reduce the interdose fluctuation and possibly bring the trough level to within the therapeutic range. Measurement of peak serum concentrations after an individual dose may be of value when clinicians wish to evaluate potential drug side effects coinciding with peak concentrations. Knowledge of both peak and trough concentrations may be desirable for drugs with narrow therapeutic indexes, such as aminoglycosides or lithium. Unfortunately, however, the time of peak concentration can seldom be predicted with certainty.

If the dosage interval is not regular, or if the drug is taken intermittently, then the best time to sample is not necessarily so obvious, since there is no single "trough" concentration (Fig 10).

Artefacts due to Collection Tubes

The Vacutainer brand of blood collection tubes is reported to contain TRIS (2-butoxyethyl) phosphate, a plasticizing agent. Blood samples drawn into these tubes can give spuriously low serum drug levels when the serum is analyzed for imipramine, alprenolol, propranolol, lidocaine, and quinidine.[32] The mechanism for the lowering of serum levels appears to involve displacement of drugs from α_1-acid glycoprotein (but not from albumin) by TRIS (2-butoxyethyl) phosphate. This in vitro phenomenon results in an increase in unbound drug, which quickly diffuses into and equilibrates with the red blood cells present in the tube. Thus, when the serum is aspirated after centrifugation, the resultant serum drug level is spuriously low. However, the whole blood level is unchanged. Any drug that is extensively bound to α_1-acid glycoprotein is likely to be influenced by this collection artefact.

Analytic Methodology

Knowledge of the methodology used by a laboratory in analyzing serum for drug levels may be of critical importance for the clinician in interpreting the results. Ideally, an assay procedure for a particular drug should (1) resolve compounds of similar structure, such as the parent drug and its metabolic products or other substances present in the serum (specificity); (2) consistently conform to accepted standards for accuracy and replicability for the range of concentrations encountered clinically; and (3) be sensitive enough to quantitate levels well below the therapeutic range. In addition, the need for cost containment must always be considered. Procedurally straightforward analytic methods that can be automated are generally less expensive and therefore preferred. However, such procedures, although less costly, may not provide adequate specificity, accuracy, replicability, and sensitivity. More complex and often more expensive analytic methods may be needed to provide meaningful serum concentration data.

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