THE THERAPEUTIC DRUG MONITORING AS A BASIS FOR INDIVIDUALIZING PATIENT DOSAGE REGIMEN

Jozef Novotný, Tomáš Ëech

ABSTRACT

In many cases, the plasma concentration of a drug is measured as a guide in the individualization of therapy. Furthermore, the problem of noncompliance with prescribed regimens during continuing therapy is an endemic and elusive cause of therapeutic failure. Clinical indicators assist in the titration of some drugs into the desired range, but no chemical determination is a substitute for careful observations of the response to treatment. However, the therapeutic and adverse effects are not precisely quantifiable for all drugs, and, in complex clinical situations, estimates of the action of a drug may be misleading. Because clearance, half-life, accumulation, and steady-state plasma levels are difficult to predict, the measurement of plasma levels is often useful as a guide to the optimal dose. This is particularly true when there is a narrow range between the plasma levels yielding therapeutic and adverse effects. For drugs having such characteristics – e.g. digoxin, theophylline, aminoglycosides and anticonvulsants – dose optimization should involve modification of the standard dose on the basis of the pharmacokinetic principles. Measurement of the concentration of a drug in plasma is the most effective way to detect failure to take a drug. Such „non-compliance“ is a frequent problem in the long – term treatment of diseases (e.g. coronary heart disease, epilepsy, diseases of the respiratory system and the others). The process may be improved by involvement of clinical pharmacologist and other paramedical personnel. Minimizing the complexity of the regimen is helpful in terms of both the number of drugs and the frequency of administration.

Therapeutic drug monitoring aims to promote optimum drug treatment by maintaining serum drug concentration within a „therapeutic range“. Therapeutic drug monitoring is a practice applied to a small group of drugs in which there is a direct relationship between concentration and response. The notion of a therapeutic range is more a probabilistic concept than an absolute entity. It represents a range of drug concentrations within which the probability of a desired clinical response is relatively high and the probability of unacceptable toxicity is relatively low (e.g. digoxin, vancomycin, gentamycin). The most common reasons for using a serum drug level as a guide are to provide additional information to be used in conjunction with other clinical data to assist in determining patient status – to provide a basis for individualizing patient dosage regimen. Characteristics of drugs applicable for therapeutic drug monitoring: 1. Serum drug concentration is the most practical intermediate endpoint to be used when there is no clearly observable therapeutic or toxic endpoint. 2. Serum concentration is a proxy for drug concentration at the site of action. 3. The range of therapeutic and safe serum concentrations is narrow. 4. There is no predictable dose-response relationship. 5. Toxicity or lack of effectiveness puts the patient at great risk. 6. The pharmacologic effect observed persists for a relatively long time. 7. A drug assay is available that is accurate, precise, and specific, requires a small sample volume, yields results quickly, and is relatively inexpensive.

1 University of South Bohemia, Faculty of Health and Social Studies, Ëeské Budìjovice, ÈR.
The determination of individual drugs (eg. digoxin, lithium, phenytoin, theophylline, among the others) have shown benefit of therapeutic drug monitoring, depending on the specific study, through one or more of the following indices: improved effectiveness, reduced toxicity, decreased length of stay, fewer hospital admissions, more patients with serum levels within the appropriate therapeutic range, and more rational use of serum concentration measurements. The presented data demonstrated that therapeutic drug monitoring service should recommend guidelines for and influence the use of serum drug concentrations, advise when samples should be taken, interpret concentrations, recommend dosage regimens based on the data, educate physicians through seminars and newsletters, and participate in studies collecting and analyzing data.

Key words:

1. INTRODUCTION

Therapeutic drug monitoring, or TDM as it is commonly called, is about using drug serum concentrations, pharmacokinetics, and pharmacodynamics to individualize and optimize patient response to drug therapy (30). It is also about understanding the merits, limitations, and applications of using serum drug concentrations in quantitative decision making. Therapeutic drug monitoring aims to promote optimum drug treatment by maintaining serum drug concentration within a „therapeutic range“. Therapeutic drug monitoring is a practice applied to a small group of drugs in which there is a direct relationship between concentration and response. Serum concentrations are used as the most practical intermediate endpoint to gauge treatment when there is no clearly observable therapeutic or toxic endpoint (eg. blood pressure, prothrombin...). The notion of a therapeutic range is more a probabilistic concept then an absolute entity. It represents a range of drug concentrations within which the probability of a desired clinical response is relatively high and the probability of unacceptable toxicity is relatively low (eg. digoxin, theophylline, lithium) (5, 21, 30). Similarly, some patients have toxic reactions within the therapeutic range. The most common reasons for using a serum drug level as a guide are to provide additional information to be used in conjunction with other clinical data to assist in determining patient status - to provide a basis for individualizing patient dosage regimen. Therapeutic drug monitoring blends knowledge of therapeutics, pharmacology, pharmacokinetics, laboratory technology, and clinical medicine and applies it to certain drugs that require determination of patient-specific dosage regimens to maximize therapeutic effectiveness while minimizing toxicity (5, 4, 21, 30, 6, 37, 36).
2. CHARACTERISTICS OF DRUGS APPLICABLE FOR THERAPEUTIC DRUG MONITORING

2.1. Digoxin

Digoxin is 3β-[(O-2,6-dideoxy-β-D-ribo-hexopyranosyl-(1’→4)-O-2,6-dideoxy-β-D-ribo-hexopyranosyl (1’→4)-2,6-dideoxy-β-D-ribo-hexopyranosyl)-oxy]-12β-dihydroxy-5β-card-20(22)-enolide. It is a glycosylated steroid-like drug with distinct cardiogenic properties. When used in patients with congestive heart failure, digoxin increases cardiac output; decreases heart size, venous pressure, and blood volume; and enhances diuresis and relieves edema (5, 2, 38-40, 73, 4, 21, 30, 6, 37, 36, 29).

All of these functions are related to the inotropic action of digoxin. Excitation of myocardium is dependent upon formation of an electrochemical gradient across the cell membrane. Formation of this gradient is under control of the enzyme sodium potassium ATPase (Na+K+ ATPase). The enzyme utilizes ATP to drive the sodium pump which forces the exchange of intracellular sodium ions for extracellular potassium ions. Digoxin binds reversibly with Na+K+ATPase, inhibits the binding of ATP, and thus inactivates the pumps. With an inactivated sodium pump, intracellular sodium concentration increases, which stimulates an ATP-independent exchange of intracellular sodium ions for extracellular calcium ions. An increase in calcium-ion concentration in the cell has been observed by a number of researchers (46, 73).

Increased concentration of calcium ion acts to enhance actin-myosin interaction, the mechanism which initiates contractions. Digoxin, then, induces the heart to contract and reduces the probability of dysrhythmias by slowing down the sodium pump (49, 2, 44, 32, 40, 41, 36).

It is interesting to note that while knowledge of digoxin’s unique cardiac properties has been available for centuries (Withering first mentioned its use in 1785), current literature continues to offer new insight into the mechanism by which digoxin increases the force of cardiac contractions and decreases atrial-ventricular node conduction. The pharmacology of digoxin has been well defined. Bioavailability is somewhat variable, but usually 70-85% is absorbed within 1 hour. Drugs that affect intestinal motility will influence absorption: anticholinergics will increase it while metaclopramine will decrease it.

Other drugs, such as antacids and lipid solubilizers, will decrease absorption. Once absorbed, the drug redistributes between plasma, where it is approximately 25% protein-bound, and other tissues. Digoxin accumulates in cardiac tissue and may reach concentrations 30 times
that observed in plasma (40, 14, 61, 51).

Only a small portion of digoxin is metabolized prior to excretion, the principal metabolite being dihydrodigoxin. In rare situations, dihydrodigoxin has been shown to accumulate to 50% of the total digoxin present. Digoxin and metabolites are eliminated by the kidneys unconjugated. Because of the great degree of tissue binding, the biological half-life of digoxin is long-36 h. Blood concentrations that have been suggested as therapeutic range from 0.5 to 2 μg/L.

The major signs of cardiac toxicity due to digoxin are cardiac dysrhythmia, principally paroxysmal atrial tachycardia with A-V node block or nonparoxysmal junction tachycardia (46, 49, 39, 73, 67, 51).

These phenomena are due either to direct depolarization of Purkinje fibers or to direct excitation of the central nervous system which results in norepinephrine-stimulated oscillatory after potentials in the ventricle.

Noncardiac signs of toxicity include anorexia, nausea, abdominal discomfort, and visual distortion. Unfortunately, numerous studies have shown that there is a limited correlation between toxicity and blood concentration above the therapeutic range. While the general rule thumb applies that with increasing concentration toxicity becomes more likely, many patients displaying clinical signs of toxicity will have blood concentrations within the normal range.

Disruption of renal function will influence blood concentrations and therefore requires dosage adjustment (31, 39, 4, 27, 14, 24). Renal insufficiency commonly associated with cardiovascular disease will decrease the elimination rate of digoxin with resulting elevated blood concentrations. Equally important, the use of diuretics to control edema may alter electrolyte balance, a condition, which influences the relative inotropic effect of digoxin. Hypokalemia and hypercalcemia will enhance the effect of digoxin. Recently, attention has been drawn to the influence of quinidine on the excretion rate of digoxin. When quinidine and digoxin are used in combination, supertherapeutic concentrations of digoxin may result. Careful monitoring of blood concentration of digoxin and close monitoring of the clinical course are necessary in situations where digoxin is used in renally impaired patients or patients using digoxin combined with certain drugs (66, 81, 64, 61, 62, 68, 79).

Indications for digoxin monitoring:
- congestive heart failure (increases contractile force);
- atrial fibrillation;
- atrial flutter.
2.2. Lithium
The manic state, an incapacitating psychiatric disorder, is characterized by a bizarre increase in psychomotor activity, grandiosity, and emotional lability. Manic attacks are paroxysmal. They occur repetitively with relatively normal periods of behavior between attacks. Most commonly, manic cycles alternating with cycles of depression are observed. This particular presentation is commonly referred to as manic-depressive disorder (20, 11, 3, 17, 7, 14, 30).

Lithium is accepted as therapy of choice for the manic phase. Lithium is ineffective for the abolition of depression. Thus manic-depressives are often treated with antidepressant drug during the depressive cycle. If the mania is severe lithium may be supplemented with antipsychotic drugs. Lithium was first utilized for the treatment of mania in 1949; however, its widespread clinical utility and application only become recognized in the sixties.

The optimal plasma concentration of lithium is 0.8-1.0 mmol/L. Levels below the 0.8 mmol/L are not fully effective, whereas no additional clinical benefit is usually observed at concentrations above the upper limits of the therapeutic range. Higher plasma concentrations of lithium are generally necessary to bring about remission of mania than are necessary for a maintenance of mania-free state. As a rule of thumb, 2/3 of the initial lithium plasma concentration required to initially attain remission will maintain the therapeutic effect (9, 5, 12, 31, 25, 21, 30, 68).

Theoretically since the half-life of lithium is 24 h, the drug could be administered once daily. However, the gastrointestinal side-effects of lithium prevent the administration of a single daily dose. The undesirable side-effects of lithium can occur at any plasma concentration. However, they are much more frequent when plasma concentrations exceed 1.5 mmol/L (15, 72, 5, 20, 11, 25).

The major side-effects of lithium are a consequence of decreased ability to excrete lithium in renal failure or water and electrolyte loss. Increased sodium intake enhances lithium excretion while decreased sodium intake reduces lithium excretion. Development of impaired renal function may present a significant problem since lithium is only cleared via renal excretion.

Clinically, mild lithium toxicity presents at plasma concentrations of 1.5-2.5 mmol/L as drowsiness, slurred speech, muscle tremors or coarse tremors. With plasma concentrations of 2.5-3.5 mmol/L, side-effects are more severe and may include vomiting, tremor, myoclonic jerks, and cogwheel rigidity. Levels above 3.5 mmol/L are life-threatening and death usually occurs as a consequence of pulmonary complications. Prompt treatment of lithium intoxication involves discontinuation of the drug and supportive therapy. Enhanced
clearance of lithium can be achieved by increasing sodium intake and alkaline diuresis in patients with normal renal function. It is to be emphasized that prevention of lithium toxicity by close monitoring of plasma concentrations and appropriate dosage regimen adjustments is the most effective therapeutic approach (85, 51, 37, 36, 79).

It is recommended that lithium concentrations be monitored 2 and 5 days after the initiation of therapy. This should be followed by weekly monitoring for the first month. During chronic lithium therapy plasma concentrations should be monitored monthly or as clinically indicated. Plasma samples obtained 12 h after the last dose are the most effective guide to lithium therapy. Plasma levels of lithium change rapidly so trough sampling times are important to correct interpretation and clinical effectiveness of lithium monitoring (5, 30, 68).

The mechanism of action by which such a simple ion as lithium can control mania is still under investigation. Lithium displaces sodium intracellularly and thus prevents the efflux of sodium. It may also interact with calcium and magnesium to alter synaptic transmitter release. It can be stated that lithium through its action at multiple sites is a membrane stabilizer.

At the present time, no drug for the treatment of mania which is more effective than lithium has been found. Although lithium has a narrow therapeutic range careful monitoring of lithium plasma concentrations aids the clinician in establishing and maintaining complete control of manic states. Today no patient would be started on lithium without routine monitoring of lithium concentrations. Indications for lithium monitoring: manic-depressive illness.

2.3. Phenytoin
The major hydantoin used in the treatment of the epilepsies is phenytoin (5, 8, 21, 30, 37). It is widely used and is effective for all types of seizures except absence seizures. Its introduction in 1938 by Merritt and Putnam was hailed as a milestone because it was the first nonsedative antiepileptic drug to become available for the treatment of the epilepsies. Mephenytoin (Mesantoin) is also used for the treatment of refractory seizures, particularly focal seizures, and does not have many of the undesirable side effects of phenytoin. However, 10% of all patients treated with mephenytoin develop adverse drug reactions, and deaths from blood dyscrasias have been reported. The most common side effect of phenytoin therapy is gingival hyperplasia (overgrowth of the gums over the teeth), which occurs in about 20% of all patients receiving the drug (76, 78, 82, 21, 30, 14, 28, 79).

The optimal therapeutic concentration of phenytoin is 10-20 mg/mL. Most patients will show a marked reduction or complete control of seizures when phenytoin plasma
concentrations are in this range. However, there are certain groups of patients where plasma concentrations over 20 mg/mL may be necessary for seizure control. Mild signs of intoxication (nystagmus, ataxia) may appear at levels of 20 to 30 mg/mL. Plasma concentrations above 40 mg/mL of phenytoin have been associated with an exacerbation of seizures in some patients. Steady state plasma concentrations of phenytoin are usually reached within five to seven days, since the half-life of the drug is 24 h. The common adult dose is 4-6 mg/kg/d which usually produces blood levels of 12-18 mg/mL (30, 28, 51, 68, 24).

2.4. Theophylline

Theophylline, and the closely related alkaloids caffeine and theobromine, are a group of central-nervous-system stimulants collectively referred to as xanthines. They have been consumed in beverages for ages and their origins are obscure. Coffee, tea, cocoa, matú, and cola are all aqueous extracts of various plants which contain either one or several of these xanthines. It is thought that it is their content of these CNS stimulants that makes these beverages so popular (5, 1, 10, 4, 21, 30, 6).

Theophylline and aminophylline, its ethylenediamino salt, are commonly used in the treatment of bronchial asthma. Theophylline is a potent smooth-muscle relaxant, especially of bronchial smooth muscle. It is used as a bronchodilator in the treatment of asthma and the reversible bronchospasm of obstructive pulmonary diseases (9, 8, 13, 14, 27, 22, 24).

In addition to its inhibitory effect on smooth muscle, theophylline is a cardiac muscle stimulant. The drug has a narrow therapeutic index. The therapeutic range is 10-20 mg/mL, yet serum levels of 20 mg/mL have been associated with toxicity. Pharmacokinetic studies have shown that infants, children, and adults can demonstrate markedly different half-lives for theophylline. Premature infants, in particular, have prolonged half-lives. The variability of the steady-state level resulting from any given regimen makes the use of
plasma level monitoring mandatory, especially in children (33, 47, 53, 35, 55, 57, 58, 28, 42, 29).

The drug has numerous side effects, related mostly to its CNS stimulatory action. Irritability, insomnia, and headache have been reported. The xanthines are known to enhance gastric secretion, and the use of theophylline has resulted in nausea, vomiting, and gastric irritation. Palpitations and sinus tachycardia can result from the stimulatory effect on the myocardium (52, 50, 55-59, 51, 37, 36, 60).

Theophylline is an inhibitor of cyclic-nucleotide phosphodiesterases. Administration of theophylline results in elevation of cyclic-AMP levels in some tissues. Since catecholamines also cause elevated cyclic-AMP levels, although by a different mechanism, it can be expected that theophylline will potentiate the effect of catecholamines. For the same reason, theophylline has a synergistic effect when combined with ephedrine (65, 70, 61, 62, 59, 68, 60).

The tendency of theophylline to elevate cyclic AMP levels results in cortical, medullary, and spinal cord stimulation, augmentation of cardiac chronotropy and inotropy, cardiovascular dilatation, smooth muscle relaxation, and diuresis (71, 74, 75, 84, 86, 79).

Indications for monitoring:
- bronchial asthma;
- relief of bronchospasm as seen in Cheyne-Stokes respiration;
- obstructive pulmonary disease;
- emphysema;
- relief of paroxysmal dyspnea due to left heart failure.

3. DISCUSSION

Characteristics of drugs applicable for therapeutic drug monitoring (31, 21, 30, 6, 24, 37):

1. Serum drug concentration is the most practical intermediate endpoint to be used when there is no clearly observable therapeutic or toxic endpoint.
2. Serum concentration is a proxy for drug concentration at the site of action.
3. The range of therapeutic and safe serum concentrations is narrow.
4. There is no predictable dose-response relationship.
5. Toxicity or lack of effectiveness puts the patient at great risk.
6. The pharmacologic effect observed persists for a relatively long time.
7. A drug assay is available that is accurate, precise, and specific, requires a small sample volume, yields results quickly, and is relatively inexpensive.

The determination of individual drugs (eg. digoxin, lithium, phenytoin, theophyllin, among the others) have shown benefit of therapeutic drug monitoring, depending on the specific study, through one or more of the following indices: improved effectiveness, reduced toxicity, decreased length of stay, fewer hospital admissions, more patients with serum levels within the appropriate therapeutic range, and more rational use of serum concentration measurements. The presented data demonstrated that
therapeutic drug monitoring service should recommend guidelines for and influence the use of serum drug concentrations, advise when samples should be taken, interpret concentrations, recommend dosage regimens based on the data, educate physicians through seminars and newsletters, and participate in studies collecting and analyzing data (30, 51, 62, 63, 36).

Selecting a steady-state serum concentration goal is frequently referred to as using a target concentration strategy, a term coined (30, 51, 37, 68, 36). The target concentration falls within the range of effective and safe concentrations determined for the population at large. So the practitioner begins by assuming that the patient behaves like the average member of his or her population with respect to pharmacokinetics, serum level, and expected response, and uses average pharmacokinetics parameters to calculate the dose needed to meet the target concentration objective. If after administering the dosage regimen until steady state is reached, the patient is responding appropriately and the measured concentration is within the therapeutic (target concentration) range, no adjustment is necessary. If, however, the starting assumption that the patient behaves similarly to the average turns out to be incorrect, because the response is subtherapeutic or toxic, due to either pharmacokinetic or pharmodynamic behavior that is atypical for the population, then the only maneuver available to the practitioner is to manipulate the practitioner-controlled input variables, dose and frequency, to bring the pharmacologic or therapeutic response within the accepted range. Usually, but not always, an effective and safe response occurs after the dosage regimen has been adjusted to bring the serum concentration within the target concentration range. Some patients, however, will surely achieve the desired response below or above the target concentration range.

Straightforward as this process may appear, a number of factors mitigate against widespread application of therapeutic drug monitoring and restrict it to a few drugs for which the benefits of TDM outweight the reservations:

- Therapeutic drug monitoring (TDM) is very costly, in terms of equipment, supplies, personnel to draw the levels and interpret the results, and investment in research to collect the necessary concentration versus response data.
- Some drugs have such a broad range of regimens that are effective and safe that using an intermediate gauge like serum concentrations is unnecessary.
- Even for some of the drugs that may potentially benefit from TDM, because they appear to have a narrow range of flexibility in dosage, the relationship between serum concentration and response is not firmly established.
The population of which data have been obtained from studies of serum concentration versus effect (eg. males younger than 50 with congestive heart failure and normal values for renal and liver functions, thyroid, and electrolytes) may differ from the population to which the patient belongs (eg. females older than 70 with congestive heart failure, but impaired renal and/or liver function and abnormal electrolytes) for which reference data are not available.

- And for some drugs, more effective intermediate measures of response than serum level (eg. Blood pressure, blood coagulation time) are available.

- Even when properly designed studies are conducted, they may be carried out in patient populations that differ from the population in which the practitioner intends to use them. For example, a therapeutic range obtained from studies in well young volunteers may not be applicable to elderly patients. The therapeutic range for a drug obtained from patients with congestive heart failure may not apply to the drug when treating patients with arrhythmias.

Stated most simply, therapeutic drug monitoring aims to promote optimum drug treatment by maintaining serum drug concentrations within a "therapeutic range", above which toxicity occurs too often and below which the drug is too often ineffective (30, 59, 60). In the present work we make a more rigorous definition by restricting the term therapeutic drug monitoring (TDM) to a small group of drugs in which there is a direct relationship between concentration and response, as well as narrow range of concentrations that are effective and safe, and for which serum drug concentrations are used in conjunction with other measures of clinical observation to assess patient status. This probably seems too wordy but the definition includes a number of important considerations and qualifications.

- Using a drug concentration implies that a more direct measure of patient response (blood pressure, blood coagulation time, etc.) is not readily available.

- Noting the restriction to drugs with a narrow range of effective, safe concentrations excludes the majority of drugs for which such meticulous scrutiny is unnecessary as a wide range of dosage or variation in response may be tolerated without risk.

- Evaluating patient response on the basis of serum drug level alone is risky because this measure is only one of many factors (eg. age, severity of disease, electrolytes levels, other drugs being taken) that must be taken into account in evaluating a patient’s response to a drug.

- For some types of drugs, serum drug concentrations were postulated to be a better index than dose to guiding treatment. Serum levels were expected to be...
a better indicator of drug concentrations at receptor sites, perhaps could be used to correlate drug levels and patient responses, and should be useful in determining pharmacokinetic parameters of drugs in individual patient.

So the growth in therapeutic drug monitoring was due to a combination of interacting and mutually reinforcing factors (59, 60). With the appreciation that standard dosage regimens led to varying outcomes, clinicians needed more scientific knowledge and supporting assay technology to tailor drug therapy for individual patients.

- Therapeutic drug monitoring in a hospital or clinic may be as limited as providing consultation on one drug class such as the aminoglycosides for hospitalized patients or antiepileptics for patients in the neurology clinic, or the practice may include a number of drugs for inpatients and outpatients. In some facilities, TDM may include responsibility for assaying samples as well as interpreting the results.

4. CONCLUSION AND GUIDELINES TO SPECIMEN COLLECTION.

Therapeutic drug monitoring (TDM) is employed to measure blood drug levels so that the most effective dosage can be determined, with toxicity prevented. TDM is also utilized to indentify noncompliant patients (those patients who, for whatever reason, either cannot or will not comply with drug dosages as prescribed by the physician).

Because so many different factors influence blood drug levels, the following points should be taken into consideration during TDM: the age and weight of the patient; the route of administration of the drug; drug’s absorption rate, excretion rate, delivery rate and dosage; other medications the patient is taking; other diseases the patient has; the patient’s compliance regarding the drug treatment regimen; and the laboratory methods used to test for the drug.

Therapeutic drug monitoring is important for patients who have other diseases that can affect drug levels, or who take other medicines that may affect drug levels by interacting with the drug being tested. As an example, without drug monitoring, the physician cannot be sure if a patient’s lack of response to an antibiotic reflects bacterial resistance, or is the result of failure to reach the proper therapeutic range of antibiotic concentration in the blood. In cases of life-threatening infections timing of effective antibiotic therapy is critical to success. It is equally crucial to avoid toxicity in a seriously ill patient. Therefore, if toxic symptoms appear with standard dosages, TDM can be used to determine changes in dosing.

Drawn blood, used for TDM, demonstrates a drug action in the body at any specific time, whereas
drug levels examined from urine samples reflect the presence of a drug over many days (depending on the rate of excretion). Therefore, blood testing is the procedure of choice when definite data are required. However, for adequate absorption and therapeutic levels to be accurate, it is important to allow for sufficient time to pass between the administration of the medication and the collection of the blood sample.

Blood specimens for drug monitoring can be taken at two different times: during the drug’s highest therapeutic concentration ("peak" level), or its lowest ("trough" level). Occasionally called residual levels, trough levels show sufficient therapeutic levels; whereas peak levels show poisoning (toxicity). Peak and trough levels should fall within the therapeutic range.

In preparing for TDM, the following guidelines should be observed:

- Depending on the drug to be tested, the physician should decide if the patient is to be fasting (nothing to eat or drink for a specified period of hours) before the test.
- For patients suspected of symptoms of drug toxicity, the best time to draw the blood specimen is when the symptoms are occurring.
- One of the most common reasons for misinterpretation of serum drug concentrations is incorrect sampling time. This problem can be avoided by knowing a few basic principles.

It is imperative that the clinician know what questions are to be answered by the sample being drawn. Different questions may require different sampling times and possibly different numbers of samples. For example, the question of toxicity may be answered by only one stat sample whereas a determination of half-life will require at least two samples drawn at a more precise time after the drug is administered.

It is also essential to know the time since the last dose. This information will help to determine at what point on the serum concentration vs time curve the sample was drawn i.e., before, on or after time of peak serum concentration. For example, the sample drawn before the peak concentration would be of little value in determining the half-life of the drug. If drawn on or shortly after the time of peak serum concentration it would serve as an initial reference point in calculating the half-life of the drug.

Peak levels alone are useful for monitoring possible toxic levels. Trough levels alone are useful to insure constant maintenance within the therapeutic range.

Patients receiving a drug at a dosing interval longer than the half-life of the drug will demonstrate large fluctuations between peak and trough levels. Serum concentrations of drugs dosed at intervals shorter than their half-lifes would show less
fluctuation between peak and trough levels.

For chronically administered oral medications the peak levels usually occur 1-2 hours after the dose and the trough serum concentration shortly after the dose is administered. Drawing the trough level at the time the dose is given is usually sufficiently accurate. Digoxin is one exception to the previous statement. The 2 hour serum level does not correlate well with the intensity of its action. The serum level to determine peak activity should be drawn after the serum Digoxin has had time to equilibrate with the tissue i.e., 6-10 hours after the oral dose.

Intravenous medications should also be given time to equilibrate before the peak level is drawn. Equilibration between the serum and the site of action is fastest for drugs acting in the heart, brain and other highly perfused tissues while drugs whose site of action is in tissues with low rates of blood flow may require more than an hour to equilibrate. In general, intravenous medications should be sampled S-1 hour after administration. For example, the peak serum level of Gentamycin should be drawn thirty minutes after infusion of the drug ends and not immediately after the infusion.

Intramuscularly administered medications if injected in an area with good blood flow will achieve peak levels within a similar time frame as intravenous. Medications that are poorly soluble at body pH, however, may precipitate at the site of injection and achieve very low and late peak serum levels.

The fact must always be remembered that there is a large interpatient variability in all aspects of therapeutic drug monitoring and sampling time is no exception.

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ჰიდროქორიტისთან არანორგანოთან, მოლუსქა პანდემიისთან რეაქციითი სიმპტომები

შიგის ხელშეწყობა, მოსახლე ჯერში

მესამე პერიოდში ხდეს მედიკამენტური პელაგის კონტროლის შედეგად, რომელზეც მედიკამენტური პრობლემების გზავნილობა დაბრუნდება. ვრცელ დაბრუნდება უშუალოდ შესაძლოა ანიმაციის მიგრის შემდეგ, რაც შეიძლება დაახლოებით პანდემიის შემდეგ შეიძლება შეიძლოდეს ჰიდროქორიტის გამოყენებით ამოდით პაციენტზე შემდეგ, რაც შესაძლოა მოხდა ჰიდროქორიტის გამოყენებით. ეს შეიძლება გამოთქვამდე ჰიდროქორიტის გამოყენებით სხვა პელაგის თეთროვანი მოვლენა შემცირდება, როდესაც მედიკამენტის გამოყენებით შეიძლოდეს მექანიზი მოქმედება. თუმცა, ეს შეიძლება ელასტიკურ დამოკიდებულობა შეიძლოდეს მექანიზმი მოქმედებაში ამოწმებაში. მათგან, ელასტიკურ დამოკიდებულობა შეიძლოდეს პირადი მოქმედე მაგალითში მედიკამენტის გამოყენება სიმპტომების შემდეგ სამართავი ადამიერ იყო.