Therapeutic Drug Monitoring:

Definition: The use of drug measurements in biological fluids as an aid to the management of patients receiving drug therapy for the alleviation or prevention of diseases.

Fundamental Assumptions

The basic assumptions underlying therapeutic drug monitoring are that drug metabolism varies from patient to patient and that the plasma level of a drug is more closely related to the drug's therapeutic effect or toxicity than is the dosage.

Indications for Drug Monitoring

Drugs with a **narrow therapeutic index** (where therapeutic drug levels do not differ greatly from levels associated with serious toxicity) should be monitored.

Example: Lithium.

Patients who have **impaired clearance** of a drug with a narrow therapeutic index are candidates for drug monitoring. The clearance mechanism of the drug involved must be known.

Example: Patients with renal failure have decreased clearance of gentamicin and therefore are at a higher risk for gentamicin toxicity.

Drugs whose **toxicity is difficult to distinguish from a patient's underlying disease** may require monitoring.

Example: Theophylline in patients with chronic obstructive pulmonary disease.

Drugs whose **efficacy is difficult to establish clinically** may require monitoring of plasma levels.

Example: Phenytoin.

Conditions in Which Drug Monitoring

MAY NOT BE USEFUL

Drugs that can be given in extremely high doses before toxicity is apparent are not candidates for monitoring.

Example: Penicillin.

If there are better means of assessing drug effects, drug level monitoring may not be appropriate.

Example: Warfarin is monitored

Bioavailability:

The bioavailability of a drug depends in part on its formulation. A drug that is significantly metabolized as it first passes through the liver exhibits a marked "first-pass effect," reducing the effective oral absorption of the drug. A reduction in this first-pass effect (e.g., because of decreased hepatic blood flow in heart failure) could cause a clinically significant increase in effective oral drug absorption.

2. *Volume of distribution and distribution phases*

The volume of distribution of a drug determines the plasma concentration reached after a loading dose. The distribution phase is the time taken for a drug to is tribute from the plasma to the periphery. Drug levels drawn before completion of a long distribution phase may not reflect levels of pharmacologically active drug at sites of action.

Examples: Digoxin, lithium.

3. *Clearance*

Clearance is either renal or non renal (usually hepatic). Whereas changes in renal clearance can be predicted on the basis of serum creatinine or creatinine clearance, there is no routine liver function test for assessment of hepatic drug metabolism. For most therapeutic drugs measured, clearance is independent of plasma drug concentration, so that a change in dose is reflected in a similar change in plasma level. If, however, clearance is dose-dependent, dosage adjustments produce disproportionately large changes in plasma levels and must be made cautiously.

Example: Phenytoin.

4. *Half-life*

The half-life of a drug depends on its volume of distribution and its clearance and determines the time taken to reach a steady state level. In three or four half-lives, the drug level will be 87.5% to 93.75% of the way to steady state. Patients with

decreased drug clearance and therefore increased drug half-lives will take longer to reach a higher steady state level. In general, since non-steady state drug levels are potentially misleading and can be difficult to interpret, it is recommended that most clinical monitoring be done at steady state.

5. *Protein binding of drugs*

All routine drug level analysis involves assessment of both protein-bound and free drug. However, pharmacologic activity depends on only the free drug level. Changes in protein binding (eg, in uremia or hypoalbuminemia) may significantly affect interpretation of reported levels for drugs that are highly protein-bound.

Example: Phenytoin. In such cases, where the ratio of free to total measured drug level is increased, the usual therapeutic range based on total drug level will not apply.

Drug Interactions

For patients receiving several medications, the possibility of drug interactions affecting drug elimination must be considered.

Example: Quinidine decreases digoxin clearance.

Therapeutic Drug Monitoring

Drug	Effective Concentrations	Half-Life (hours)	Dosage Adjustment	Comments
Amikacin	Peak: 10–25 μg/mL Trough: < 10 μg/mL	2–3 ↑ in uremia	↓ in renal dysfunction	Concomitant kanamycin or tobramycin therapy may give falsely elevated amikacin results by immunoassay.
Amitriptyline	160–240 ng/mL	9–46		Drug is highly protein-bound. Patient-specific decrease in protein binding may invalidate quoted range of effective concentration.
Carbamazepine	4–8 μg/mL	10–30		Induces its own metabolism. Metabolite 10,11-epoxide exhibits 13% cross-reactivity by immunoassay. Toxicity: diplopia, drowsiness, nausea, vomiting, and ataxia.
Cyclosporine	150–400 mg/mL (ng/L) whole blood	6–12	Need to know specimen and methodology used	Cyclosporine is lipid-soluble (20% bound to leukocytes; 40% to erythrocytes; 40% in plasma, highly bound to lipoproteins). Binding is temperature-dependent, so whole blood is preferred to plasma or serum as specimen. High-performance liquid chromatography or monoclonal fluorescence polarization immunoassay measures cyclosporine reliably. Polyclonal fluorescence polarization immunoassays cross-react with metabolites, so the therapeutic range used with those assays is higher. Anticonvulsants and rifampin increase metabolism. Erythromycin, ketoconazole, and calcium channel blockers decrease metabolism.
Desipramine	100–250 ng/mL	13–23		Drug is highly protein-bound. Patient-specific decrease in protein binding may invalidate quoted range of effective concentration.

↔ = unchanged; ↑ = increased; ↓ = decreased; CHF = congestive heart failure

For Further Reading

GM Shenfield: Therapeutic drug monitoring beyond 2000