CCTC Clinical Chemistry Trainee Council | AACC Better health through laboratory medicine.

PEARLS OF LABORATORY MEDICINE

www.traineecouncil.org

TITLE: Therapeutic Drug Monitoring—Chemotherapeutic agents

PRESENTER: Jieli Shirley Li MD, PhD

Slide 1:

Hello, my name is **Jieli Shirley Li**. I am an **assistant professor and lab director at Ohio State University Wexner Medical Center**. Welcome to this Pearl of Laboratory Medicine on "**Therapeutic Drug Monitoring—Chemotherapeutic agents**"

Slide 2:

Therapeutic drug monitoring, briefly called TDM, offers clinicians better management of patients and potential improvement of patient quality of life, through optimizing dose, supporting compliance, and minimizing toxicity. The practice of TDM has been expanded and enhanced by rapid, sensitive, and specific analytical techniques for a wide variety of therapeutic agents.
The best candidate drugs for TDM are those meeting one or more of the following criteria: (1) a narrow therapeutic index; (2) used for long-term therapy; (3) correlation between serum concentration and clinical response; (4) wide interindividual or intraindividual variability in pharmacokinetics; (5) absence of a biomarker associated with therapeutic outcome; or (6) administered with other, potentially interacting compounds.

Slide 3:

In practice TDM is performed for drugs administered multiple times over many days, weeks, or even years. Usually, doses are administered before the preceding dose has been completely eliminated. As shown in this figure, drugs administered at regular intervals will accumulate to a point termed steady state, which means the amount of drug entering the systemic circulation is

in balance with the amount being eliminated. Assuming doses are given at each half-life, a drug with first-order kinetics will require three to five doses to approach steady-state concentrations. Similarly, at the end of therapy, five to seven half -lives after the last dose must pass for more than 95% of the steady-state concentration to be eliminated.

Slide 4:

The simplest and most direct route of administering a drug is intravenous delivery, because infusion places the complete dose of a compound into the circulation. However, practically, and for reasons of patient preference, drugs can be delivered by alternate ways, the common way is oral administration. Oral dosing differs from intravenous due to the drug required to pass from the gastrointestinal tract into the vascular system. This process is known as absorption. The ability of absorption is determined by the rate and extent of drug absorption, the nature of the drug itself, for example, solubility and pKa, the formulation matrix and the physiologic environment, for example gastrointestinal motility.

The distribution of drugs extensively depends on lipophilicity, their facilitates passage through cell membranes. Many drugs bind to one or more plasma proteins, mostly albumin, globulins such as α1-acid glycoprotein, and lipoproteins. In general, acidic drugs associate primarily with albumin, while basic drugs bind globulins and lipoproteins. An equilibrium between the amount of drug is protein-bound and free drug, which means, not bound to protein. Free drug is more readily accessible to cell membranes, drug receptors, and elimination mechanisms; therefore the free fraction is considered the active component of the drug responsible for its biological effects.

Metabolism is typically thought to enhance excretion of drugs, where endogenous and exogenous compounds are converted to more polar products to increase water solubility. Drugs can be metabolized by oxidation, reduction, hydrolysis, hydration, conjugation, condensation, or isomerization.

Excretion, or elimination is the final removal of drugs from the body. This includes secretion into sweat, breath, and breast milk, incorporation into hair and nails, or even crossing the placenta into the fetal bloodstream. However, the most common ways of drug elimination is excretion into urine or stool, depending on the water solubility of the compound. The rate of elimination into urine can be estimated using the glomerular filtration rate.

Slide 5:

Serum drug concentrations are useful in many stages of treatment. Initial selection and dosing of a drug may be guided by TDM, particularly if wide interpatient variability in absorption, metabolism, or other parameters of drug disposition is noted. Without measuring drug concentrations, it is difficult to discern which patients respond poorly to therapeutic concentrations of a particular drug and which ones simply are not within the therapeutic range. Particularly, population pharmacokinetics often does not adequately address comorbidities or drug interactions, so TDM is necessary for these patients.

Slide 6:

TDM analysis includes many of the same concerns as other areas of clinical chemistry: the need for accurate, reproducible methods; the requirement for quality assurance and proficiency testing programs; and the necessity of establishing target ranges. A wide variety of analytical techniques are available to facilitate TDM, including numerous immunoassay methods such as enzyme multiplied immunoassay technique (EMIT), fluorescent polarization immunoassay (FPIA), cloned enzyme donor immunoassay (CEDIA), and chromatographic techniques such as gas chromatography-mass spectrometry (GC-MS), liquid chromatography-mass spectrometry/mass spectrometry (LC-MS/MS), and high performance liquid chromatography-ultraviolet (HPLCUV).

Immunoassays provide rapid results and ready automation; chromatographic techniques improve specificity and limits of detection, although at a lower throughput. Unfortunately, commercial immunoassays are not available for many of the newer-generation drugs. LC-MS/MS is progressively replacing other HPLC-based methods; it displays greater selectivity and fewer analytical interferences, allowing development of multi-analyte assays with higher throughput and less influence from metabolites or other potentially co-eluting compounds. The choice of analytical method typically depends on the availability of resources and the clinical demand for turnaround.

Slide 7:

Busulfan is a chemotherapeutic drug that inhibits the growth of malignant cells by alkylating DNA. Busulfan is currently used in hematopoietic stem cell transplant preparative regimens to maximize an antitumor effect. In addition, busulfan is also used to treat malignant and

nonmalignant bone marrow disorders, such as acute and chronic leukemias, myelodysplastic syndromes, β-thalassemia major, polycythemia vera, and sickle cell anemia.

Slide 8:

Busulfan pharmacokinetics is affected by age, weight, disease status, hepatic function, and drug interactions. The optimal range of therapeutic area under the plasma concentration versus time curve (AUC) for standard dosed busulfan is 900 to 1350 μmol•min/L. Patients with busulfan concentrations below the therapeutic range are thought of as having an increased risk of relapse as well as of rejection. Conversely, patients with plasma concentrations greater than 1500 μmol•min/L have an increased risk of severe treatment-related toxicity.

Slide 9:

Busulfan is metabolized through both cytochrome P450 isoenzymes (primarily CYP3A4) and conjugation with glutathione via glutathione S-transferase. Slowed busulfan clearance could be anticipated with coadministration of a CYP3A4 inhibitor or a competitive substrate. Fluconazole is known to inhibit the drug metabolizing enzyme CYP3A4, therefore it inhibits busulfan metabolism and delays its clearance.

Slide 10:

Methotrexate inhibits DNA synthesis by decreasing the availability of pyrimidine nucleotides. Methotrexate has proved useful in the (1) management of acute lymphoblastic leukemia in children; (2) management of choriocarcinoma and related trophoblastic tumors in women; (3) management of carcinomas of the breast, tongue, pharynx, and testes; (4) maintenance of remission in leukemia; and (5) treatment of severe, debilitating psoriasis. High-dose methotrexate administration followed by leucovorin rescue is effective in treatment of carcinoma of the lung and osteogenic sarcoma.

Slide 11:

Methotrexate is a nonspecific cytotoxin, and prolongation of blood concentrations appropriate to killing tumor cells. It may lead to severe, unwanted cytotoxic effects such as myelosuppression, gastrointestinal mucositis, and hepatic cirrhosis.

Serum concentrations of methotrexate are commonly monitored during high-dose therapy to identify the time at which active intervention by leucovorin rescue should be initiated. Criteria for serum concentrations indicative of a potential for toxicity after single-bolus, high-dose therapy are shown in the table:

1. Methotrexate concentration greater than 10 μmol/L 24 hours after dose.
2. Methotrexate concentration greater than 1 μmol/L 48 hours after dose.
3. Methotrexate concentration greater than 0.1 μmol/L 72 hours after dose.

Characteristically, serum concentrations are monitored at 24, 48, and 72 hours after the single dose, and leucovorin is administered when methotrexate concentrations are inappropriately high for a postdose phase.

Slide 12:

The route of elimination for methotrexate is primarily renal excretion. During the period of high serum concentrations, particular attention must be paid to maintaining output of a large volume of alkaline urine. The pKa of methotrexate is 5.5; therefore small decreases in urine pH result in significant reduction in its solubility. Keeping urinary pH alkaline diminishes the risks of intratubular precipitation of the drug and obstructive nephropathy during the treatment period. So monitoring serum concentrations provides the basic ideas for decisions related to timing of initiation and continuance of leucovorin treatment and for management of urinary pH.

Low-dose methotrexate, is used to manage rheumatoid arthritis, Crohn’s disease, psoriasis, or inflammatory bowel disease. It is not typically monitored because analytical methods are not sensitive enough to monitor once-weekly dosing, and also because methotrexate concentrations have not been shown to correlate well with disease control.

Slide 13:

The side effect profile of MTX varies markedly according to dose. Regimens containing MTX are classified as high, intermediate, or low-dose. Most clinicians reserve the term high-dose MTX for doses ⩾500 mg/m2, and require a two to three day period of multiple leucovorin doses to terminate the toxic effect of MTX (called leucovorin "rescue"). Leucovorin (also called citrovorum), is N-5-formyltetrahydrofolate, the product of dihydrofolate reductase. Leucovorin rescue is critical in cases in which it is necessary

to administer high doses of methotrexate to individuals with tumors that do not respond to normal doses of this drug. In such cases, leucovorin is given 18 to 36 hours after the initial methotrexate dose, while serum levels of methotrexate are monitored. In addition, leucovorin should immediately be administered to a patient receiving low-dose methotrexate when methotrexate overdose is suspected. Serum methotrexate levels should be monitored during this time.

Toxicity of methotrexate can also be treated using continuous flow hemodialysis. Alternatively, intravenous infusion of carboxypeptidase G2, a methotrexate-cleaving enzyme, results in rapid clearing of the drug.

Slide 14: References

Slide 15: Disclosures

Slide 16: Thank You from www.TraineeCouncil.org

Thank you for joining me on this Pearl of Laboratory Medicine on "**Therapeutic Drug Monitoring—Chemotherapeutic agents**."

Question Bank

After approximately how many drug half-lives is steady-state serum drug concentrations achieved?

a) One

b) Two

c) Five

d) The number varies with the drug

Answer: **c**

Discussion: steady-state of drug concentrations are achieved after approximately five half-lives.

Source: Tietz Textbook of Clinical Chemistry and Molecular Diagnostics - 6th Edition

Difficulty: Easy

Which of the following is TRUE regarding the drugs that require therapeutic drug monitoring?

a) Wide therapeutic index

b) No need of correlation between serum concentration and clinical response

c) No interindividual or intraindividual variability in pharmacokinetics

d) Administered with other, potentially interacting compounds

Answer: **d**

Discussion: The best candidate drugs for TDM are those meeting one or more of the following criteria: (1) a narrow therapeutic index; (2) used for long-term therapy; (3) correlation between serum concentration and clinical response; (4) wide interindividual or intraindividual variability in pharmacokinetics; (5) absence of a biomarker associated with therapeutic outcome; or (6) administered with other, potentially interacting compounds.

Source: Tietz Textbook of Clinical Chemistry and Molecular Diagnostics - 6th Edition

Difficulty: Easy