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PRIMER ON DRUG INTERFERENCES WITH TEST RESULTS

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OBJECTIVES

After completing this chapter, the reader should be able to

- Distinguish between in vivo and in vitro drug interferences with laboratory tests
- Identify suspected drug–laboratory test interference in a logical, systematic manner given a drug and a laboratory test
- Devise a stepwise process to confirm that a drug is causing a clinically significant drug–laboratory test interference
- Distinguish among tertiary, secondary, and primary literature resources about drug–laboratory test interferences
- Apply a systematic process to search and identify medical literature relevant to a suspected drug–laboratory test interference situation

Through a variety of mechanisms, drugs can interfere with laboratory test results. If the clinician who has ordered the laboratory test is not aware that the drug has altered the results of the test, inappropriate management of the patient may follow including unnecessary hospitalization, extra office visits, or additional laboratory or clinical testing—all of which may increase the cost of healthcare. This chapter addresses this situation and provides resources that health professionals can use to better interpret laboratory tests when a drug is suspected to interfere with test results.

IN VIVO AND IN VITRO DRUG INTERFERENCES WITH LABORATORY TESTS

When a drug interferes with a laboratory test result, it alters the laboratory value. Mechanisms for drug interference of clinical laboratory tests can be classified as either in vivo or in vitro.[1] *In vivo drug interferences* can also be called physiological and can be subclassified as pharmacological or toxicological. In vivo interferences account for most effects of drugs on laboratory tests.[2] In contrast, the term *in vitro interference* is used synonymously with analytical or methodological interference.

In Vivo Interference

An in vivo interference is an actual change in the analyte concentration or activity prior to specimen collection and analysis. The assay measurement is actual and accurate and reflects a change in the measured substance that has occurred in the patient. Therefore, an in vivo interference will always change a laboratory test result, independent of the assay methodology. A drug can produce an in vivo interference in several ways. By a direct extension of its pharmacological effects, a drug can produce changes in some laboratory test results. For example, thiazide and loop diuretics will commonly cause increased renal elimination of potassium. Therefore, decreased serum potassium levels can occur in treated patients. In these patients, hypokalemia is actual and accurate. Similarly, increased blood urea nitrogen (BUN) levels can occur as a result of excessive fluid loss during treatment with thiazide and loop diuretics.

Other drugs produce changes in laboratory test results by producing in vivo toxicological effects. As the drug damages a particular organ system, abnormal laboratory tests may be one of the first signs of the problem. For example, as isoniazid and rifampin produce hepatotoxicity, elevated hepatic transaminases will signal the onset of liver inflammation. Similarly, as a prolonged course of high-dose aminoglycoside antibiotic causes acute proximal tubular necrosis, serum creatinine and serum trough aminoglycoside levels will increase steadily if the antibiotic is not stopped or if the antibiotic dose is not reduced. In the face of cyclophosphamide-induced bone marrow suppression, neutropenia will become evident 10–14 days after the dose has been administered.

In Vitro Interference

Drugs in a patient's body fluid or tissue can directly interfere with a clinical laboratory test during the in vitro analytical process. This type of drug–laboratory test interaction is highly dependent on the laboratory test methodology, as the reaction may occur with one specific assay method but not another. For example, serum digoxin levels are commonly determined using a radioimmunoassay, a fluorescent polarization immunoassay, or a TDx assay. However, these assays are based on the three-dimensional structure of the digoxin molecule, and many other drugs with a similar chemical structure to digoxin (e.g., spironolactone, estrogen replacement products, cortisol, or digoxin-like substances) can cross-react with the assay.[3] A falsely increased or decreased serum digoxin level can result.[3,4] To determine the true serum digoxin level in this situation, another assay technique (e.g., high-pressure liquid chromatography [HPLC]) may be used. A similar problem occurs with fosphenytoin, which cross-reacts with phenytoin when measured with immunoassay methods.[5] In addition, substances that are prepackaged in or added to the in vitro system before or after sample collection can cause laboratory test interference in vitro. As an example, test tubes sometimes contain lithium heparin or sodium fluoride. Heparin can interfere with aminoglycoside assays, and fluoride can cause false increases in BUN when measured by the Ekatchem assay.

Alternatively, a drug may cause discoloration of the body fluid specimen, which may interfere with colorimetric, photometric, or fluorometric laboratory-based assay methods. For example, phenazopyridine causes an orange-red discoloration of urine that may be mistaken for blood. Nitrofurantoin may cause a brown discoloration of the urine that may cause alarm for the patient. These types of drug interference with laboratory testing can be detected visually and appropriate attribution of the abnormality should be made by knowledgeable clinicians and clinical laboratory staff.

Other common mechanisms by which drugs cause in vitro interferences with laboratory tests include the following:

- A drug reacts with reagent to form a chromophore (e.g., cefoxitin or cephalothin) with the Jaffe-based creatinine assay.
- A drug reacts with immunoassay's antibody that is intended to be specific for the analyte. For example, caffeine cross-reacts in the theophylline assay; digitoxin, digoxin metabolites, antigen-binding fragments derived from antidigoxin antibodies (used for treating digoxin intoxication), spironolactone, and canrenone (the major metabolite of spironolactone) cross-react with digoxin immunoassays.[3]
- A drug alters the specimen pH (usually urine) so that reagent reactions are inhibited or enhanced. For example, acetazolamide produces an alkaline urinary pH that causes false-positive proteinuria with reagent dip strips.
- A drug has chemical properties similar to the analyte. For example, patients who receive radiographic contrast media, which contain iodine, may exhibit altered laboratory values for protein-bound iodine.
- A drug chelates with an enzyme activator or reagent used in the in vitro laboratory analysis.
- A drug absorbs at the same wavelength as the analyte. For example, methotrexate interferes with analytic methods using an absorbance range of 340–410 nm.

In addition to the parent drug, other drug-related components may cause significant interferences with laboratory tests. Metabolites can cross-react with the parent drug in an assay, such as in the case with cyclosporine. Its metabolites cross-react with the parent drug in HPLC assays and can produce a falsely high measurement of the concentration of cyclosporine.[6] Contaminants in herbal products, which are subject to less regulation than medications in the United States, may interfere with some laboratory tests.[7] Inactive ingredients of some drug products, which includes excipients such as lactose or starch, preservatives, colorants, or flavoring agents, may influence assay results. Although most manufacturers do report the inactive ingredients in their products, little systematic research has been performed to assess the impact of these substances on laboratory tests. Compounding these factors, many laboratory test interferences are concentration-related, and many drug metabolites and their usual plasma concentrations have yet to be identified. Therefore, systematic study of all of these potential causes of interactions is difficult to conduct and is not available in many cases.[8]

Simultaneous In Vitro and In Vivo Effects

Some drugs can affect an analyte both in vivo and in vitro. In these situations, interpretation is extremely difficult because the degree of impact in each environment cannot be determined easily. For example, when a drug produces hemolysis in a patient with glucose-6-phosphate dehydrogenase deficiency that is exposed inadvertently to ciprofloxacin, hemolytic anemia may result. Hemolyzed red blood cells produce a red discoloration of the plasma or serum. The hemoglobin released from the damaged red blood cells can interfere with analysis of alkaline phosphatase or γ-glutamyl transferase, both of which can be assayed using a spectrophotometric analysis that depends on color changes after a chemical reaction.[8,9] Simultaneous in vitro and in vivo drug interferences with laboratory tests can also occur commonly when drugs increase bilirubin or when a drug causes lipemia.[10]

IDENTIFYING DRUG INTERFERENCES

Incidence of Drug Interferences

The true incidence of drug interferences with laboratory tests is unknown. This is because many situations probably go undetected. However, as the number of laboratory tests and drugs on the U.S. commercial market increase, it is likely that the number of cases of in vivo interferences will also increase. As a reflection of this, consider the number of drug–laboratory test interferences reported by D. S. Young, author of one of the classic literature references on this topic. In the first edition