The Effect of Drugs on Clinical Laboratory Determinations

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Many of the physiologic and biochemical changes produced by drugs within the body are susceptible to testing. An incomplete data bank sometimes prevents us from realizing that the effects and measurements may be in areas other than the one of primary interest. If laboratory people are unable to recognize this as a problem, the clinician is also unlikely to do so. The results are sometimes disastrous to the patients to whom we are all ultimately responsible.

The literature related to drug interactions with the effect on patients and laboratory determinations has become immense in the past few years. The purpose of this discussion is to underscore this problem of mounting importance to clinical chemists as well as physicians.

To illustrate the point, an article by Llerena and Pearson (1) demonstrated the interference of nalidixic acid (Negram) with urinary 17-ketosteroid determinations. False elevations of urinary 17-ketosteroid and 17-ketogenic steroids were found in two patients who were taking this antibacterial agent, frequently used in urinary tract infections. They were erroneously thought to have an adrenal tumor and one of them was even subjected to exploratory surgery in a vain attempt to find it. The spurious nature of the elevations was later documented, after it was realized that both patients were taking the same drug.

This example demonstrates the caution with which laboratory data must be interpreted. Many substances interfere with urinary steroid determinations (2) and it is therefore best to insist that, when possible, the patient abstain from all medication for an appropriate period of time before and while the specimen is being collected. A history of drug ingestion would also be a helpful thing to have at hand so that possible interferences with a true value may be anticipated and called to the attention of the physician ordering the test.

While it would not be appropriate at this time to mention all of the papers on the subject of drugs and laboratory values, or drug interactions, a few are important references in this area and must be mentioned. Caraway’s article (3) is a classic. Much of this data was rearranged and supplemented from other sources by Wirth and Thompson (4). Elking and Kabat (5) treated the material in a different tabular form, and Lubran (6) has presented a very complete discussion. An updated chart formulation of Lubran’s work was made available by the Boehringer Mannheim Corp. in July, 1970. Sunderman (7) addressed the material in an updated and supplementary form. The points are always made that caution is necessary and that either a pharmacist, laboratory person, or both should be aware of the possible pitfalls and call them to the attention of the attending physician. More recently it is suggested that computer technology will be required for storage and dissemination of information concerning known interactions. Perhaps prospective warnings might be forthcoming relative to potential interactions based on knowledge of the chemistry, pharmacology, and physiology of the agents to be used in a specific situation. Perhaps the reason for the expanding literature is the increasing number of new drugs, more widely prescribed, along with increased use of laboratory testing, frequently for screening.

A knowledge of the fate of drugs after administration is important. While drugs act on the body, the body likewise acts on the drugs. Metabolic changes may vary with different individuals and environmental conditions. Conney (8) points out that the metabolic effects of one drug on another are also of importance and not only may alter therapeutic dosage but may also alter some of the measurements of body fluid constituents. Duration and intensity of action of many drugs depends on the activities of drug-metabolizing enzymes in the endoplasmic reticulum of liver cells. These enzymes

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catalyze metabolism of drugs through many pathways—hydroxylation, dealkylation, deamination, sulfoxidation, glucuronide formation, and others. These enzymatic reactions may be synergistically or antagonistically affected by other drugs. Some of the metabolites have pharmacologic activity and may also be the agents responsible for spurious laboratory results.

A sequence of events in a drug interaction involving enzyme induction may be as outlined by Azarnoff and Hurwitz (9) and observed by most physicians who prescribe anticoagulant therapy: A patient who has a myocardial infarction is anticoagulated with warfarin. Accompanying apprehension and anxiety is treated with phenobarbital. The dosage of warfarin is adjusted each day according to the prothrombin time. Although it is noted that he requires more warfarin than many patients, the prothrombin time remains fairly constant in the therapeutic range. Upon discharge from the hospital, the patients barbiturate is discontinued, though the warfarin dose is kept the same. A few days later a severe hemorrhage from the nose or urinary tract is reported.

When phenobarbital was withdrawn, the stimulus to increased enzyme synthesis was removed and, consequently, the rate of warfarin inactivation gradually decreased. The warfarin level in the patient, which was adequate at the previous metabolic rate, gradually accumulated at the lower rate of metabolism and bleeding followed.

The metabolism of warfarin anticoagulants can be affected by many other drugs as well as barbiturates. Lubran (6) listed 36 specific drugs or categories that qualify, and there are others that have been reported since his compendium.

Robinson and Sylwester (10) reported that, at the Medical Center Hospital of Vermont, the patient on warfarin therapy receives on the average five other drugs during hospitalization. He has access to many more proprietary preparations at home. This only further points out the magnitude of the problem and the need for careful drug history data when unexplained laboratory aberrations are discovered.

Success as a sleuth is frequently rewarding to the patient. Recently a patient was referred for evaluation of a coagulopathy manifested by severe epistaxis. He had been hypertensive and part of his therapy was hydrochlorothiazide. No obvious reason was apparent for a prothrombin time of less than 10%. Nasal packs were placed, blood was transfused, and vitamin K was administered. When, upon request, his family brought the medicine bottles in, it was found that the pharmacist had inadvertently given the patient warfarin instead of hydrochlorothiazide. The patient dutifully took his pills without benefit of laboratory control until he bled; this could have had a much more serious outcome.

If many drugs have an effect on warfarin it could be expected that the reverse would also be the case. An example is the potentiation of tolbutamide by dicoumarol (a warfarin precursor) to produce hypoglycemia, first described by Kristensen and Hansen (11). Four diabetic patients who were on tolbutamide were given dicoumarol in quantities sufficient to depress the prothrombin level to a therapeutic range. Tolbutamide concentrations in the plasma then increased to about two to four times the control values and blood sugars decreased correspondingly. By observing that dicoumarol slowed the disappearance rate of tolbutamide from a half-life of 4.9 to one of 17.5 h, these authors related the increase in tolbutamide plasma concentrations to decrease in the rate of oxidation of tolbutamide in the liver in the presence of dicoumarol.

We have already discussed the barbiturates in relationship to warfarin. Other drugs interact with warfarin by other mechanisms. Phenytoin potentiates the action of warfarin by displacing it from binding sites on plasma protein. The result is a paradoxical situation in which, in spite of a more rapid turnover rate for warfarin, the pharmacologic effect from a given plasma concentration is greater, since there is more free drug available for this effect as well as for metabolism. Another mechanism by which the effectiveness of warfarin is altered is through a change in the availability of vitamin K to the liver enzyme system that synthesizes clotting factors. Antibiotics are thought to increase the sensitivity to warfarin by inhibiting bacterial synthesis of vitamin K in the intestine.

Warfarin preparations have been prominently in view in discussions and investigations concerning drug incompatibilities and cross reactions. There must be many other interactions of a more subtle or obscure nature taking place, of which we are unaware. The wide range of tolerance for many drugs and the lack of methods of measurement make their detection very difficult. The list keeps growing longer nonetheless.

Meador (12) has written of "The Art and Science of Nondisease." Some of what he said has applicability in the field of laboratory medicine and in relationship to drugs and their effect on laboratory determinations. Occasionally patients are referred for evaluation of a specific finding that on exhaustive investigation fails to reveal a disease entity. Dr. Meador calls this a "nondisease."

Among the broad categories of nondisease syndromes of interest to clinical chemists as described might be (a) upper-lower limit syndrome, (b) normal variation syndrome, and (c) laboratory error syndrome.

Familiar to all is the nonhypothyroidism in the patient who has a FTI of 2.5 μg/100 ml, who has been taking diphenylhydantoin (Dilantin), and
the nonhyperthyroidism in the patient on birth-control pills, who has a PBI of 10.5 mg/100 ml.

Laboratory-error syndromes are more unusual since the widespread use of proficiency testing and quality control programs. However, documented cases of nondisease in this sphere still do occur by the thousands and are the easiest things to cure. It needs only to have the test repeated once or twice.

Iatrogenic nonhyperthyroidism, accompanied by an abnormally high PBI, is well known to present itself after a variety of iodinated contrast media are used in x-ray procedures. Patients contribute by producing factitious nongastrointestinal bleeding, black stools caused by the iron salts in vitamin-mineral or bismuth preparations.

It follows that modification of laboratory test results by medications will continue to play an increasing role in producing patients who will require evaluation, and eventually will produce such things as nonpheochromocytoma, nonadrenal-cortical tumor, nonthyroid disease, noncarcinoid, nonpancreatitis, nondiabetes, nongout, nonrenal disease, and nonheart disease. All of these are especially apt to appear in massive screening centers where lab data frequently are collected out of context with history and physical evaluation.

Aberrations in the results of laboratory determinations caused by drugs clearly set traps that make it possible for all of us to do harm to humans who have come for help. We have never before been in a position to do so much good on the one hand or harm on the other because of the potent therapeutic agents available to us. It is therefore doubly important for all of us in the health field to remain alert and make every effort to point out the potential pitfalls to those who use our services.

References