Additive-Aggravated Assays: An Authoritative Answer

Immunoassay interferences are diverse in scope (1–8) and are the subject of several recent large-scale studies (9, 10), opinions, and editorials (6, 11). Most interferences originate from components of the sample (e.g., human anti-animal antibodies, lipid, bilirubin, drug metabolites) that interact with assay reagents or the detection system.

The latest interference to rear its ugly head has been an interference originating from an additive in a blood collection tube (12–14). In this issue of Clinical Chemistry, Remaley et al. (13) have extended their original work (12) on this problem and have now identified a common tube surfactant as the probable interferent. They show that Silwet™ L-720, an organosilane surfactant additive to Becton Dickinson Vacutainer® SST™ blood collection tubes, causes interferences by desorbing capture antibodies from the solid phase used in the Immulite total triiodothyronine immunoassay. This desorption effect was supported by sodium dodecyl sulfate–polyacrylamide gel electrophoresis and by immunoblotting analysis of Silwet™ L-720 eluates of the solid-phase antibody used in the Immulite assays.

Now that the source of this interference has been identified, a pertinent question is this: “How can this type of interference be detected in the future?”

Clearly, now that blood collection tube additives have been identified as a possible source of interference in immunoassays, manufacturers of blood collection tubes and immunoassay tests should implement additional quality-control measures. In addition, various control measures may be prudent in the clinical laboratory. One action could be increased vigilance of the running means of patients’ results, to detect an unexpected shift. However, this may be of limited or no use for endocrine assays because the range of patient values can be very large in the population tested (e.g., follicle-stimulating hormone concentrations in pre- and postmenopausal women vary over 10-fold and 100-fold ranges, respectively). Hence, there is a large spread of values that would obscure shifts in assay values caused by interference. Another action might be to adhere strictly to the basic tenet of quality control, namely, that the control sample should be treated in exactly the same manner as a specimen from a patient. In most, if not all, clinical laboratories, quality-control samples are poured from the bottle into an assay tube and then placed on the analyzer for analysis. Unlike the specimen from the patient, they do not encounter the contents of a blood collection tube. It would thus seem expedient to analyze samples of quality-control serum that have been poured into a blood collection tube and then processed along with patients’ specimens. Comparison of results for control sera that have and have not been exposed to blood collection tubes should reveal adverse effects resulting from additives in the tubes. This strategy would provide a means to detect future interferences resulting from changes in the formulation of additives in blood collection tubes. However, the diverse production lots of blood collection tubes used in various in- and outpatient locations also obscure lot-dependent interferences. It seems more feasible to have manufacturers expose quality-control sera to blood collection tubes on a lot-by-lot basis.

In the meantime, we need to remain vigilant for other immunoassay interferences. Nutritional supplements such as herbal medicines are widely used in the United States (15) and are a potential source of interfering substances that have not been thoroughly investigated. Indeed, assay interferences attributed to traditional Chinese medicines have already been reported in digoxin immunoassays (16–19). An additive-attributable assay aberration is not the first interference to be reported in immunoassays, and it certainly will not be the last.

References


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