

Avoiding Incorrect Laboratory Assay Results Caused by Paraproteins

Background

Paraproteinemia, also known as monoclonal gammopathy, is characterized by the presence of a paraprotein (a monoclonal immunoglobulin) in the serum due to the clonal proliferation of a cell of B-cell lineage. It is typically detected by the appearance of a single, well defined band in serum protein electrophoresis. Paraproteinemia occurs in a variety of conditions, including multiple myeloma, Waldenström's macroglobulinaemia, plasmacytoma, amyloidosis, and monoclonal gammopathy of undetermined significance (MGUS). The overall prevalence of paraproteinemia has not been rigorously studied; however, the prevalence of MGUS, the most common cause of paraproteinemia, is approximately 3-4% in individuals > 50 years old and 6-8% for those individuals > 80 years old. Approximately 70% of paraproteins are IgG, versus 15-20% IgM and 10-15% IgA (1).

Paraproteins present in serum can interfere in a variety of ways with a number of laboratory assays, leading to a range of incorrect laboratory results. These incorrect results can potentially lead to incorrect diagnoses, inappropriate treatments, longer hospital stays, and increased patient morbidity (2).

Paraproteins – Mechanisms of Interference

There are a number of ways in which paraproteins can lead to falsely elevated or reduced assay results (3):

- 1) The paraproteins may precipitate when exposed to assay reagents (typically acidic assay reagents). Precipitates can cause either positive or negative interference in assays employing turbidimetric or colorimetric detection methods.
- 2) Paraproteins can interfere with detection of analyte, either by inactivating assay reagents or by directly interacting with the analyte.
- 3) Paraproteins can increase the solid phase fraction of plasma, which can lead to a clinically significant negative interference in indirect sodium ion-specific electrode (ISE) methods (see CL11670 for an in-depth discussion of this issue).

Examples and Frequency of Paraprotein Interference

Paraproteins have been shown to interfere with routine automated methods for several chemistry analytes, leading to a variety of incorrect laboratory results, including the following:

- Falsely elevated phosphate (pseudohyperphosphatemia, ref 4-6)
- Falsely reduced phosphate (pseudohypophosphatemia, ref 7)
- Falsely reduced sodium (pseudohyponatremia, ref 8-10)
- Falsely reduced High-density lipoprotein (HDL) (pseudohypolipidemia, ref 2,11-12)
- Falsely elevated total and direct bilirubin (pseudohyperbilirubinemia, ref 2,11,13)
- Falsely reduced direct bilirubin (2),11,13)
- Falsely elevated calcium (pseudohypercalcemia, ref 14-15)
- Falsely reduced uric acid (16)
- Falsely reduced blood urea nitrogen (17-18)
- Falsely reduced creatinine (19)
- Falsely elevated creatinine (20)
- Falsely reduced thyroxine (21)
- Falsely elevated ferritin (22)
- Falsely reduced albumin (23)

The frequency of paraprotein-induced laboratory errors is variable and probably underreported (2,3,24). In one study, half of patients with paraproteinemia showed interference in phosphate assay (6). Paraprotein interference in laboratory testing is intermittent and unpredictable. It is seen in some patients, but not in others; in addition the severity of the interference can vary over time with a given patient. This unpredictability is further complicated by reagent / assay protocol modifications made by assay manufacturers, which can either minimize or exacerbate these interferences (3).

Avoiding Paraprotein Interferences Through Technology

One way to minimize the risk of incorrect laboratory results caused by paraprotein interference is to utilize assay technologies that are inherently less sensitive to this interference. VITROS® MicroSlide assays minimize the risk of paraprotein interference through a basic features of dry slide technology: the spreading layer, which removed paraproteins from a sample prior to the sample contacting the assay reagents, which are contained in subsequent slide layers (2,25). In many cases, VITROS MicroSlide assays have been shown in the peer-reviewed literature to protect against many of the incorrect laboratory results listed above, including pseudohyperphosphatemia, pseudohypophosphatemia, pseudohyperbilirubinemia, pseudohypobilirubinemia, pseudohyponatremia, and pseudohypolipidemia (2-3). The VITROS® MicroSlide spreading layer should also protect against many other incorrect laboratory results including falsely low or falsely elevated creatinine. Some VITROS® MicroSlide assays are not susceptible to the listed incorrect laboratory results simply due to the fact that they employ a reaction scheme that protects against paraprotein interference (3); however, this is more by chance than by design, as paraprotein interference is already minimized by the spreading layer, a basic design feature of the technology.

In a similar manner, the VITROS® MicroWell heterogeneous immunoassay technology (26) should minimize the risk of paraprotein-associated incorrect laboratory results (such as falsely reduced free T4) that have been observed with homogenous immunoassay formats (3,25).

Paraproteins can interfere with homogenous methods either by generating false signal through precipitation or by coating latex particles and directly interfering with the interaction of the binding antibody and the analyte of interest. In contrast, VITROS® MicroWell technology is inherently less prone to paraprotein interference because it is a heterogeneous immunoassay method that does not use latex beads and does not employ turbidity as a detection methodology.

Summary

Paraproteinemia is a common condition, affecting 3-4% of individuals > 50 years old and an even higher proportion of the elderly population. Paraproteinemia can interfere with a number of chemistry assays, typically by either: 1) forming precipitates that lead to false reading in assays that employ turbidity or colorimetry or 2) interfering with the detection scheme, either by binding to the analyte of interest or by binding to an assay reagent. Homogeneous assays are particularly susceptible to this interference, which can lead to both incorrectly elevated and incorrectly low laboratory results for a variety of analytes. The basic design of most VITROS® MicroSlide and MicroWell assays minimizes the risk of incorrect laboratory results due to paraprotein interference. In the case of MicroSlide assays, this is primarily due to the spreading layer, which removes paraproteins prior to the sample contacting assay reactants. In the case of MicroWell assays, the potential for paraprotein interference is minimized by: 1) the heterogeneous design of the assays and 2) the use of chemiluminescence-based detection (rather than turbidity or colorimetry).

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