To the Editor:

All Bayer ACS:180® and ADVIA® Centaur™ system chemiluminescent immunoassays are evaluated during product development for performance characteristics based on specimen collection tube type, anticoagulant, and sample handling. Recommendations are reported in the product inserts in the Specimen Collection and Handling section. The approved specimen types for the ACS:180/ADVIA Centaur CKMB II, Troponin I, and myoglobin assays are serum and heparinized plasma. EDTA plasma was evaluated and is not approved for these tests. In paired specimen studies of the CKMB II assay, we observed ~20% positive bias between heparinized plasma and serum. For the cTnI assay, we also report a negative bias of ~16% for heparinized plasma compared with serum. These biases are reported along with NCCLS sample handling and storage guidelines, which when rigorously followed minimize errors attributable to pre-analytical variables (1). The authors are correct in noting that the small variations in the four cases cited for cTnI are well within the 95% confidence intervals of the reported precision of the test (total CV of 6.7% at 1.4 μg/L).

We also clearly recommend that heparinized plasma and serum from the same patient not be used interchangeably in testing, especially when repeat samples and serial profiling are the accepted testing protocol for confirming diagnosis. Good laboratory practice suggests that for an individual patient and study series, sample collection should be uniform regardless of whether there is a bias between sample collection types.

We support the National Academy of Clinical Biochemistry’s guidelines regarding the necessity of serial sampling of several cardiac markers at defined time intervals to most rapidly and accurately rule in or rule out acute coronary syndromes (2). As long as sample handling is the same on repeat testing, the linear relationship (r = 0.995) between serum and heparinized plasma makes any bias inconsequential with regard to obtaining an accurate diagnosis.

References


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High and Higher Sensitivity CRP

To the Editor:

The article by Roberts et al. (1) provided interesting data on automated methods for C-reactive protein (CRP) determinations. The inclusion of the Beckman Coulter IMMAGE® method was inappropriate because the company has made no claims regarding “high sensitivity” CRP in its labeling. We currently list our usable range for the method as 1.0–960 mg/L.

Furthermore, Beckman Coulter is planning to introduce a higher sensitivity CRP assay in the near future. We do not want your readers to be confused by referring to the currently available IMMAGE method as “hs-CRP”.

Reference


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Measurement of Total Protein Is Not a Useful Inclusion in Liver Function Test Profiles

To the Editor:

Biochemical and hematological pathology investigations often are requested using groupings or profiles of tests. In Australia, “liver function test” (LFT) is recognized by legislation (1) and consists of six or more tests, including alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, albumin, (total) bilirubin, γ-glutamyl transpeptidase, lactate dehydrogenase, and (total) protein. Historically, although total protein has been included as a part of LFT, the total protein measurement is not specific for abnormal liver function or liver damage. We have examined whether the routine inclusion of total protein as a component of LFT leads to new diagnoses or alters patients’ clinical management.

At the time of this study, our laboratory primarily serviced a large, tertiary referral university teaching hospital. Total protein was measured using the Biuret method (2) on a Hitachi 747 analyzer (Boehringer-Mannheim/Roche Diagnostics). Using a computer, we examined 15,000 consecutive unselected requests, including ambulatory and hospitalized patient populations.
patients, received by our laboratory over a 3-month period in which the requesting clinician had specified (among other things) that a “LFT” biochemical profile was to be performed. From this sample population of 15,000 LFT requests, we selected all cases in which the total protein was greater than the upper reference limit of 83 g/L. We found 247 samples whose total protein was increased, drawn from 207 different patients. The medical records and histories of 206 of these 207 patients could be located. For each patient, we noted the provisional diagnosis before investigation and the final diagnosis after the results of the LFT and any other investigations performed were known. We specifically noted whether a diagnosis of paraproteinaemia, myeloma, collagen disorder, chronic infection, inflammation, or any liver disease had been recorded. We also noted whether the increased total protein result changed clinical management, and we specifically noted whether subsequent investigations for protein electrophoresis (PEPG) or immunoelectrophoresis (IEPG) had been performed or requested as a result of the increased total protein.

Three of the 206 patients were found to have a prior known monoclonal gammopathy, confirmed by a diagnostic PEPG and IEPG. The medical records of these three patients noted that the abnormal total protein reported as part of the LFT request was consistent with the prior known diagnosis. One of the 206 patients had a new diagnosis of myeloma, based on a biopsy of a mandibular mass. PEPG and IEPG were specifically requested to support this new diagnosis and to identify and characterize the immunoglobulins and light chains; the increased total protein was reported subsequent to the above investigations and did not contribute to a new diagnosis. In 11 cases, a PEPG and IEPG had been requested as a result of the increased total protein, but a nondiagnostic polyclonal increase in immunoglobulins was found. In the final 191 subjects, no diagnostic action was taken as a result of the increased total protein.

The most significant clinical diagnosis expected from the detection of an increased total protein is one associated with a paraproteinaemia, such as myeloma. Although we found subjects in our series who had myeloma or monoclonal paraproteins, we found no new diagnoses of myeloma or other conditions associated with a paraproteinaemia, the diagnosis of which could be attributed to the measurement of total protein as part of the routine LFT. Although in 11 cases in our large series management was affected by the finding of an increased total protein and led to further investigation by PEPG and IEPG, these represented “false” positives because none were subsequently shown to have a paraprotein.

One possible reason for the failure to detect new cases of paraproteinaemia might be that our sample population was subject to ascertainment bias. We reasoned that patients with high total protein might be detected in a primary care setting and that only those already diagnosed and under treatment and with reduced total protein were actually referred to our tertiary referral institution. We tested and excluded this possibility by examining the total protein values found in newly diagnosed patient samples specifically submitted for PEPG and IEPG testing; we found that many of these patients did indeed have a total protein at time of diagnosis that was above our upper reference limit. We also calculated that, for our hospital population, the proportion of patients with a new diagnosis of myeloma or significant paraproteinaemia was 1.5–2% (calculations not shown), consistent with the predicted incidence (3). However, by auditing only patients with an increased total protein estimation, we cannot exclude the possibility that we might have missed those with a low albumin fraction, increased globulin fraction, and total protein within reference values.

We conclude that, although not seeking to exclude ready access to total protein for the investigation of patients in whom a paraprotein is suspected, the routine inclusion of total protein in LFT does not appear to contribute to clinical management. Even if total protein analysis adds only the marginal cost of the chemical reagents to the total cost of investigations, extrapolating these data to the whole of Australia (4) produces the predicted expenditure of $1.2 million (Australian) for unnecessary testing for this one investigation alone, and even this figure ignores the costs of additional investigations (such as PEPG and IEPG) arising from spuriously increased total protein detected in patients for whom myeloma is not present.

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References


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