measured prolactin concentration depends on the choice of reagent antibody. Because the presence of macroprolactin does not appear to contribute to the hyperprolactinemic syndrome in the majority of patients, it is important to raise awareness of the problem in clinical chemistry laboratories and with physicians. We recommend that manufacturers of prolactin reagents state in their product leaflets to what extent macroprolactin interferes in their prolactin assay and have available a validated method to confirm the presence of macroprolactin. It is also important that manufacturers address the problem with prolactin assays to minimize reaction with macroprolactin. In the meantime, polyethylene glycol (PEG) precipitation has been shown to be a valid screening test for macroprolactin when used with the Wallac DELFIA assay (2). It cannot, however, be used for all methods because of interference from PEG, and it needs to be validated with other assay systems before being brought into use.

Confirmation of the presence of macroprolactin can be made by gel filtration chromatography, but this is time-consuming, costly, and beyond the scope of most clinical laboratories. Laboratories in the United Kingdom have been using mainly PEG precipitation techniques to identify macroprolactinemia, but we urge equipment manufacturers to address this problem. As highlighted in these two clinical cases, macroprolactin needs to be identified early in a patient’s work-up to avoid unnecessary, costly, and invasive procedures.

References

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Plasma Ferritin in Acute Hepatocellular Damage

To the Editor:

Plasma ferritin concentrations are increased in iron overload, liver diseases, infections, inflammatory conditions, and malignancy. Very high concentrations (>10 000 μg/L) have been described in Still disease (1) and less commonly in hemochromatosis. There are very few reports of ferritin concentrations in patients with acute hepatocellular damage (AHD). A review of extreme increases in ferritin found that liver disease was the cause of 20% of cases but did not specify actual concentrations seen and did not differentiate acute and chronic liver disease (2).

We have determined ferritin concentrations in AHD patients.

Plasma ferritins were measured in eight patients who had plasma alanine aminotransferase (ALT) values <100 U/L pre-AHD and >1000 U/L post-AHD. ALT, iron, and transferrin were measured on a Hitachi 917 (Roche Diagnostics), and ferritin was measured on the ACS:180 (Bayer Diagnostics).

The results for individual patients are shown in Table 1. In one patient, serum ferritin did not exceed the upper limit of the reference interval during AHD. This patient was iron deficient with a basal ferritin of 22 μg/L.

The plasma ALT increased from a basal mean (SD) of 45 (29) U/L to 2970 (1540) U/L during AHD, and ferritin increased from 200 (130) μg/L to 18 260 (17 860) μg/L. The mean plasma iron increased from 12 (11) μmol/L to 16 (19) μmol/L, transferrin decreased from 27 (11) μmol/L to 22 (7) μmol/L, and transferrin saturation increased from 18% (7%) to 31% (30%).

The rapid increase in ferritin in AHD suggests that ferritin is present in the cytosol of the hepatocytes. There was significant (P<0.01) correlation between the increase in ALT and ferritin in AHD. Despite the marked increase in ferritin in five of six patients in whom iron and transferrin were measured, the transferrin saturation increased above the reference interval in only one of these patients.

In conclusion, ferritin concentrations were markedly increased after AHD and are of no diagnostic value during this time. These data imply that ferritin and ALT are present in the cytosol of the hepatocytes.
To the Editor:

Oral Anticoagulant Treatment in Thromboembolic Patients Undergoing FII G20210A Gene Mutation in Prothrombin (FII) because many carriers of the FII20210A mutation have hyperprothrombinemia by functional assays. However, increased FII does not specify for this mutation (1, 3, 6). Even some carriers do not exhibit hyperprothrombinemia because of the variability in vitamin K metabolism or hepatic function. A functional, rapid, low-cost assay, preferably not influenced by the oral anticoagulant (OA) (7) required by many patients, would be desirable for screening purposes. Because factor X (FX) has a half-life close to that of FII, we used FX activity to control for changes in concentrations of vitamin K-dependent factors. The ratio of FII activity to FX activity (FII/FX) was used to screen for subjects with high FII activity during OA therapy. We studied 123 outpatients objectively diagnosed with venous thromboembolism (59 men and 64 women; mean age, 63 years; range, 17–87 years) to identify a reliable screening test for this genetic anomaly. All were receiving OA (120 were receiving acenocumarol, and 3 were receiving warfarin). Informed consent was required. The mean international normalized ratio (INR) was 2.43 (0.76) with 66% of the patients in the therapeutic range (INR, 2.0–3.5) at the time of sampling. The INR range was 1.3–2.0 in 26% of the patients, and none had an INR >4.5. The subjects were classified as carriers and non-carriers after a standard PCR assay for this prothrombin mutation (1).

For the standard functional clotting tests (FII:C/FX:C), we avoided the large oscillations in the INR (especially during the first month of anticoagulant therapy). We used deficient plasmas and recombinant thromboplastin (Innovin®) from Dade-Behring® on a Sysmex® CA-6000® coagulometer. We calculated the imprecision for plasmas with an equivalent range of activity (<500 units/L). The intraassay CVs were 4.0% and 2.5%, and the interassay CVs were 4.6% and 3.0% for the FII and FX activities, respectively.

During OA therapy, FII:C remains higher than FX:C (8). We observed activities of 320 (120) vs 160 (90) units/L, respectively (P <0.0001). The FII20210A allele was identified recently been associated with venous thromboembolism in a Dutch population (1). The prevalence of this genetic variation in Western countries is 5–15% among thrombotic patients and 1–5% in healthy controls (2–5). The main pathogenic mechanism appears to be the increase of plasma prothrombin (FII) because many carriers of the FII20210A mutation have hyperprothrombinemia by functional assays. However, increased FII does not specify for this mutation (1, 3, 6). Even some carriers do not exhibit hyperprothrombinemia because of the variability in vitamin K metabolism or hepatic function. A functional, rapid, low-cost assay, preferably not influenced by the oral anticoagulant (OA) (7) required by many patients, would be desirable for screening purposes. Because factor X (FX) has a half-life close to that of FII, we used FX activity to control for changes in concentrations of vitamin K-dependent factors. The ratio of FII activity to FX activity (FII/FX) was used to screen for subjects with high FII activity during OA therapy.

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