The Appropriate Use of Diagnostic Services (VI) Which Biochemical Liver Tests should We Use ?

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INTRODUCTION

"From the clinical point of view current tests of liver efficiency are disappointing. In a small proportion of cases only do they add information of value. Since bilirubin is a coloured compound estimations of blood bilirubin are not so essential in liver diseases as are estimations of blood urea in kidney diseases. The writer's routine practice is to examine thoroughly the urine and to determine bilirubin in the serum. In jaundice the presence and degree of obstruction is judged from the appearance of the faeces, coupled with tests for stercobilinogen when necessary. All other tests could be scrapped probably with advantage".[1] Forty years and many other suggested tests of liver function later, are these comments still valid? Do we need a plethora of investigations to determine the origin of jaundice in a patient when the cause can be determined by techniques other than those used in the chemical pathology laboratory ? Does the elderly patient with pale stools need intensive chemical pathology investigations before being referred for imaging techniques or do serum tests reduce the need for these expensive investigations ? Is the referring doctor more confident because he has numbers to support his clinical judgement ? The continuing concern about the cost of pathology services and the difficulties in coping with an increasing workload with inadequate funding means that requesting patterns must be critically examined. Heads of chemical pathology departments must educate their users as to which are the most efficient liver tests to cover all their demands.

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Many biochemical tests have been introduced which are said to assess liver "function" — an inaccurate term. Some liver tests currently in use, for example aspartate aminotransferase, can detect cell injury or the response to injury while others, for example serum bilirubin, indicate impairment of a particular aspect of liver function. The role of biochemical investigations in liver disease must be viewed in relation to the history and examination of the patient and what imaging techniques are available for further investigations. Dame Sheila Sherlock has stated "a few simple tests of established value should be used"[2] but Solberg Skrede and Rootweld[3] used 22 clinical chemistry tests, 4 immunological tests and 2 calculated ratios from the Oslo field study to identify efficient combinations of laboratory tests. It is unusual for laboratories to offer so many liver tests, so what tests should be offered by a clinical chemistry laboratory to satisfy the requirements of its various users ?

AVAILABLE TESTS

Liver tests are used to determine the presence of hepatobiliary disease, to try and establish a diagnosis, to estimate the severity of the disease, to assess prognosis and to evaluate therapy. The tests offered by a laboratory should be able to help its general practitioner users as well as the consultant gastroenterologists.

The question usually asked by the primary care specialist is whether anything is wrong. Liver tests should therefore be sensitive, i.e. the test should be positive in the setting of disease; ideally they should also be specific, i.e. negative in the setting of non-disease. Many liver tests have been introduced in the hope that they fulfil these criteria, but those which have proved most useful are total serum

bilirubin, alkaline phosphatase, γ-glutamyltransferase, aspartate aminotransferase, total protein and albumin. In the absence of clinical suspicion it is unlikely that a patient has hepatobiliary disease if the results of these tests are normal. If there is suspicion of hepatobiliary disease it is often possible also to exclude disease if the results are normal.

Serum Bilirubin

Jaundice is often the presenting sign which causes patients to see a doctor. Jaundice can be classified as prehepatic, hepatic or cholestatic[2]; liver tests can assist the clinician to classify the jaundice, thus assisting in diagnosis and management.

Prehepatic jaundice may be due to haemolysis or familial disturbances of bilirubin metabolism, for example Gilbert's syndrome. In general practice it is not unusual to find in symptomless patients a slightly elevated serum bilirubin but results of the three enzyme tests and the plasma proteins are within the reference range. In these patients no further tests to detect hepatobiliary disease need be performed (assuming haemolysis has been excluded). Greater sensitivity in detecting hepatobiliary disease has been claimed for serum bile acid measurement (fasting and post-prandial) and for the bromsulphalein excretion rate. The prothrombin time has also been suggested, but it is an insensitive test of liver cell damage.[4] These tests add little if anything to the enzyme tests listed above in detecting minimal cell damage. Symptomless patients with a mildly elevated serum bilirubin and other tests within the reference range are usually said to have Gilbert's syndrome. However, a total serum bilirubin level higher than 80 μmol/l does indicate impairment of hepatic excretion of bilirubin whatever the cause of the jaundice.

Cholestatic jaundice is due to failure of adequate amounts of bile to reach the duodenum. Elevated conjugated (direct reacting) bilirubin is found in cholestatic and hepatic jaundice and is supposed to distinguish these types of jaundice from haemolytic jaundice, but conjugated bilirubin as conventionally measured has recently been shown to be a mixture of forms having different reactivities with the diazo reagent, and this measurement should be discontinued. The same is true for its use in assessing the need for exchange transfusion in neonatal jaundice; the newer technique of high pressure liquid chromatography may be necessary to distinguish between the forms. Measurement of non-protein-bound bilirubin and of the reserve binding capacity for bilirubin in infant sera[5] are also unreliable since the basic premise that only unconjugated bilirubin binds reversibly to albumin has been shown to be untrue.

Alkaline Phosphatase

Alkaline phosphatase in serum is heterogeneous[6]: the enzyme can originate in liver, bone and the small intestine. Placental alkaline phosphatase becomes detectable in the serum of pregnant women between the 16th and 20th week of pregnancy. Carcinoplacental alkaline phosphatases occur in the serum of 3–15% of patients with cancer, depending on the sensitivity of the methods used.

The enzyme is elevated in more than 90% of patients with hepatic disease. The test lacks specificity for liver disease, but an elevated alkaline phosphatase together with a raised bilirubin suggests hepatobiliary disease. Measurement of the γ-glutamyltransferase ir addition to alkaline phosphatase increases the specificity of the combined tests. An alkaline phosphatase greater than three times the upper limit of the reference range together with elevated γ-glutamyltransferase and bilirubin levels suggests cholestasis. If the bilirubin is normal the elevated enzyme levels may indicate hepatobiliary disease, for example a tumour, partial obstruction or stone in an intrahepatic duct. This pattern of results is also consistent with hepatic steatosis.

Isolated observations of a raised alkaline phosphatase can cause diagnostic problems because of the lack of specificity for liver disease; then, electrophoresis of the serum to identify the source of the alkaline phosphatase can help. This isoenzyme analysis is unnecessary if the other enzyme results indicate cholestasis.

The alkaline phosphatase level is always difficult to interpret in growing adolescents because it is usually higher than the adult reference range. If hepatobiliary disease is suspected in this age group electrophoresis to demonstrate isoenzymes may show the presence of liver alkaline phosphatase in addition to the normal elevated bone alkaline phosphatase.

γ-Glutamyltransferase[7]

This enzyme is a sensitive index of hepatobiliary dysfunction, but this sensitivity is marred by a lack of specificity: the serum level of the enzyme is increased in various clinical conditions, for example in diabetes mellitus and after a myocardial infarction, and by many drugs, including anticonvulsants and alcohol. γ-Glutamyltransferase is of little value in the differential diagnosis of hepatobiliary disease. Elevation of the γ-glutamyltransferase only, with normal bilirubin and alkaline phosphatase levels, suggests drug induction of the enzyme. If the alkaline phosphatase is also elevated, hepatobiliary disease must be suspected.

Aspartate Aminotransferase

The aminotransferase are conventionally determined as part of a "liver profile" but it is better practice to measure aspartate aminotransferase alone. The enzyme is a sensitive indicator of hepatocellular necrosis but it is not specific for liver disease: elevated levels are found for example after myocardial infarction and in myositis.

Plasma Proteins

An elevated level of globulins suggests a chronic liver disease; if there is also moderate elevation of asparate aminotransferase this suggests chronic active hepatitis or cirrhosis. Further help may be given by the electrophoretic pattern of the serum proteins. There is no need to scan each strip with a densitometer; this adds nothing to the report of an experienced observer. In liver disease the pattern is almost always a polyclonal gammopathy, sometimes with bridging between the beta and gamma regions. IgM is often elevated in primary biliary cirrhosis, IgA in alcoholic cirrhosis and IgG in chronic active hepatitis and cryptogenic cirrhosis, but their predictive value in liver disease is poor.

The measurement of a number of other proteins may be helpful in suspected liver disease. α1-Antitrypsin measurement may confirm suspected cirrhosis in childhood, and caeruloplasmin determinations can detect Wilson's disease in a suspected chronic active hepatitis. High serum α-foetoprotein will confirm suspected hepatoma.

Lactate dehydrogenase

This enzyme, another sensitive indicator of cell damage, is not specific for liver disease and should not be included in any liver tests. Fractionation of its isoenzymes, contrary to many claims, yields no further useful information in the diagnosis of hepatobiliary disease.

Tissue Antibodies

These insensitive and non-specific tests are of little value in the investigation of liver disease.

Viral Markers

Screening of blood for hepatitis B markers is justified only in "high risk" patients with jaundice: those who have been treated with blood or blood products, patients from areas known to have a high incidence of hepatitis B, intravenous drug abusers and male homosexuals.

The tests described indicate the presence and sometimes a diferential diagnosis of hepatobiliary disease. Tests outside the laboratory are then often required to complete the diagnosis: for example ultrasound to determine whether the bile ducts are dilated in cholestasis, endoscopic retrograde cholangiopancreatography and percutaneous transhepatic cholangiography to investigate extrahepatic cholestasis, and liver biopsy to investigate hepatic disease.

CONCLUSION

This article was written in response to the question of what liver tests should be performed. The question cannot be comprehensively answered for all doctors using the laboratory: the general practitioner may need to know whether disease is present whereas the consultant often needs help in determining the type and severity of disease and also in monitoring treatment. These needs are best met by providing a number of tests (serum bilirubin, alkaline phosphatase, γ-glutamyltransferase and aspartate aminotransferase) to detect or exclude disease and further tests such as immunoglobulins and specific proteins to help determine the cause of the liver disease.

There have been many tests of liver "function" in the past. Many such as sorbitol dehydrogenase,

leucine aminopeptidase and the galactose tolerance test are of historical interest. Much effort has been made to try and use biochemical liver tests for diagnosis of disease particularly by discriminant analysis[8] rather than "instinct". The impact of decision analysis in interpreting liver tests has yet to be fully explored but in future, newly recommended liver tests (and those currently used) must be subject to analysis using receiver operating characteristic (ROC) curves which are plots of the true positive rate against the false positive rate of a test. Budgetary pressure will force heads of departments to use these techniques to determine the cost effectiveness of investigational programmes[9]. It is only by critical evaluation of tests offered and requests received that we can hope to provide the best possible service within a limited budget.

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