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Dynamic tests to study liver function

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Abstract. – **Two approaches have generally been used to assessing liver function: one is to measure the products of liver synthesis, the other is to monitor hepatic clearance function. The exogenous dyes that can be used to study liver function are sulphobromophthalein (BSF) and indocyanine green (ICG). One valuable way to measure hepatic function is to use non-toxic substances (stains, sugar, drugs) that are selectively metabolized by the liver and determine the rates of metabolism of these substances in vivo. The antipyrine clearance test is the most common and correlates well with the degree of liver damage. The caffeine clearance test is beneficial in severe liver lesions, but practically useless in the case of moderate liver damage.**

The galactose clearance test can be used early in the clinical course of jaundice to distinguish between hepatocellular disease and biliary obstruction.

The MEGX test is useful as a real-time method for quantitatively assessing pre- and post-transplant liver function.

In short, quantitative liver function tests are not suitable for use in screening for liver disease. They are more complex to perform and more expensive than conventional biochemical tests, but superior in monitoring the degree of liver dysfunction.

Key Words:

Liver, Sulphobromophthalein, Indocyanine green, MEGX, Antipyrine, Caffeine.

Introduction

The main functions of the liver are the clearance, metabolism and excretion of endo- and xeno-biotics, and the synthesis of biologically important compounds, such as clotting factors and albumin[1].

Two approaches have generally been used to assessing liver function: one is to measure the products of liver synthesis, the other is to monitor hepatic clearance function. The different approaches depend on organ perfusion and extracts, and both may be modified by the presence of liver disease. The key determinants for enabling hepatic function are the functional portions of hepatocytes and blood-liver exchange.

Specific liver function determination can include measuring the capacity to transport organic anions, as reflected by serum levels of bilirubin or bile acids, or by the rates at which exogenous dyes are metabolized. The metabolic capacity of the liver is measured by the clearance of drugs, or by the liver's capacity to synthesize urea or eliminate galactose.

Organic Anion Transport

The liver has the ability to remove lipophilic molecules from the plasma and excrete them, unchanged or after polar conversion, in the bile. The exogenous dyes that can be used to study liver function are sulphobromophthalein (BSF) and indocyanine green (ICG).

The use of a phthalein dye to investigate hepatic function was first suggested by Roundtree in 1913[2].

BSF is completely soluble in water and, when injected intravenously, it binds to plasma proteins (albumin and α_1-globulin)[3], then interacts with hepatocyte plasma membrane receptors[4]. The arrival of protein-bound BSF is followed by a rapid build-up of BSF in the liver, where the dye is conjugated with glutathione[5] and then excreted in the bile.

The standard BSF test involves injecting 5 mg of BSF/kg body weight as a 5% aqueous solution into the vein of one arm, sampling venous blood from the other arm after a preset time.

The dye is assumed to become distributed only in a plasma volume of 50 ml/kg body weight.

Percentage retention is calculated as the concentration in the plasma after 45 minutes divided by the assumed zero-time concentration (10 mg/dl) multiplied by 100.

Ten percent plasma retention of BSF at 30 minutes and 5% retention at 45 minutes are frequently considered to be the upper limits of normal.

There is no significant difference between males and females in the results of standard BSF retention tests when adjusted for lean body weight or surface area, despite the greater hepatic storage capacity and Tm in males[6].

Numerous factors can affect BSF test results: a drop in plasma albumin or a displacement of BSF due to protein binding by other drugs can increase hepatic clearance[7,8]; moreover, BSF removal from the plasma is closely associated with hepatic blood flow.

This is a valuable test, but it of limited clinical use in the routine diagnosis of hepatobiliary disease.

It is nonetheless the procedure of choice in the precise definition of any hepatic organic anion transport defect, e.g. congenital conjugated hyperbilirubinemia: in Dubin-Johnson syndrome, Tm is near zero[9,10], whereas in Rotor's syndrome the storage capacity is markedly reduced[11,12].

Because of their sensitivity, BSF tests have been recommended for detecting subclinical hepatic dysfunction before other test results become abnormal. The test results are not helpful in predicting the clinical course of the disease, however.

The ICG test was recommended for measuring blood flow in 1957, given the good recovery of the dye in bile[13]; ICG binds more avidly to plasma proteins than BSF, resulting in a more predictable distribution volume; it is excreted unchanged in the bile and is unaffected by any changes in the bioconversion processes.

The standard ICG test involves the intravenous injection of 0.5 mg/kg ICG, measuring a single blood level 20 minutes later. Plasma levels of ICG can be determined directly by spectrophotometry.

Since there is less non-hepatic removal of ICG than of BSF, plasma levels of ICG should reflect hepatic uptake more accurately, thus enhancing the discriminatory ability of a standard, single-injection, single-sample test.

But because of ICG's greater clearance by the liver, its sensitivity in detecting minimal hepatic dysfunction may not be as good as that of the BSF test.

Hepatic Metabolic Capacity

One valuable way to measure hepatic function is to use substances that are selectively metabolized by the liver and determine the rates of metabolism of these substances in vivo. Orally or parenterally administered exogenous, non-toxic substances (stains, sugar, drugs) are used. They are metabolized exclusively in the liver and may be detected in blood, saliva and expired air. Based on pharmacological principles, we know that drugs that have a low intrinsic hepatic clearance have elimination features determined primarily by the functional mass (metabolic capacity) of the liver, regardless of any hepatic blood flow alterations.

The antipyrine clearance test is the most common and correlates well with the degree of liver damage expressed using Child's classification. Its disadvantage lies in that it correlates poorly with "in vivo" loading of the liver's microsomal capacity, while its metabolism is influenced by age, diet, alcohol consumption, smoking and toxic substances.

The caffeine clearance test is beneficial in severe liver lesions, but practically useless in the case of moderate liver damage.

The galactose elimination test: the disappearance of galactose from the blood is the result of its rapid phosphorylation inside hepatocytes. Generally speaking, a bolus dose of 350 mg/kg of galactose is used. At this dose, galactose serum levels are low and its elimination is primarily a reflection of hepatocellular metabolic capacity[14]. Abnormal clearance was frequently seen in patients with metastatic liver neoplasms (50% abnormal), cirrhosis (48% abnormal), and hepatitis (58% abnormal), but rarely in obstructive jaundice (7% abnormal)[15]. The galactose clearance test can be used early in the clinical course of jaundice to distinguish between hepatocellular disease and biliary obstruction. However, the numbers of patients studied have been insufficient to enable any firm conclusions on its clinical usefulness.

The MEGX test is useful as a real-time method for quantitatively assessing pre- and post-transplant liver function. This test con-

sists in measuring MEGX formation after intravenous lidocaine, which depends on the activity of the hepatic cytochrome P-450, that catalyses oxidative N-demethylation lidocaine. MEGX determination may be a useful test for selecting potential donors for liver transplantation[16,17]. Graft survival is considerably extended when the donor's MEGX test is > 90 ug/L. Seven days after transplantation, this test correlates significantly with the number of rejection episodes. By comparison with standard liver tests, the MEGX test is highly sensitive (82%) and specific (80%) in distinguishing chronic hepatitis from cirrhosis[17-19].

In short, quantitative liver function tests are not suitable for use in screening for liver disease. They are more complex to perform and more expensive than conventional biochemical tests, but superior in monitoring the degree of liver dysfunction.

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