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Conventional liver tests (serum bilirubin, alanine and aspartate aminotransferases, alkaline phosphatase) only assess presence of hepatobiliary injury, and do not answer the question ‘How much of the functional liver mass is still left?’ The tools that answer this are tests for quantitative liver function. These tests are believed to be true dynamic liver function tests as they are based on uptake, metabolism, and excretion of a particular substance. Such tests have several possible uses: to define the residual liver function, to follow up the course of liver disease, to assess prognosis in patients with acute or chronic liver disease, to predict the surgical risk and postoperative course in patients with liver disease, and to determine an optimal time for liver transplantation.

An ideal quantitative liver function test should be inexpensive, easy to perform and interpret, safe, and have a high predictive value. The agent used for such a test should have a single pharmacokinetic profile with minimal drug interactions. Unfortunately, the available tests do not fulfill all these requirements and are still quite crude.

Quantitative liver function tests are broadly of two types: those based on elimination of a substance (e.g., indocyanine green clearance test, caffeine clearance test, and galactose elimination test) and those measuring metabolite(s) of an administered substance (aminopyrine breath test and monoethylglycinexylidide [MEGX] test). Hepatic clearance of a substance can be estimated by measuring its concentrations in the blood entering and leaving the liver during a steady state. Thus, hepatic clearance = Q.(Ca-Cv)/Ca = Q.E, where Q is the hepatic blood flow rate, and Ca and Cv are the concentrations of drug in the blood entering and leaving the liver, respectively. ‘E’ represents the steady-state hepatic extraction ratio, with high E values indicating greater clearance of the substance by the liver.

The above equation indicates that hepatic clearance of a substance is a function of the liver blood flow (Q) and extraction ratio of the substance (E). For substances with high total intrinsic clearance, such as antipyrine, caffeine and lidocaine, hepatic clearance becomes relatively independent of the hepatic blood flow. For these substances, changes in free intrinsic clearance and/or binding of the test substance to blood constituents are more important determinants of the overall hepatic clearance. Hepatic clearance of such substances is thus controlled by the intrinsic clearance capacity of the liver and is said to be ‘capacity-limited’. Thus, quantitative liver tests such as the indocyanine green, sorbitol and galactose clearance tests depend mainly on hepatic perfusion, whereas others such as galactose-elimination capacity and aminopyrine demethylation depend primarily on functional capacity of the liver.

The MEGX test is a relatively newer and commonly used quantitative liver function test. In humans, cytochrome P450 enzyme CYP3A4 catalyzes the hepatic conversion of lidocaine to its metabolite MEGX. The test is done by injecting 1 mg/Kg lidocaine intravenously and measuring serial serum MEGX concentrations before and up to 60 min after the injection. The concentration generally rises from 0 to 15 min, and remains relatively unchanged thereafter. Because of the relatively high extraction ratio of lidocaine, this test depends on both hepatic metabolic capacity and hepatic blood flow.

The use of lidocaine and MEGX to assess liver function was first proposed by Oellerich et al in 1987. They found that the MEGX concentration obtained 15 min after lidocaine injection was substantially lower in patients with liver cirrhosis; further, it correctly predicted the success or failure of liver transplantation in most cases. Since that report, several studies have assessed the value of this test in determining the liver function in donor and transplanted livers, with variable results. Studies on patients with cirrhosis and viral hepatitis and in children with liver disease have found some merit in the MEGX test for assessing synthetic liver functions.

The production of MEGX from lidocaine declines stepwise with the severity of chronic hepatitis. In patients with cirrhosis, MEGX production declines with worsening Child class. Shiffman et al reported that nearly all persons with MEGX value of <20 ng/mL had liver cirrhosis at histology. One-year su-
vival rates for patients with MEGX values of <10 and >10 ng/mL were approximately 50% and 80%, respectively. Thus, MEGX may be used as a test of the synthetic capacity of the liver, and to predict morbidity and mortality related to chronic liver disease. Serial MEGX estimations may be useful to assess the functional and metabolic capacity of the liver in patients with chronic hepatitis and cirrhosis. Women have a lower concentration of MEGX at 15 min than men, which is further reduced with oral contraceptive intake. The rate of conversion of lidocaine to MEGX depends on the mass of cytochrome P-450 in the liver. However, the mass of cytochrome P-450 varies among individuals on the basis of genetic heterogeneity. Several medications are also known to induce the cytochrome P-450 system. Furthermore, women have a lower concentration of MEGX at 15 min than men, which is further reduced with oral contraceptive intake. These factors possibly account for the wide range of MEGX concentrations in apparently healthy individuals found in the current and previous studies. Timing of the blood collection for measurement of MEGX that provides the best discrimination is also not settled. Previous studies have variously used one (15 minute), three (15, 30 and 60 minutes) or four (15, 30, 60 and 90 minutes) blood samples. In a few studies, late (60 minute) MEGX measurement showed a better diagnostic accuracy.

Thus, several factors other than liver disease may influence the rate of hepatic conversion of lidocaine to MEGX. These extraneous factors may adversely influence the accuracy of this test to assess hepatic parenchymal dysfunction. The calibrator for comparison of MEGX results has also varied among various published studies. Many studies including the current study used the CPT score to grade the degree of severity of liver disease for comparison with MEGX results. This classification is based on clinical components (ascites and encephalopathy) and laboratory components (total bilirubin, albumin and prothrombin time). A few studies have used a classification for pediatric patients based on a history of ascites, and laboratory tests (cholesterol, indirect bilirubin and partial thromboplastin time). Other studies have used liver biopsy, the type and extent of liver impairment are factors that may affect the clinical application of the MEGX test. Steatosis, the degree of hepatic inflammation, and fibrosis may also affect MEGX production independently.

Whether etiology of cirrhosis of the liver influences the test results is unknown. The study by Bhise et al is important in that it showed a good correlation between the MEGX test and CPT score in cirrhotic patients. However, it has several shortcomings. Correlation of MEGX data with histological findings would have been helpful. The study was cross-sectional in nature, and whether baseline and/or serial changes in MEGX test could predict the development of future complications was not studied. This is an important area of investigation with some studies showing good prognostication by using quantitative liver function tests, whereas other failed to show such a relation. Comparison of performance of MEGX with other quantitative function tests would also have been interesting. One study concluded that the MEGX test was more feasible in the clinical setting, but that antipyrine test was more sensitive in staging liver cirrhosis. Another study found that the serum MEGX levels were proportional to the galactose elimination capacity, and inversely proportional to indocyanine green retention ratio.

Several other quantitative function tests have been used in the past for specific purposes. The antipyrine clearance test shows a good correlation with the degree of liver damage. Its disadvantage is that it correlates poorly with in vitro loading of hepatic microsomal capacity of liver, while its metabolism is influenced.
by the age, diet, alcohol consumption, smoking and toxic substances. Aminopyrine breath test may be useful for prognostication in patients with alcoholic hepatitis and cirrhosis, and in patients undergoing surgical interventions. Its shortcoming is a low sensitivity to detect hepatic dysfunction in cholestasis or extrahepatic biliary obstruction. Caffeine clearance test is useful in severe liver lesions, and is almost useless in a moderate liver damage. The transformation of galactose into glucose after galactose loading depends on both the hepatic functional mass and hepatic blood flow. This test is abnormal in severe acute and chronic liver diseases, and in metastatic hepatic neoplasms; however, it remains normal in obstructive jaundice.\(^3^\)

Thus, although many studies found MEGX to be a useful quantitative liver function test for assessing severity and prognosis of cirrhotic patients, its ultimate clinical utility has remained limited due to wide inter-individual variability and a variety of hepatic and non-hepatic factors that affect the handling of lignocaine. In view of the definite need for a reliable test to quantify the liver function in health and various disease states, it is hoped that hepatology as a science would attract biochemists and pharmacologists to address these issues in greater detail and stimulate them to develop more reliable quantitative tests to measure the functional hepatic reserve.

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References


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