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Review Article

MEGX: A DYNAMIC LIVER FUNCTION TEST

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ABSTRACT

The dynamic liver function tests are more sensitive and provide qualitative or quantitative assessments of the functional capacity of the liver. The dynamic tests like indocyanine green, caffeine clearance and galactose elimination capacity are more time consuming, technically cumbersome and expensive while aminopyrine and erythromycin breath tests have the potential hazard of exposure to radioactive compounds. Whereas, Monoethylglycinexylidide (MEGX) test is a simple, rapid test and can complement established static liver function tests in assessing liver function.

Lidocaine is metabolised primarily by the liver cytochrome P450 through oxidative N- dealkylation to MEGX. Because of the relatively high hepatic extraction of lidocaine, MEGX test depends on both hepatic metabolic capacity and hepatic blood flow. The formation of MEGX in serum can be determined by various methods like fluorescence polarization immunoassay technique, high performance liquid chromatography and gas liquid chromatography methods.

Various studies have shown that life threatening complications can be developed in patients with MEGX values <30ng/ml while MEGX values <10ng/ml have a particularly poor 1- year survival rate. The MEGX test is a useful tool that can help in selecting transplant candidates, pre-transplant monitoring and post-transplant outcomes. It can also be used for the assessment of progressive functional deterioration of liver in cirrhosis and for the prediction of multiple organ failure in critically ill patients after trauma or with sepsis. Hence, the MEGX test is a promising tool for the real time assessment of hepatic function.

Keywords: Monoethylglycinexylidide, lidocaine metabolism, liver function tests, hepatic function.

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1.0 INTRODUCTION

The traditional static tests such as alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma glutamyl transpeptidase (GGTP), alkaline phosphatase (AP), bilirubin, albumin and clotting factors provide only an indirect measure of hepatic function as they reflect a level of disease at a point in time. However, dynamic tests provide qualitative or quantitative assessments of the functional capacity of the liver. They are the most sensitive for early detection of sub clinical liver injury. The various dynamic liver function tests[1] are outlined in figure 1.

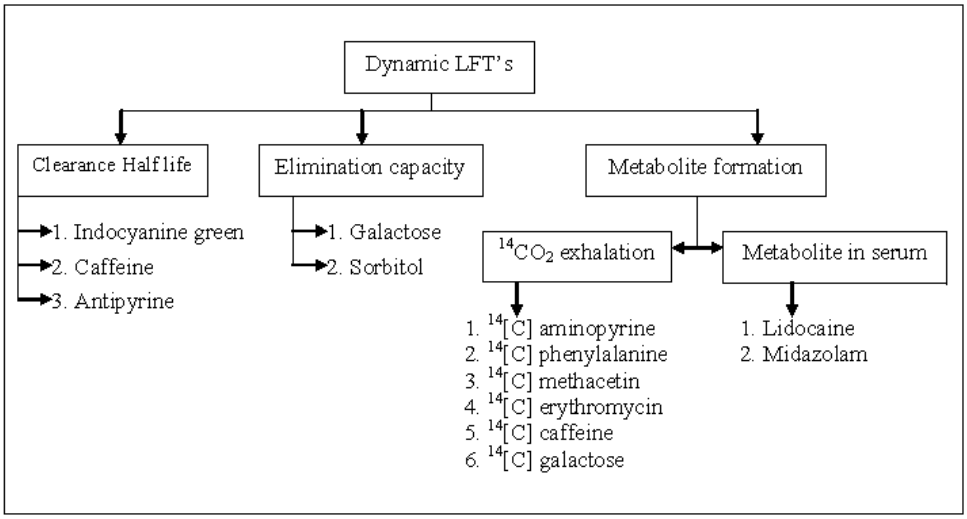

Figure 1 Dynamic Liver Function Tests

The capacity of the liver to metabolise certain drugs is used as a measure of hepatic function. The clearances of indocyanine green[2], caffeine[3] and antipyrine[4] have been used as a measure of liver function. Galactose elimination capacity can also be used as an index of residual hepatic function[5]. After administration of ^{14}C-aminopyrine, ^{14}C-methacetin, ^{14}C-erythromycin or ^{14}C-phenylalanine[9] $^{14}CO_2$ exhalation gives a measure of hepatic oxidative function[6]. The metabolite formation of lidocaine and midazolam can be measured 30 minutes after administration, which can provide the tool to test the metabolic capacity of liver.

The elimination of the compounds like midazolam with low or intermediate hepatic extraction ratio depends on hepatic metabolic capacity rather than hepatic blood flow while the elimination of the compounds like indocyanine green with high hepatic extraction ratio primarily depends on liver blood flow. But the elimination of lidocaine depends not only on hepatic metabolic capacity but also on hepatic blood flow due to its relatively high hepatic extraction ratio. Therefore, the formation of

monoethylgycinexlidide (MEGX) from lidocaine is widely used as a real- time dynamic liver function test. Moreover, other dynamic liver function tests are cumbersome to perform and may not accurately reflect small changes in liver histological status[7]. Also, the ease of use and rapid turnaround time has made MEGX test more promising. Lidocaine is metabolized primarily by the hepatic cytochrome P450 system through sequential oxidative N-dealkylation to MEGX, a major metabolite. The capacity of the liver to metabolise lidocaine to MEGX will provide the knowledge regarding its functional capability.

Test Procedure

In the standard MEGX test[8], a sub therapeutic dose of 1 mg/kg of lidocaine is given intravenously slowly over 2 minutes. The blood specimens for MEGX determination are taken at 0, 15 or 30 minutes after the injection. MEGX formation is calculated by substracting the predose concentration from the concentrations obtained at 15 or 30 minutes if serial MEGX monitoring is performed.

Various studies have shown that the inter-individual variability in MEGX concentration decreases with increased sampling time and is minimal at 60 min. Therefore, blood for MEGX determination should be sampled preferably 60 min after lidocaine injection[9]. The study by Reichel et al., has reported that the low dose of 0.5mg/kg or absolute dose of 50 mg, if used to assess liver function, then the incidences and intensity of side effects are found to be low and that the incidences of side effects are inversely related to liver function[10]. MEGX concentrations obtained after 50mg lidocaine intravenously were normalized to MEGX test results after 1 mg/kg lignocaine using the following equation: $C_N = C_{50}$ x m x 0.02 /kg where C_N is MEGX concentration normalized to MEGX test result after 1 mg/kg body weight lidocaine intravenously; C_{50} is MEGX concentration 30 min after 50 mg lidocaine intravenously; and m is body weight. The oral application of lidocaine by using test dose of 5mg/kg has also been investigated and a time point of 60 minutes was found to have the highest sensitivity[11].

Analysis of MEGX

The analysis of MEGX in serum can be done by various methods like fluorescence polarization immunoassay (FPIA) technique, high performance liquid chromatographic (HPLC) methods and gas chromatographic (GC) methods.

The FPIA method of determining MEGX concentration has been reported as the most convenient, sensitive with a detection limit of 3ng/ml and requiring short time analysis of 20 min[8]. But the MEGX measurements by this method were influenced by high blood concentrations of bilirubin, triglycerides and cholesterol. One approach to deal with this interference was proposed by Zoppi and Fumagalli, who precipitated the protein-bound bilirubin with the precipitation reagent from the Digoxin II assay supplied by Abbott Laboratories[12]. The method was then simplified

and validated by Schutz et al., and found to be effective in hyperbilirubinemia[13]. But still, lidocaine concentrations >10ng/ml cross react in the FPIA, which can present problems in experiments with cell cultures or microsomal preparations and in assaying samples from patients whose blood still contains lidocaine from the test dose[11]. Moreover, 3-OH-MEGX, major metabolite of lidocaine in rats, also cross reacts in the FPIA, rendering this method unsuitable for use in this species[14].

HPLC methods to determine lidocaine and its metabolites are studied widely[15-17]. Many different HPLC protocols involving liquid-liquid or solid phase extraction have been used to achieve analytical sensitivity comparable with that of the FPIA and that too with superior specificity. But, HPLC procedures with UV or electrochemical detection have not been able to accurately measure MEGX concentration less than 10 ng/ml[15]. The assessment of serum MEGX concentration <10ng/ml are particularly relevant in patients with end-stage liver disease while MEGX concentration <5ng/ml are relevant in pediatric patients with end-stage liver disease[18]. Therefore, Andreeva et al. developed an HPLC procedure with fluorescence detection which had the lower limit of quantification 2.5 ng/ml and a limit of detection of 1-7ng/ml[17]. Bilirubin did not interfere with this method. This method proved to be cost effective alternative to FPIA. The disadvantage of this HPLC method was the necessity to derivatise MEGX.

A capillary GC method with nitrogen-phosphorus detection was developed which achieved an adequate sensitivity with a limit of detection of 1ng/ml and a working range of 2.5-50ng/ml[19]. Liquid chromatography-tandem mass spectrometry (LC-MS-MS) technique was then reported which was found to be a rapid, specific and reproducible[20]. This method requires only a small sample volume of 100 µl as compared to HPLC- fluorometry and capillary GC methods, which requires sample volumes of 0.5 and 1ml respectively, to achieve a similar analytical sensitivity. Further, LC-MS-MS method takes very shorter analysis time of 3 min as compared to other methods, which takes the analysis time of 15-20 min.

Factors Influencing MEGX Test

The major routes of metabolism of lidocaine in the liver were thought to be through CYP4503A4[21]. The study by Imaoka et al., suggested that CYP3A4 and CYP1A2 are the major enzymes involved in the N-deethylation and 3-hydroxylation of lidocaine, respectively[22]. But Isohanni et al. reported that CYP1A2 plays a major role in the N- deethylation of lidocaine at clinically relevant concentrations[23]. Further, Wang et al. showed that fluvoxamine, an inhibitor of CYP1A2, was a more potent inhibitor of the N-deethylation of lidocaine than ketoconazole and erythromycin. Thus, it was observed that formation of MEGX from lidocaine was not a suitable marker of hepatic CYP3A4 activity in

vivo because both CYP1A2 and CYP3A4 are involved in lidocaine N- deethylation[24].

The study on experimental diabetes in rats has suggested that diabetes can enhance lidocaine elimination with accompanied increase in MEGX concentration[25]. For a proper evaluation of the MEGX test in patients with renal impairment, renal function should be taken into consideration because MEGX concentrations are increased significantly with declining renal function[9]. It has been shown by Oellerich et al., that MEGX concentrations are significantly lower in women and even more so in those taking contraceptives[26]. In studies comparing healthy subjects and patients with liver dysfunction, controls and patients should be strictly matched for age, since MEGX levels decline significantly with age[27]. The drugs that can influence lidocaine metabolism such as propranolol, 17α-ethynylestradiol, cimetidine, omeprazole, and antiepileptic drugs may also affect the MEGX test results[28]. However, MEGX test does not impair psychometric performance in patients with chronic hepatitis or cirrhosis[29].

Advantages of MEGX Test

1. MEGX test gives better idea about residual function of the liver.
2. It's ease of use and rapid turn around time makes it more promising.
3. It has good prognostic ability than CTP score.
4. It can be applied in the area of liver transplantation.

Disadvantages of MEGX Test

1. It is invasive test requiring frequent blood sampling.
2. It requires sophisticated instrumentation.
3. It shows wide inter-individual variability in results.
4. The patients may show adverse reaction to lidocaine.
5. Being costly, cannot be used routinely.

Applications of MEGX Test

1. Use of MEGX in cirrhosis:

Many studies have proved the worth of MEGX test in detection and staging of cirrhosis. The study by Ercolani et al., have shown that the mean MEGX value was significantly higher in patients without cirrhosis as compared to patients with cirrhosis (77.8 ± 25ng/ml v/s 35.6 ± 30ng/ml; $p<0.05$)[30]. Among patients with cirrhosis, there was a significant difference between those patients classified as Child A and those classified as Child B and C (43.3 ± 25ng/ml v/s 11.5 ± 7.1ng/ml; $p<0.05$). It has been demonstrated that all patients in whom major life threatening complications of cirrhosis developed had MEGX production less than 30ng/ml and that all deaths related to such complications were confined to patients with MEGX less than 10ng/ml[31-32]. Testa et al., in their study have concluded that MEGX test could integrate both the histological grading of chronic hepatitis and the clinical staging of cirrhosis[33].

2. Use of MEGX in resective liver surgery:

Postoperative liver failure is one of the most feared complications and the major cause of death after liver resection. The possibility of having a reliable index of resectability remains one of the main problems. In the study involving MEGX, a significant difference was found in the preoperative value of MEGX between patients who experienced postoperative complications related to liver impairment and patients who did not experience them. The patients with a MEGX value less than 25ng/ml showed a significantly higher incidence of complications[34].

3. Use of MEGX in pretransplant monitoring:

The common lab tests do not reflect the seriousness of cirrhosis, and they are unable to predict patients at risk of deterioration. The MEGX value has been used as reliable predictor of 1 year survival in patients awaiting liver transplantation and found to be more sensitive than Child-Pugh classification[35]. The cut off of 10ng/ml accurately discriminates patients with severe liver impairment and patients with a better functional reserve[36-37]. The patients with MEGX values less than 10ng/ml should get prioritisation for operation while those with MEGX values >10ng/ml may be followed routinely by MEGX test. A declining MEGX values suggests a progression of the disease to decompensated cirrhosis, which will require a liver transplantation in a short time.

4. Use of MEGX in Liver donors:

The use of MEGX in evaluating liver donors was investigated by many studies. It was shown that there was a significant difference in graft function among donors with MEGX values of more than 90ng/ml and donors with MEGX values of less than 90ng/ml[38]. However, there are the incidences where good function has been reported with the use of liver graft with MEGX values of less than 90ng/ml, and, on the other hand, primary graft non-function with the use of graft with MEGX values of more than 90ng/ml. Also, it was shown that even if low cut-off values of MEGX serum concentrations of 60ng/ml were chosen before accepting a donor organ, more than 90 % of well performing organs would have been rejected[39]. The reasons attributed to these discrepancies may be the hemodynamic changes and the energetic depletion during the stay in the intensive care unit, the different drugs used in monitoring the donor, the polymorphism of the CYP450 in different subjects, and the manipulation of the graft during the back table and warm ischemic period. Therefore, it was concluded in their study that MEGX may be helpful in aiding the judgment process but should not be taken in isolation or used as the sole arbitrary criterion for acceptance or refusal of donor liver[40].

5. Use of MEGX in Post transplant monitoring:

It was found that the MEGX concentration in the recipients after transplant was independent of the donor MEGX concentration and MEGX concentration less than 25ng/ml in the first 36 hr after revascularisation were predictive of greater

morbidity and mortality[37]. Further, MEGX was also found to be lower during the first 14 days in patients who died within 150 days of transplantation than in patients who survived[41]. MEGX has also been reported to decrease before clinical rejection and to recover rapidly in most patients after therapy[42].

6. Use of MEGX in prognosis of liver diseases:

MEGX test has been widely used for prognosis of various liver diseases. One year survival in adults with MEGX production less than 10ng/ml was only 50% compared with 90% when MEGX was greater than or equal to 10ng/ml[43]. In patients with biliary cirrhosis, MEGX test was found to have an independent prognostic value alongwith Mayo score[44]. The best discrimination between probability of death or survival was achieved with a cut off value of 25ng/ml for the MEGX test and of 6 for the Mayo score.

However, in the recent studies, it is shown that MELD score is superior to MEGX values[45-46].

7. Use of MEGX in oncology:

It has been proposed that the MEGX test may be of value in assessing liver function in cancer patients. A significant decrease of MEGX values (median 28ng/ml) was found in patients with advanced breast cancer and liver metastases[47]. MEGX test can also be used in patients undergoing chemotherapy for planning, treatment and monitoring hepatic toxicity. It was shown that vinorelbine dose individualization may be prudent in patients with liver dysfunction and that it could be based on the MEGX test result[48].

8. Other Applications:

There is evidence that the MEGX test may be of prognostic values in assessing liver function of critically ill patients at risk for developing multiple organ failure (MOF). The serial monitoring of critically ill patients showed a sharp decrease in median MEGX values in patients who developed multiple organ failure while MEGX values remained stable in patients who did not develop MOF[49, 50]. The study on MEGX disposition in critically ill trauma patients suggested that liver function might be affected by severity of injury[51]. The critically ill patients develop significant hepatic dysfunction due to mismatch between hepatic metabolic demand and blood flow, and the MEGX test is reported to be an extremely effective means of assessing liver function and flow in these group of patients[52].

MEGX test is also reported to be a valuable tool for assessing the degree of fibrosis[53]. Hein et al., have used the MEGX test to show the benefit of N- acetylcysteine therapy in patients with compromised hepatosplanchnic function, such as patients with septic shock due to peritonitis[54]. MEGX can also be used as an indicator of the vital state of a patient during cardiopulmonary resuscitation[55]. As a predictor of hepatic failure after transcatheter arterial chemoembolisation (TACE), the MEGX test has been reported as better than conventional liver function tests and clinical parameters. Thus, it can be used to select

patients with relatively good liver reserves for safe TACE treatment[56]. MEGX test can also be a sensitive marker of liver dysfunction early in sepsis and low MEGX values are associated with an enhanced inflammatory response[57].

3.0 CONCLUSION

The dynamic liver function tests are more sensitive and provide qualitative or quantitative assessments of the functional capacity of the liver at given point of time. Indocyanine green clearance is a convenient method but both blood flow and hepatocellular function affect the test results. Tests of caffeine clearance, galactose elimination capacity and antipyrine clearance all require time-consuming, technically cumbersome and expensive serial blood sampling. The aminopyrine breath test is non-invasive, but gastric emptying and the patient's physical state affect results. The potential hazard of exposure to radioactive compounds limits the wide clinical use of both aminopyrine and erythromycin breathes tests.

But, MEGX test is a simple, rapid test, which represents a complementary method in hepatology and liver transplantation. MEGX test can be combined well with indocyanine green test and Child Pugh classification and it can be a better predictor of residual liver reserve capacity. The test can be applied in the area of transplantation, in assessment of progressive functional deterioration of liver in cirrhosis and in prediction of multiple organ failure in critically ill patients with trauma or sepsis.

Thus, the MEGX test is a real time dynamic liver function test that can complement standard liver function tests, particularly if prognosis is important.

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