A Reassessment of the Optimal Sampling Time for the MEGX Liver Function Test

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Summary

The measurement of a single plasma concentration of the lidocaine (lignocaine) metabolite monoethylglycinexylidide (MEGX), after a standard intravenous dose of lidocaine, is now widely used as a test of liver function. However, apart from the dose of lidocaine, the test has not been rigorously standardised, and various postinjection times, ranging from 15 to 60 minutes, have been claimed to be optimal for sampling. The purpose of this study was to re-evaluate the optimal sampling time for the MEGX test. Plasma MEGX concentrations were measured 15, 30, 45 and 60 minutes after intravenous lidocaine administration in 10 healthy volunteers and 20 age-matched patients with either grade A or grade C liver cirrhosis according to Child’s classification. Differences in MEGX concentrations between controls and patients with cirrhosis or between the 2 groups of patients with cirrhosis were statistically significant at all sampling times, but the level of significance markedly increased with increased sampling time as a result of a progressive decrease in interindividual variability within each group. Discriminant analysis showed that the MEGX test was far superior to conventional liver function tests in distinguishing between the 3 study groups. The specificity, sensitivity, diagnostic accuracy and predictive values of the MEGX test increased with the sampling time and, overall, were maximal at 60 minutes. All measured MEGX concentrations were significantly related to serum albumin, prothrombin time and Pugh’s score. The 60-minute MEGX concentration showed the strongest relationship with all 3 variables and the most significant correlation was observed with the Pugh’s score (r = –0.71, p = 0.00001). These results indicate that MEGX concentrations determined 60 minutes after lidocaine administration provide the most accurate data for discriminating between either healthy subjects and patients with cirrhosis or between patients with different degrees of liver dysfunction.
Lidocaine (lignocaine), a drug subject to high hepatic extraction, has long been used as a metabolic probe of liver function.\cite{1,2} Its primary metabolite monoethylglycinexylidide (MEGX) is formed via oxidative N-deethylation of lidocaine by cytochrome P450 (CYP) 3A4.\cite{3} Oellerich and co-workers\cite{4,5} have shown that the rate of MEGX formation reflects the rate of lidocaine clearance, and have suggested that the formation kinetics of MEGX can be used to assess liver function. The proposed test requires the measurement of a single plasma MEGX concentration after a standard intravenous dose of lidocaine.

Because of its safety, rapidity and sensitivity as an indicator of liver dysfunction, the MEGX test has gained wide acceptance, particularly in the field of liver transplantation.\cite{6,7} It has also been claimed to be useful for distinguishing patients with cirrhosis from normal subjects,\cite{5,8} although the results of one study have not been as favourable.\cite{9} However, there is no general consensus as to the optimal blood sampling time for measuring the MEGX concentration. In the initial studies by Oellerich et al.,\cite{4,5} the most significant differences in MEGX levels between normal subjects and patients with cirrhosis were noted during the first 30 minutes after lidocaine administration. Following these observations, 15-minute samples were used by the majority of investigators.\cite{6}

A communication later appeared stating that the best specificity of the test for distinguishing normal subjects from patients with cirrhosis is obtained 45 minutes after lidocaine administration.\cite{10} In a further study, Testa et al.\cite{11} found equally significant differences between normal subjects and patients with cirrhosis at 15, 30 and 60 minutes after lidocaine administration. Various factors may account for these discrepancies, including the use of control subjects not matched for age,\cite{5} differences in the mode of lidocaine injection, and differences in the average degree of liver dysfunction of the patient groups.

The present study was designed to reassess the optimal sampling time for the MEGX test and its usefulness for distinguishing patients with liver dysfunction from normal subjects. For this purpose, we compared a group of healthy volunteers with age-matched patients with cirrhosis classified into 2 pathologically homogeneous groups according to Child’s criteria.\cite{12}

**Methods**

**Patients and Controls**

Thirty male subjects (10 healthy volunteers and 20 patients with biopsy-proven liver cirrhosis) were studied after informed written consent had been obtained. The study design was approved by the local Ethics Committee.

Criteria for selection of healthy volunteers were that they should not be heavy consumers of alcohol or tobacco (less than 50g of ethanol or 10 cigarettes a day) and that they did not require any regular medication. They were diagnosed as healthy subjects by means of a thorough clinical examination, including medical history, physical examination, electrocardiogram, complete blood count and laboratory tests indicating normal kidney and liver functions. Only patients with clinically stable cirrhosis were selected, i.e. showing no significant changes in clinical profiles or biochemical variables during a 1-month period prior to the initiation of the study. These patients had posthepatic (n = 17) or alcoholic (n = 3) cirrhosis. Ten patients were in a compensated state and were categorised as Child’s class A,\cite{11} whereas 10 had ascites and were categorised as Child’s class C. The functional reserve of the liver was scored according to Pugh et al.\cite{13}

Patients were excluded from this study if they had a recent history of gastrointestinal bleeding, severe encephalopathy or any other disease. Exclusion criteria for both controls and patients were known allergy to lidocaine or history of cardiac disease.

For ethical reasons, pharmacological treatment of patients with cirrhosis was not suspended. However, none of the administered drugs [frusemide (furosemide), canrenone, ranitidine, famotidine, vitamin supplements] was known to interfere with