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# The effect of liver disease and food on plasma MEGX concentrations

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Plasma monoethylglycinexylidide (MEGX) concentrations were measured in 15 healthy controls (age 23–46 years) and 12 patients with biopsy proven cirrhosis (age 34–70 years) 30 min after 1 mg $kg^{-1}$ intravenous lignocaine. Mean (± s.d.) MEGX concentrations were 57 ± 33 ng $ml^{-1}$ in the controls compared with 21 ± 18 ng $ml^{-1}$ in the cirrhotics ($P < 0.05$), but there was overlap in the range of concentrations. MEGX concentrations were inversely correlated with age, but not disease severity, in the cirrhotic patients ($r = 0.62$, $P = 0.04$) but not in the control subjects. In a second study 20 healthy subjects were given 1 mg $kg^{-1}$ intravenous lignocaine on two occasions; either fed or fasted, and samples taken at 15, 30 and 60 min after dosage. MEGX concentrations were not significantly different at any time within either day or between fed and fasted study days. There was no correlation with age. The plasma lignocaine concentration at 15 min was significantly higher fed than fasted (2.88 ± 2.44 and 1.82 ± 0.96 μg $ml^{-1}$, $P = 0.01$). Measurement of plasma MEGX after i.v. lignocaine is a useful test of liver function and may be performed in fed or fasted subjects. It is reproducible within an individual but is not specific for cirrhosis and appears age-related in liver disease.

**Keywords** liver function lignocaine (lidocaine) monoethylglycinexylidide (MEGX) food

## Introduction

The majority of commonly used liver function tests measure liver cell damage or biliary obstruction rather than true 'liver cell function'. Although serum albumin and prothrombin time are true tests of liver cell function they have not proved useful prognostic predictors [1], and the more widespread use of liver transplant has increased the need for a rapid, sensitive and specific test of liver function [2].

Lignocaine, the local anaesthetic and antiarrhythmic agent, has been shown to be a sensitive indicator of hepatic dysfunction [3]. It has a moderately high extraction ratio in normal subjects [4], and is converted to several metabolites including monoethylglycinexylidide (MEGX). This is produced by oxidative *N*-deethylation catalysed by cytochrome P4503A4 [5]. The measurement of MEGX concentration after a standard intravenous dose of lignocaine has recently been developed as a test of liver function [6]. It has been shown to be a useful measure of donor liver function with greater sensitivity than any other 'liver function tests' including indocyanine green clearance [7]. Its use as a predictor of liver survival in the recipient is still being assessed [8].

It has also been claimed that MEGX can be used as a diagnostic test to distinguish patients with cirrhosis of the liver from normal subjects [9], and it is being commercially promoted as a routine liver function test with claimed reference ranges in normal and cirrhotic adults and children [10].

Previous studies have established appropriate single intravenous lignocaine doses and recommended a 30 min post-infusion sampling time [9], but did not standardise the procedure in any other way. In particular, none of the studies stipulated whether subjects were fed or fasted. Thus, it may be relevant that a high protein meal has been shown to lower plasma concentrations of lignocaine following a 15 min intravenous infusion [11]. The present study was in two parts. Initially we evaluated the usefulness of MEGX measurement as a specific test

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for liver cirrhosis. Secondly, we assessed the effect of food and sampling times on plasma MEGX concentrations in normal subjects after i.v. injection of lignocaine.

## Methods

Both studies were approved by the Royal North Shore Hospital Medical Research Ethics Committee and all subjects gave informed consent in writing.

*Study 1*

Fifteen healthy control subjects (eight male, seven female, age 23–46 years, weight 69 ± 15 kg (range 38–98 kg)) and 12 patients with chronic liver disease (nine male, three female, age 34–70 years, weight 69 ± 12 kg (range 49–92 kg)) were studied. The control subjects had no history of liver disease, normal results for conventional liver and renal function tests and an alcohol intake of less than 40 g $day^{-1}$; four were smokers and three of the females were taking oral contraceptives. The patients all had abnormal conventional liver function test results and some form of chronic cirrhosis proven by liver biopsy. Their Child-Pugh score [12] was calculated as a measure of liver dysfunction and ranged from 5 to 12. Exclusion criteria for both groups were known allergy to lignocaine, any hepatotoxic drugs, pregnancy, or a history of cardiac disease.

Subjects were studied in the morning but were given no specific instructions about when or what to eat. They were given an intravenous infusion of lignocaine hydrochloride over 15 min, in a dose of 1 mg $kg^{-1}$ after a 10 ml baseline blood sample had been taken from the other forearm. A further 10 ml blood sample was taken 30 min after the dose and analysed for MEGX.

*Study 2*

The volunteers were five males and 15 females of age range 18–70 years, weight 64 ± 8 kg (range 54–82 kg) and were recruited with the same inclusion and exclusion criteria as in Study 1. They included six smokers and seven females taking oral contraceptive preparations. Each of the 20 volunteers was studied on two occasions at least 1 week apart. In random order they presented either after an overnight fast or 1 h after a standard breakfast of cereal with milk, two pieces of toast with butter or magarine and jam or other spread as desired and tea or coffee (estimated carbohydrate content 60 g and fat content 25 g). After a 10 ml baseline blood sample was taken an intravenous infusion of lignocaine hydrochloride 1 mg $kg^{-1}$ was given over 15 min. Subsequent samples were taken from a cannula in the opposite arm at 15, 30 and 60 min after the end of the infusion.

*Assay methods*

In both studies blood was taken into heparinised tubes, centrifuged and the plasma samples stored at −20° C and assayed for MEGX (both studies) and lignocaine (second study) by fluorescence polarisation immunoassay (TDx, Abbot Laboratories, USA). Results were expressed in mass units for comparison with the published literature. For MEGX the within assay coefficient of variation was 2.8% at 63 ng $ml^{-1}$ and 1.6% at 151 ng $ml^{-1}$ and for lignocaine the within assay coefficient of variation was 8.8% at 1.7 μg $ml^{-1}$ and 5.5% at 5.0 μg $ml^{-1}$. To convert MEGX ng $ml^{-1}$ to nmol $l^{-1}$ multiply by 4.85 and to convert lignocaine μg $ml^{-1}$ to μmol $l^{-1}$ multiply by 4.27.

*Statistical analysis*

In Study 1 linear regression was used to correlate age with MEGX concentrations and Spearman's Rank Correlation Test to compare Child-Pugh scores with MEGX concentrations. Results between groups were compared by the Mann-Whitney U Test. In Study 2 results on the two days were compared by the Wilcoxon matched-pairs signed ranks test. $P < 0.05$ was taken to be significant.

## Results

*Study 1*

In the control group MEGX concentrations were 57 ± 33 ng $ml^{-1}$ (95% confidence intervals 45–69) range 27–116 ng $ml^{-1}$. In the patients MEGX concentrations were 21 ± 18 ng $ml^{-1}$ (95% confidence intervals 12–30) (range 8–48 ng $ml^{-1}$) ($P < 0.05$). Using a cut off point of 30 ng $ml^{-1}$ [10] there were four cirrhotics with higher values and one normal subject with a lower value (Figure 1). For the combined data there was a significant relationship ($r = -0.53$, $P = 0.006$) between age and plasma MEGX concentration (Figure 1). This was also statistically significant in patients with liver disease ($r = -0.62$, $P = 0.04$) but not in control subjects ($r = 0.41$, $P = 0.14$). MEGX concentration did not correlate with the Child-Pugh score ($r = -0.043$, NS). There was no association between MEGX concentration and sex in controls or patients.

*Study 2*

Table 1 shows MEGX and lignocaine concentrations at the three sampling times after lignocaine administration. There was no significant difference between MEGX concentrations at any of the times within each study day. There was also no significant difference between MEGX concentrations on the fed day compared with the fasting day, at any sampling time.

Lignocaine concentrations were significantly higher at 15 min than at 30 or 60 min after dosage on both fed and fasting days ($P < 0.01$). In addition the 15 min concentrations were significantly higher on the fed than the fasting day ($P = 0.01$).

There was considerable interindividual variation in plasma MEGX concentrations, but for any given subject they were similar on the two study days. Four normal subjects took part in both studies 1 and 2 and for three subjects there was close agreement between the 30 min

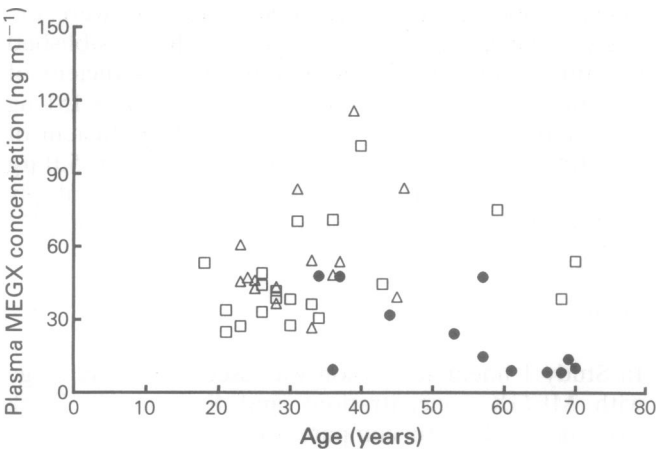


**Figure 1** Relationship of plasma MEGX concentrations (ng $ml^{-1}$) to age (years) in both studies. (△) Control subjects, Study 1. (□) Control subjects, Study 2, fasting. (●) Cirrhotic patients.

**Table 1** Plasma MEGX and lignocaine concentrations at three times after an i.v. lignocaine dose of 1 mg $kg^{-1}$, in both fed and fasted states ($n$ = 20)

| | Fed | | | Fasted | | |
|---|---|---|---|---|---|---|
| *MEGX (ng $ml^{-1}$)* | | | | | | |
| Time (min) | 15 | 30 | 60 | 15 | 30 | 60 |
| Range | 15 | 19 | 19 | 16 | 25 | 16 |
| | 140 | 125 | 106 | 98 | 102 | 100 |
| Mean | 47 | 50 | 48 | 43 | 47 | 49 |
| s.d. | 29 | 23 | 19 | 21 | 19 | 19 |
| 95% confidence | 35 | 38 | 38 | 32 | 37 | 39 |
| intervals | 58 | 59 | 55 | 51 | 54 | 57 |
| *Lignocaine (μg $ml^{-1}$)* | | | | | | |
| Time (min) | 15 | 30 | 60 | 15 | 30 | 60 |
| Range | 0.8 | 0.2 | 0.1 | 0.3 | 0.2 | 0.1 |
| | 11.0 | 2.6 | 1.6 | 4.5 | 1.5 | 1.3 |
| Mean | 2.9 | 0.8 | 0.5 | 1.8 | 0.7 | 0.4 |
| s.d. | 2.4 | 0.6 | 0.4 | 1.0 | 0.4 | 0.3 |
| 95% confidence | 1.8 | 0.6 | 0.3 | 1.4 | 0.5 | 0.3 |
| intervals | 3.9 | 1.1 | 0.7 | 2.2 | 0.8 | 0.5 |

MEGX concentrations on the three occasions. The fourth subject had lower MEGX values in the second study but results of conventional liver function tests remained normal. There was no significant association between either MEGX or lignocaine concentrations and age (Figure 1) or sex.

## Discussion

The range of MEGX concentrations in the two groups of Study 1 overlapped indicating that a 30 min MEGX concentration is not a specific test for biopsy proven cirrhosis. This finding agrees with that of Oellerich *et al.* [9]. However, these authors concluded that both 15 and 30 min MEGX concentrations 'clearly distinguish' cirrhotic patients from healthy volunteers. Oellerich *et al.* [9] did not quote the ranges of MEGX concentrations observed but rather median values with 16th to 84th percentiles suggesting that the concentration in the two groups would have overlapped. Unfortunately, their conclusion has led others to state that there is a clear 'cut-off' value of MEGX concentration below 30 ng $ml^{-1}$ for diagnosing cirrhosis [10]. Our findings suggest that the MEGX test is a useful test of liver function but cannot be taken as diagnostic of cirrhosis since we demonstrated one low value which is a 'false positive' in a normal subject and four 'false negative' values in the patients with proven cirrhosis who had concentrations at 30 min greater than 30 ng $ml^{-1}$.

Oellerich *et al.* [9] established that peak plasma concentrations of MEGX occurred at 15 min in normal subjects but at 60 min in cirrhotic patients. For this reason they selected 30 min as a sampling time to discriminate between normal and abnormal subjects. We did not assess other sampling times in the first study but in the second study confirmed that, in normals, there is no significant difference in MEGX concentrations between samples taken at 15, 30 or 60 min.

The inverse correlation between age and MEGX production in the patients with cirrhosis, but not in the normal subjects, was not due to severity of liver disease since the Child-Pugh score did not relate to the MEGX concentration. It is unlikely to be due solely to age as, unlike in the first study, in which our oldest control subject was forty-six, older subjects were investigated in the second study and no relationship between MEGX concentration and age was observed.

We demonstrated no difference between MEGX concentrations, at any sampling time, in the fed or faasted states in our second study. This suggests that the test is relatively robust since it can be performed irrespective of the time of a carbohydrate meal, although this may need to be confirmed for patients with liver disease. If it is assumed that the major effect of food is to alter hepatic or splanchnic blood flow, our results are in agreement with the findings of Chen *et al.* [13]. They found that in pigs, neither clamping the hepatic artery nor infusing dopamine significantly altered the time-course of MEGX.

After food there was a higher lignocaine concentration at 15 min than after fasting, but this was not associated with higher MEGX concentrations ($\delta$ = 1.05 CI: 0.15, 1.95 μg $ml^{-1}$). The reason for this difference is unknown.

There is good evidence that the production of MEGX from lignocaine is mediated by cytochrome P4503A4 [5]. Cyclosporin, universally used as an immuno-suppressant in transplant patients, is also metabolised by CYP3A4 [14]. Therefore, in theory, cyclosporin could inhibit this enzyme and thus impair MEGX production giving a false suggestion of impaired production due to liver cell failure in the recipient. Interpretation is also complicated by the fact that some MEGX can be produced elsewhere in the body since there is recent evidence for its extra-hepatic production in an anhepatic woman [15].

In conclusion, we have shown that measurement of plasma MEGX is not a specific test for cirrhosis, but that

concentrations are significantly lower in patients with liver cirrhosis compared with healthy subjects. It could be a useful test of liver function if interpreted in conjunction with other, well-established tests, and it is robust and reproducible in normal individuals. MEGX concentrations are independent of a carbohydrate meal but further studies are necessary to determine the factors that affect cytochrome P4503A4 activity and MEGX formation in health and disease.

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