Monoethylglycineylidide (MEGX), the primary metabolite of lidocaine, is produced via oxidative N-deethylation catalyzed by cytochrome P450 (CYP) 3A4 (1). The MEGX test, a new dynamic test of liver function that assesses the rate of MEGX formation after a standard intravenous dose of lidocaine, is a highly sensitive indicator of hepatic dysfunction and has gained the widest acceptance among dynamic liver function tests, especially in the field of liver transplantation (2). Although various observations have provided evidence of impaired drug metabolism in patients with renal insufficiency (3), the effect of renal function on MEGX formation rate has received limited attention. The only study comparing uremic patients with healthy subjects found no statistically significant differences in MEGX values between the two study groups (4). However, in this investigation, only patients with moderate kidney dysfunction were examined and MEGX was measured only 15 min after lidocaine injection. Although this was the sampling time originally suggested by Oellerich et al. (5), these authors later observed a lesser variability in MEGX concentrations at 30 min and proposed that blood be sampled at this time for MEGX determination (6). We have shown that the intersubject variability in MEGX decreases up to 1 h in both healthy individuals and cirrhotic patients; consequently, the efficiency of the test becomes maximal when blood is sampled 60 min after lidocaine injection (7). This result was confirmed in subsequent studies (8–10). The aim of the present study was to reassess the effect of chronic renal failure on the results of the MEGX test.

We studied 48 Caucasian men with informed written consent. The study protocol was approved by the local Ethics Committee. The subjects were divided into four groups on the basis of creatinine clearance (CLCr) values: Group 1, with CLCr >80 mL/min per 1.73 m² (mean age ± SD, 53 ± 6 years), consisted of healthy subjects with no clinically significant abnormalities in physical findings or laboratory test values, and not taking any regular medication; groups 2 and 3 consisted of patients with moderate (CLCr between 30 and 60 mL/min per 1.73 m²; mean age ± SD, 58 ± 8 years) and severe (CLCr <30 mL/min per 1.73 m²; mean age ± SD, 53 ± 7 years) renal insufficiency, respectively; group 4 included anuric patients (mean age ± SD, 54 ± 7 years) receiving hemodialysis three times a week. Controls and patients were also matched for height, weight, and body mass index. Each group consisted of 12 subjects. Criteria for selection of controls and patients were that they were not heavy consumers of alcohol or tobacco, had no history of cardiac disease or allergy to lidocaine, and had normal liver function as assessed by standard laboratory tests. Only patients with stable kidney function were selected. Because, for ethical reasons, pharmacological treatment of uremic patients could not be suspended, patients were excluded from this study if they were receiving drugs known to induce or inhibit CYP3A4 (11) or in any case suspected to alter MEGX concentrations (2).

Some of the patients examined (belonging to groups 3 and 4) were taking calcitriol, the active form of vitamin D, which during the course of this study was shown to induce CYP3A4 in vitro (12). To assess the possible interference of this drug with the MEGX test, we measured MEGX concentrations in three healthy volunteers before and 2 weeks after administration of calcitriol at daily doses similar to those taken by uremic patients. MEGX concentrations before and after calcitriol administration were virtually identical in every subject.

All participants were studied in the morning, after an overnight fast. For anuric patients, the study day was between dialysis days. Lidocaine (1 mg/kg) was administered by an infusion pump over 2 min, at 0800, and all subjects remained supine for the next 2 h. Subjects were asked to report any subjective adverse effects, and their vital signs were closely monitored. Blood samples for MEGX determination were collected in heparin-containing plastic tubes before and 10, 15, 30, 45, and 60 min after lidocaine administration. Blood was centrifuged immediately after collection, and the plasma samples were stored at −40 °C until assayed. CLCr was determined three times, at regular intervals, during the 2 weeks preceding lidocaine administration. Urine was collected from 0800 to 2000, and creatinine was measured in plasma at the beginning and end of the collection period. The clearance of each individual was taken as the mean of the three determinations. All clearance values were normalized to a standard body surface area of 1.73 m², using the formula of DuBois and DuBois (13).

MEGX was determined by means of the TDX fluorescence polarization immunoassay (FPIA) system (Abbott Laboratories). Creatinine was assayed by the enzymatic PAP method (Boehringer). The limits of detection and CVs of the above assays were as reported previously (8, 14). In three subjects from both groups 1 and 3, MEGX was also measured by an HPLC method (15). In our laboratory, the detection limit was 6 µg/L, whereas the intra- and interassay CVs (n = 10) determined at 10 and 100 µg/L were <10% and 4%, respectively.

A power analysis based on the mean differences in MEGX concentrations between groups 1 and 3 showed that, with 12 subjects per group and a significance (α) of 0.05, power (1 − β) ranged from 0.80 at 30 min to >0.99 at 60 min. Because, on the basis of the Wilk-Shapiro and the Levene tests, gaussian distribution of the data could not be rejected, inter- and intragroup comparisons were made by 1- and 2-way ANOVA, respectively. In cases of significant differences (α = 0.05), the ANOVA was followed by
MEGX concentrations were higher at all sampling times in uremic patients, especially those with severe renal insufficiency (see Table 1). On the other hand, MEGX concentrations similar to those of healthy volunteers were observed in patients undergoing hemodialysis. As shown in Table 1, the significance of differences in MEGX concentrations between group 3 and groups 1 and 4 increased with increased sampling time. This was not so much attributable to an increase in the absolute values of differences as to a decrease in the interindividual variability within each group. Fig. 1 shows the relationship between CL\textsubscript{CR} and the 60-min plasma MEGX concentration for subjects of groups 1–3. A highly significant inverse correlation was found between CL\textsubscript{CR} and MEGX concentration ($r = -0.65; P < 0.0001$). The equation of the regression line was: \[ y = 85 - 0.25x, \] with 95% confidence intervals of 78–92 µg/L and $-0.35$ to $-0.15$ for the intercept and slope, respectively. Both the strength and the significance of the correlation decreased with decreased sampling time; they were still indicative of a significant correlation for the 45- and 30-min MEGX concentrations but not for earlier MEGX concentrations. To rule out the possibility that the observation of higher MEGX concentrations in uremic subjects was an artifact attributable to cross-reactivity with the TDx FPIA by other lidocaine metabolites that may have accumulated in such patients, we compared the results of the FPIA with those of a highly specific HPLC method in three healthy volunteers and three patients with severe renal dysfunction.

**Table 1. Plasma concentrations\textsuperscript{a} of MEGX at various sampling times after intravenous administration of 1 mg/kg lidocaine to control subjects and uremic patients.**

<table>
<thead>
<tr>
<th>Sampling time, min</th>
<th>Group 1 (CL\textsubscript{CR} &gt;80)\textsuperscript{b}</th>
<th>Group 2 (30 &lt; CL\textsubscript{CR} &lt; 60)\textsuperscript{b}</th>
<th>Group 3 (CL\textsubscript{CR} &lt;30)\textsuperscript{b}</th>
<th>Group 4 (dialysis)</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>MEGX, µg/L</td>
<td>CV, %</td>
<td>MEGX, µg/L</td>
<td>CV, %</td>
</tr>
<tr>
<td>10</td>
<td>26.2 ± 13.1 (10.5–52.5)</td>
<td>50</td>
<td>28.4 ± 12.9 (10.0–50.2)</td>
<td>45</td>
</tr>
<tr>
<td>15</td>
<td>39.6 ± 14.4 (17.0–64.2)</td>
<td>36</td>
<td>43.0 ± 16.4 (19.9–69.7)</td>
<td>38</td>
</tr>
<tr>
<td>30</td>
<td>51.7 ± 10.3 (32.8–64.0)</td>
<td>20</td>
<td>59.0 ± 18.6 (38.0–94.8)</td>
<td>32</td>
</tr>
<tr>
<td>45</td>
<td>58.6 ± 9.5 (42.0–69.5)</td>
<td>16</td>
<td>66.3 ± 16.1 (40.0–95.0)</td>
<td>24</td>
</tr>
<tr>
<td>60</td>
<td>62.3 ± 8.6 (45.0–73.1)</td>
<td>14</td>
<td>70.7 ± 15.9 (41.7–100.2)</td>
<td>22</td>
</tr>
</tbody>
</table>

\textsuperscript{a}Data are presented as mean ± SD (range).

\textsuperscript{b}CL\textsubscript{CR} units are mL/min per 1.73 m\textsuperscript{2}.

\textsuperscript{c}Interindividual CV.

\textsuperscript{d}Between groups 3 and 1.

\textsuperscript{e}CI, confidence interval.

\textsuperscript{f}Between groups 3 and 4.

\textsuperscript{g}vs group 1.

\textsuperscript{h}vs group 3.
Analysis of the data according to Bland and Altman (16) showed a similarly good agreement between the FPIA and HPLC methods in controls and uremic patients. The mean difference (95% limits of agreement) between the values obtained by the FPIA and HPLC methods was 0.2 (−8.4; 8.8) µg/L in healthy subjects and −1.6 (−11.9; 8.7) µg/L in patients with severe renal dysfunction.

Our results show that MEGX concentrations are significantly higher in patients with severe renal impairment. The observed differences cannot be attributed to variables that affect MEGX production, such as sex, age, and physical characteristics, because patients and controls were matched for sex, age, and body mass index. We can also exclude that the higher MEGX concentrations observed in uremic patients were the result of positive interferences with the TDx FPIA by substances that had accumulated in uremic plasma because the predose (0 min) value was subtracted from values obtained at the various postinjection times. Because the renal clearance of MEGX is ~2% of its total body clearance (8), reduced renal excretion cannot be responsible for the higher MEGX concentrations found in uremic patients. The observation that MEGX concentrations in anuric patients are similar to those found in healthy subjects definitely rules out this possibility. Therefore, alteration of hepatic lidocaine metabolism appears to be the most plausible explanation for the observed results. “Normalisation” of altered metabolic capacity with hemodialysis is not an infrequent finding. It has been observed in both animal and human studies and has been attributed to the presence in uremic plasma of an endogenous inhibitor of drug metabolism that can be cleared by hemodialysis (3). Therefore, the possibility may be considered that a “uremic toxin” is responsible for the inhibition of further MEGX biotransformation.

Whatever the explanation for the present observations, the results of this study have various practical implications:

• They confirm previous findings indicating that the interindividual variability in MEGX concentrations decreases with increased sampling time and that the efficiency of the test is maximal at 60 min (7, 8). As can be appreciated from Table 1, in spite of our efforts to minimize known sources of variability, the CVs were still rather high at 15 min. This may explain why studies adopting this sampling time have not infrequently found the MEGX test to be of limited value [Ref. (2) and references therein]. The results of this and our previous studies (7, 8) suggest that, at variance with the prevailing current practice, 60-min blood samples should preferably be used for MEGX determination.

• Because MEGX concentrations increase significantly with declining renal function, studies comparing healthy subjects with patients suffering from liver disease or patients with different degrees of hepatic dysfunction should make use of study groups matched for glomerular filtration rate.

• The MEGX test currently is used to identify which liver grafts will guarantee satisfactory posttransplant organ function and to assign due priority to patients awaiting liver transplantation (2). Our findings imply that for a proper evaluation of the MEGX test in potential liver donors, their renal function should be taken into consideration. Studies in patients with end-stage liver disease are now necessary to see whether the same relationship between MEGX concentrations and renal function also holds in these patients.

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References