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# Liver function tests and lidocaine metabolism (MEGX test) during i.v. CMF therapy in breast cancer

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**The measurement of monoethylglycinexylidide (MEGX test) is considered a sensitive method for the evaluation of hepatic metabolic capacity. The multidrug chemotherapy CMF (cyclophosphamide 600 mg/m$^2$, methotrexate 40 mg/m$^2$, 5-fluorouracil 600 mg/m$^2$) is widely used in breast cancer patients but very few clinical studies have investigated its possible liver toxicity. We have prospectively evaluated the possible acute liver toxicity after a cycle (i.e. two courses) of CMF by means of the measurement of standard liver function tests and of MEGX, i.e. the main lidocaine (Lid) metabolite after the i.v. injection of Lid. Consecutive patients ($n = 15$), aged 43–68 years, were radically operated on because of $M_0$ primary breast cancer and candidates for adjuvant CMF because of nodal axillary involvement ($pN_1$) were studied. Tests were performed before the first (given at day 1) and 48 h after the second course (given at day 8) of an i.v. CMF regimen to be repeated every 28 days. Full blood count, serum ALT, AST, γ-GT, alkaline phosphatase and albumin were measured with standard methods. To investigate the appearance of MEGX, blood samples were taken before, and 5, 10, 15, 20, 25, 30 and 60 min after i.v. Lid injection. MEGX serum concentration was measured by means of a fluorescent polarization immunoassay. We found no significant variation between pre- and post-CMF standard liver function tests with the exception of ALT levels, which, however, decreased (mean 48%, $p < 0.05$). The MEGX serum concentration was significantly increased over the sampling time period and the 42% mean rise was statistically significant ($p < 0.001$). Moreover, the post-CMF increase of circulating MEGX was steeper than the basal pre-CMF values. The slopes relating to the curves of MEGX formation over the first 20 min were 3.30 and 2.24, respectively ($p < 0.001$). In conclusion, no hepatic acute toxicity was observed during the CMF chemotherapy. Further studies are required to understand the meaning of the unexpected MEGX rise.**

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## Introduction

The measurement of monoethylglycinexylidide (MEGX) serum concentrations, generally performed at one fixed time after the i.v. injection of lidocaine (Lid), the so-called MEGX test, has been recently proposed as a dynamic test for the study of the liver function.[1–3] After i.v. administration, Lid is rapidly metabolized into the liver by the cytochrome P-450 3A4 to its *N*-deethylated derivative, MEGX. The MEGX is further converted to other metabolites and only 4% of the injected Lid dose is excreted by the kidney as unchanged MEGX.[4–6] The so-called MEGX test is considered to represent a sensitive technique, with some advantages over other dynamic or static tests, for the evaluation of the functional hepatic reserve in cirrhotic patients[7–11] and a good index of short-term prognosis in candidates for hepatic transplantation.[12,13] Lid metabolite formation has also been used to predict the quality of the organ to be transplanted,[14–17] and early and long-term graft survival in liver recipients.[18–20] The test has also been used in intensive care unit patients and it has been proposed as a predictor of survival in these chronically ill subjects,[21] as well as in cancer patients to evaluate the extent of metastatic liver involvement.[22,23]

Liver toxicity may represent a well known adverse effect of antiblastic chemotherapy.[24,25] Thus, we have studied some standard liver function tests and also MEGX formation after Lid injection in patients with breast cancer receiving antiblastic chemotherapy. This chemotherapy was i.v. CMF (cyclophosphamide, methotrexate and 5-fluorouracil), a

combination chemotherapy used worldwide in the treatment of breast cancer.[26]

Results show that the CMF does not induce acute liver toxicity and that, after the chemotherapy, MEGX levels are increased instead of being unchanged or reduced.

## Patients and methods

After radical surgery for non-metastatic ($M_0$) primary breast cancer, 15 consecutive patients (mean age 53 years, range 43–68 years), candidates for adjuvant CMF combination chemotherapy because of axillary lymphonodal involvement ($pN_1$), were included in the present prospective study. Inclusion–exclusion criteria indicated that patients did not suffer from kidney or cardiovascular disease or heart rhythm disturbances, did not receive digoxin or cardiovascular therapy of any other type, or chronic treatments especially with benzodiazepines, and were free of hepatic disease and biliary stones (as a result of anamnesis, liver function tests, liver and biliary ultrasonography). Serological tests for A, B and C hepatitis viruses were available in all cases, and no patient was affected. Patients were not alcohol abusers or smokers (admitted 5 cigarettes/day).

Chemotherapy was based on i.v. cyclophosphamide 600 mg/m$^2$, methotrexate 40 mg/m$^2$, 5-fluorouracil 600 mg/m$^2$, day 1 and 8, every 28 days. This therapy was planned for a total of six cycles (12 administrations). Before each therapy cycle patients were also given i.v. an antiemetic therapy, i.e. granisetron 3 mg and methylprednisolone 20 mg. The quality of life measurement included careful surveillance of gastrointestinal toxicity as well as body weight recording, and the evaluation of fluid intake and escretion.

Blood samples for full blood count, ALT, AST, $\gamma$-GT, alkaline phosphatase (AP), albumin measurements and MEGX test were taken 24 h before the first and 48 h after the second CMF administration of one chemotherapy cycle. Standard liver function tests were performed by means of current nephelometric and catalytic methods. Lid at 1.00 mg/kg b.w. was i.v. injected over 2.5 min at 9.00 a.m. into the antecubital vein to the seated patient after overnight fasting. Possible adverse effects after Lid injection were carefully recorded. Blood samples were collected from the opposite antecubital vein, immediately before, and 5, 10, 15, 20, 25, 30 and 60 min after the Lid injection. MEGX concentration was detected by a TDx fluorescent polarization immunoassay (FPIA) system (Abbott Diagnostics, Chicago, IL) in a 100 $\mu$l serum volume. In our laboratory the detection limit was 2 ng/ml and the interassay coefficient of variation was 9–12%.

Each patient was the control of herself and Student's paired *t*-test was used for statistical analysis.

## Results

As far as the toxicity is concerned, after the injection of Lid a mild and spontaneously reversible ear ringing and dizziness were observed in 13 of 15 patients (87%), and the disturbances lasted no more than 5 min. No patient refused the control test after CMF because of these side effects. No emesis, diarrhea, diuresis or body weight modification occurred in the days between the two administrations of CMF.

A comparison was made between basal and post-CMF blood and liver tests. Among the hematological and standard biochemical tests performed after one CMF cycle (two courses; day 1 and 8), only the ALT activity had a statistically significant variation ($p < 0.05$) of 48.1% from the basal value. In particular, no change was observed in the hematocrit and serum albumin.

Results of MEGX test are shown in Table 1. After chemotherapy there was an increase of MEGX levels at each time point considered, with a statistical significance at 20, 30 and 60 min ($p < 0.01$), and at 25 min ($p < 0.05$). The $AUC_{5-60}$ calculated from the MEGX concentration time curves obtained before and after chemotherapy differed by 42.9%. During the first 20 min from Lid injection, the concentration–time curves (linear regression) of pre-chemotherapy and post-chemotherapy MEGX levels had slopes of 2.24 and 3.30, respectively.

**Table 1.** MEGX levels (ng/ml) before and after one course of CMF (mean ± SD)

| Time (min) | Before | After | $p^a$ | Δ% |
|---|---|---|---|---|
| 5 | 9.99 ± 7.1 | 11.92 ± 16.5 | 0.644 | 19.3 |
| 10 | 20.93 ± 11.6 | 32.76 ± 28.0 | 0.149 | 56.5 |
| 15 | 32.50 ± 15.1 | 48.62 ± 29.2 | 0.057 | 49.6 |
| 20 | 44.85 ± 20.1 | 64.13 ± 25.3 | 0.003 | 43.0 |
| 25 | 47.53 ± 17.0 | 67.41 ± 23.0 | 0.041 | 41.8 |
| 30 | 48.52 ± 17.6 | 68.65 ± 26.7 | 0.000 | 41.5 |
| 60 | 51.25 ± 12.9 | 72.94 ± 21.0 | 0.001 | 42.3 |

[a]Student's paired *t*-test

After the first 20 min the serum concentration of MEGX reached a plateau which remained unchanged up to 60 min (Figure 1).

## Discussion

Dose-related hepatotoxicity has been observed after prolonged administration of methotrexate.[27,28] When investigated by means of standard biochemical tests and measurement of bromosulfophtalein plasma concentration (only after 45 min from the i.v. injection of the dye), no cumulative liver toxicity has been reported after the so-called 'oral' CMF chemotherapy in which cyclophosphamide was given orally at 100 mg/m$^2$/day for 14 consecutive days.[29,30] A retrospective analysis was performed in a large cohort of patients treated with six or 12 oral postoperative CMF cycles as adjuvant chemotherapy after surgery for breast cancer.[29] The timing of liver function investigation, i.e. the time interval between the end of CMF and that of the liver function study, was not specified. Moreover, the comparison was not made against the results obtained before the CMF was started in the same patient, but versus a group of control subjects who did not receive CMF. After the CMF was terminated during the next follow-up period, liver function tests were analyzed and AP, either alone or associated with alteration of SGOT, SGPT and LDH, was considered as the major sign of liver damage (patients with bone metastasis were excluded).[29] On these bases, no difference was detected in the percentage of liver abnormalities either between the two treated groups (six or 12 CMF cycles) or between CMF patients and control women.[29]

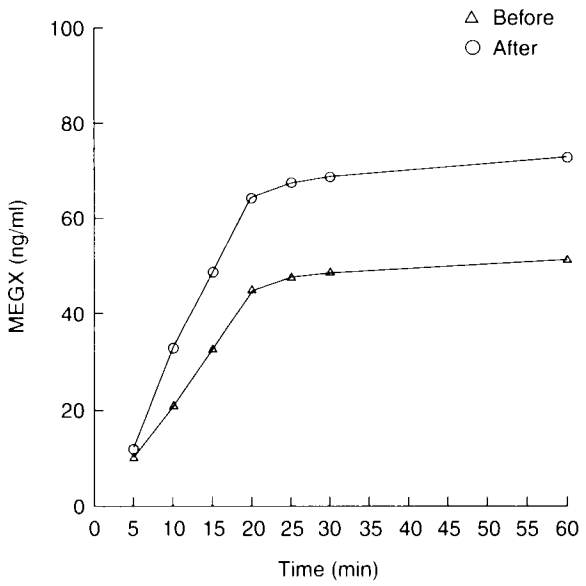


**Figure 1.** Behavior of MEGX serum concentrations (mean values) in breast cancer patients before and after one cycle of CMF.

In patients with advanced breast cancer and treated with i.v. CMF, only four enzymes, i.e. AST, ALT, γ-GT and AP, were studied before each CMF course and 24 h after its termination. Acute liver toxicity was considered when pathological values for at least three out of the four enzymes were present.[30] In 6.6% of patients, a post-CMF rise of AST, ALT and γ-GT was observed. One patient subsequently developed a gradual worsening of her hepatic scintiscan, and the liver biopsy revealed signs of steatosis and fibrosis.[30]

These two studies greatly differ from each other.[29,30] The first one was devoted to retrospectively analyze the possible cumulative effect of chemotherapy at various intervals after the oral adjuvant CMF (six or 12 cycles).[29] The second one was prospectively performed to study possible acute and chronic toxicity during palliative i.v. CMF.[30] Moreover, there were few available tests and none was based on a xenobiotic compound clearance.

In our patients during adjuvant i.v. CMF, standard liver function tests failed to demonstrate any appreciable acute toxic effect of two courses, i.e. one cycle of chemotherapy. Nevertheless, in the same patients Lid metabolism was remarkably influenced by the CMF. After Lid injection, the post-CMF serum concentration time curve showed a significant increase in MEGX levels and this rise was unexpected.

The rise of the MEGX concentration may be related to: (i) an increase of the intrahepatic blood flow,[1,13,51] (ii) a reduction of the volume of the MEGX distribution,[1,32] (iii) a modification of the activity of the different enzymes involved in Lid/MEGX metabolism,[33,34] and (iiii) the administration of methylprednisolone 20 mg and granisetron 3 mg, that might have influenced the liver Lid metabolism.

We did not measure the hepatic blood flow but it seems very unlikely that the CMF could have exerted such an effect. As far as the blood volume is concerned, in order to exclude or to consider highly improbable a reduction of plasma volume, we note that the hematocrit and the albumin concentration were found to be unchanged. The most probable explanation for the observed higher MEGX levels after CMF may be related to the third hypothesis, i.e. to the occurrence of some interference with the enzyme activity. It is possible that MEGX formation

is raised through the induction of Lid metabolism, whereas a reduction of MEGX clearance seems unlikely. Others indicators of enzyme induction as well as microsomal function should be studied.

In conclusion, we have observed that after the administration of CMF no acute modification of standard liver function tests occurred, but that MEGX serum levels, following the Lid administration, increased significantly. Further studies are needed to clarify the cause and the mechanism of this rise and its possible clinical relevance.

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