

Induction of CYP2E1 activity in liver transplant patients as measured by chlorzoxazone 6-hydroxylation

Objective: To examine the phenotypic expression of CYP2E1 in liver transplant patients, as measured by the in vivo probe chlorzoxazone, and to evaluate CYP2E1 activity over time after transplantation.

Methods: Thirty-three stable liver transplant patients were given 250 mg chlorzoxazone within 1 year after transplantation as part of a multiprobe CYP cocktail; urine and blood were collected for 8 hours. Chlorzoxazone and 6-hydroxychlorzoxazone concentrations were determined by HPLC. Twenty-eight healthy control subjects, eight patients with moderate to severe liver disease, and four patients who had not received liver transplants were also studied for comparison. The chlorzoxazone metabolic ratio, calculated as the plasma concentration of 6-hydroxychlorzoxazone/chlorzoxazone at 4 hours after chlorzoxazone administration, was used as the phenotypic index. In a subgroup of patients and control subjects, additional blood samples were obtained to allow for the calculation of chlorzoxazone pharmacokinetic parameters by noncompartmental methods.

Results: The chlorzoxazone metabolic ratio for the liver transplant patients in the first month after transplantation (mean \pm SD, 6.4 ± 5.1) was significantly higher than that after 1 month after surgery (2.1 ± 2.0), when the chlorzoxazone metabolic ratio was not different from control subjects (0.8 ± 0.5). The chlorzoxazone metabolic ratios in the patients who had not received liver transplants (1.1 ± 0.7) were equivalent to those of healthy control subjects. The maximum observed 6-hydroxychlorzoxazone plasma concentration was 3046 ± 1848 ng/ml in seven liver transplant patients in the first month after surgery compared with 1618 ± 320 ng/ml in 16 healthy control subjects ($p < 0.05$). The maximum observed concentration of chlorzoxazone, the chlorzoxazone apparent oral clearance, and the formation clearance of 6-hydroxychlorzoxazone were also significantly different between the groups.

Conclusions: We conclude that significant induction of CYP2E1, as indicated by the chlorzoxazone metabolic ratio, occurs in the first month after surgery in liver transplant patients and that drugs that are substrates for CYP2E1 may require dosage alteration during that period. Contrary to expectations, drug metabolism is not uniformly depressed after liver transplantation. (Clin Pharmacol Ther 1998;63:296-302.)

Gilbert J. Burckart, PharmD, Reginald F. Frye, PharmD, PhD,
Patrick Kelly, PharmD, Robert A. Branch, MD, Ashok Jain, MD,
John J. Fung, MD, PhD, Thomas E. Starzl, MD, PhD, and
Raman Venkataramanan, PhD *Pittsburgh, Pa.*

From the Department of Pharmaceutical Sciences, the Center for Clinical Pharmacology, and the Thomas E. Starzl Transplantation Institute, University of Pittsburgh.

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Reprint requests: Gilbert J. Burckart, PharmD, University of Pittsburgh, School of Pharmacy, 721 Salk Hall, Pittsburgh, PA 15261.

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Alterations in drug absorption, distribution, metabolism, and urinary and biliary excretion have been documented at various times after organ transplantation.¹ Drug metabolism in liver transplant patients is of particular concern because the liver is primarily responsible for the biotransformation of most xenobiotics. The procedure of transplanting a complete or partial liver from a donor to the recipient involves a number of steps that ultimately affect drug metabolism. The process of preservation, reper-

fusion injury, inflammatory changes associated with the surgical procedure, technical complications involving the flow of blood and bile, and the immunologic response of the recipient all produce complex effects that primarily or secondarily alter drug disposition.

The cytochrome P450 enzymes (CYP) are primarily responsible for the biotransformation of drugs, and more than 30 different human isoforms exist. The CYP isozyme 2E1 (CYP2E1) is responsible for the bioactivation of many suspect carcinogenic compounds including *N*-nitrosodimethylamine, aniline, chlorinated and fluorinated hydrocarbons, benzene, and *N*-alkylformides.²⁻⁵ CYP2E1 is also important in the metabolism of alcohol and pharmacologic agents such as acetaminophen (INN, paracetamol) and isoniazid.⁶⁻⁷ Because the catalytic activity of CYP2E1 may be an important modulator of the toxicity or carcinogenicity of these compounds, non-invasive methods to estimate the *in vivo* activity of this enzyme in humans have been proposed.⁸⁻⁹ Chlorzoxazone is a centrally acting skeletal muscle relaxant that primarily undergoes hydroxylation to form 6-hydroxychlorzoxazone. This oxidative reaction has been shown *in vitro* to be catalyzed by CYP2E1.¹⁰ Although CYP1A1 may also be involved in the 6-hydroxylation of the drug, many factors support chlorzoxazone as a probe of CYP2E1 activity.¹¹ The use of chlorzoxazone as a phenotypic probe has been applied in various populations.¹²

Previous work in our group had indicated that CYP2E1 activity, as measured by the 6-hydroxylation of chlorzoxazone, was reduced in the presence of moderate to severe liver disease.¹³ Whether these same changes would be observed in patients whose liver had received the preservation and surgical challenge of the liver transplant operation was unknown. The initial hypothesis related to the CYP enzymes and liver transplantation was that all of the isozymes would initially have depressed function caused by ischemic and inflammatory changes, but that a differential recovery of CYP function should be observed. This study was undertaken to examine whether changes occur in the phenotypic expression of CYP2E1 after liver transplantation as measured by the *in vivo* probe chlorzoxazone and to examine the time course of normalization if changes did occur.

METHODS

Liver transplant patients. This study was approved by the Biomedical Institutional Review Board of the

University of Pittsburgh, and all patients undergoing orthotopic liver transplantation at the University of Pittsburgh Medical Center were considered to be eligible for study participation. The transplant procedure has been described in detail previously¹⁴ and the anesthetic used in these patients was primarily isoflurane. Patients were studied only during periods in which they were considered to be clinically stable. Patients were excluded from the study if they were receiving agents known to produce significant induction (anticonvulsants or rifampin [INN, rifampicin]) or inhibition (ketoconazole, fluconazole, cimetidine, or erythromycin) of CYP enzymes or if they had an estimated creatinine clearance¹⁵ of less than 50 ml/min. Although multiple studies were not possible in all patients, attempts were made to study the subjects in the early posttransplant period (1 to 2 weeks), 1 to 4 months after transplant, and during long-term follow-up (6 to 12 months).

Patients who had not received liver transplants. To control for the concurrent administration of immunomodulating agents, kidney or heart transplant patients who were receiving the same immunosuppressive regimen as the liver transplant patients were recruited for study. The anesthetic used for these procedures was primarily isoflurane. As in the case of the liver transplant patients, these subjects were required to be clinically stable, to not be taking any known interacting medication, and to have an estimated creatinine clearance of greater than 50 ml/min.

Normal subjects and patients with liver disease. Eight patients with moderate ($n = 5$) or severe ($n = 3$) liver disease and 28 healthy control subjects participated after giving written informed consent. Patients with liver disease were classified with the Child-Pugh score.¹⁶ Subjects were instructed to abstain from caffeine- or alcohol-containing products for at least 3 days before each study visit.

Study protocol. After an overnight fast, subjects received 250 mg chlorzoxazone as part of an oral multiprobe cocktail that also included 100 mg caffeine, 100 mg dapsone, 100 mg mephenytoin, and 10 mg debrisoquin (INN, debrisoquine). None of the five agents given in this cocktail influences the metabolism of the other agents given concurrently.¹⁷ The five drugs were taken simultaneously with approximately 240 ml water. Venous blood was collected through an indwelling catheter before and at 4 and 8 hours after drug administration. In some liver transplant patients ($n = 7$) and healthy control subjects ($n = 16$), blood samples were obtained

Table I. Patient demographics from each of the study groups

| | Healthy control subjects | Patients with liver disease | Patients who had not received liver transplants | Liver transplant patients |
|----------------------------|--------------------------|-----------------------------|---|---------------------------|
| <i>n</i> | 28 | 8 | 4 | 30 |
| Age (yr) | 33.9 ± 17.1 | 51.8 ± 16.1 | 49.9 ± 17.1 | 49.2 ± 11.5 |
| Gender | | | | |
| Male | 26 | 6 | 3 | 21 |
| Female | 2 | 2 | 1 | 9 |
| Weight (kg) | 80.6 ± 16.1 | 85.8 ± 24.9 | 77.7 ± 16.9 | 82.2 ± 18.9 |
| CL _{CR} (ml/min) | 109.8 ± 34.6 | 90.1 ± 29.5 | 62.5 ± 11.5 | 77.8 ± 31.7 |
| Postoperative days (range) | | | 10-161 | 7-336 |

CL_{CR}, Creatinine clearance.

before and at 2, 4, 6, 8, and 12 hours after drug administration. Plasma was harvested and stored at -20° C until analysis. Urine was collected before drug administration and for 8 hours after. The total volume was recorded and an aliquot was stored at -20° C until analyzed.

Sample analysis. Concentrations of chlorzoxazone and 6-hydroxychlorzoxazone in plasma and 6-hydroxychlorzoxazone in urine were measured with use of a reversed-phase HPLC procedure described previously.¹⁸ The within- and between-day coefficients of variation of this assay are less than 10%. Serum and 8-hour urine creatinine determinations provided the basis for the calculation of *measured* creatinine clearance in each subject.

Data analysis. Subjects were excluded from analysis if they had a *measured* creatinine clearance of less than 40 ml/min. The activity of CYP2E1 was estimated with the ratio of 6-hydroxychlorzoxazone to chlorzoxazone in the 4-hour plasma sample (chlorzoxazone metabolic ratio). In those patients in whom more blood samples were obtained, additional chlorzoxazone pharmacokinetic parameters were calculated by noncompartmental methods. The elimination rate constant and half-life were obtained by nonlinear least-squares regression of the terminal concentration-time data. The area under the concentration versus time curve (AUC) was calculated by the trapezoidal rule with extrapolation to infinity. The apparent oral clearance of chlorzoxazone was determined as follows: Dose/AUC(0-∞). The total urinary recovery of 6-hydroxychlorzoxazone was determined, and the formation clearance was calculated as the total amount recovered in urine divided by the chlorzoxazone plasma AUC over the same period.

Statistical analysis. The metabolic ratios were compared between all groups by ANOVA. Chlor-

zoxazone pharmacokinetic parameter estimates in liver transplant patients and healthy control subjects were compared by *t* test. Differences were considered statistically significant when *p* ≤ 0.05. Relationships between the chlorzoxazone metabolic ratio and selected patient variables were assessed by linear regression analysis. All calculations were performed with use of SAS Software, version 6.11 (SAS, Cary, N.C.).

RESULTS

Thirty-three liver transplant patients were enrolled in this study; one patient was studied on five separate occasions, two patients were studied four times, three patients were studied three times, eight patients were studied twice, and 19 patients were studied one time. Even though all subjects had an *estimated* creatinine clearance of greater than 50 ml/min, nine patient studies had to be excluded from analysis because the *measured* creatinine clearance was less than 40 ml/min, which eliminated three patients from the final analysis. Four patients who had not received liver transplants were studied on five occasions, two kidney transplant patients were studied at 10 and 20 days after surgery, and two heart transplant patients were studied (one at 24 days, and one at 102 and 161 days after surgery). The demographics of the subjects who were included in the analysis are presented in Table I.

The chlorzoxazone metabolic ratios of the liver transplant patients were significantly elevated in the first month after liver transplantation compared with healthy control subjects, patients with liver disease, and the patients who had not received liver transplants (Fig. 1). This elevated ratio gradually declined over the subsequent months to values similar to those observed in normal volunteers (Fig. 2). Sequential studies for the liver transplant patients

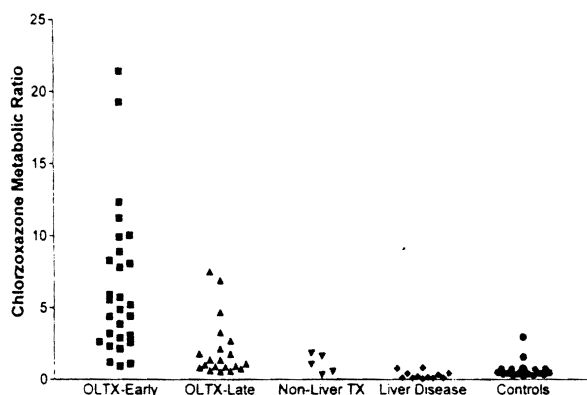


Fig. 1. The 4-hour chlorzoxazone metabolic ratio in the five study populations: liver transplant patients in the first month after transplantation (OLTX-Early), liver transplant patient studies beyond one month after transplantation (OLTX-Late), patients who had not received liver transplants (Non-Liver TX), patients with liver disease, and healthy control subjects. Only the OLTX-Early patients were significantly different from the other groups by ANOVA.

with at least three studies after the elimination of the renally impaired subjects are shown in Fig. 3. The 8-hour urinary recovery of 6-hydroxychlorzoxazone did not change significantly over time when plotted against days after liver transplant ($r = -0.19$, $p = 0.21$).

The concentration versus time profile of chlorzoxazone and 6-hydroxychlorzoxazone were markedly different in liver transplant patients in the first postoperative month compared with healthy control subjects (Fig. 4). In the liver transplant patients, 6-hydroxychlorzoxazone concentrations exceeded the chlorzoxazone concentrations at all time points, whereas this did not occur in normal volunteers. The kinetic parameters calculated for the seven liver transplant patients and for the 16 healthy control subjects are presented in Table II.

No significant relationship was observed between the chlorzoxazone metabolic ratio and the daily milligram per kilogram dose of tacrolimus ($r = 0.10$; not significant), but a weak correlation was found with the milligram dosage of prednisone ($r = 0.33$; $p = 0.04$). The chlorzoxazone metabolic ratio was significantly correlated with the serum biochemical markers γ -glutamyltransferase ($r = 0.37$; $p = 0.014$), bilirubin ($r = 0.76$; $p < 0.001$), and ALT ($r = 0.31$; $p = 0.038$) but did not correlate with AST ($r = 0.06$; not significant).

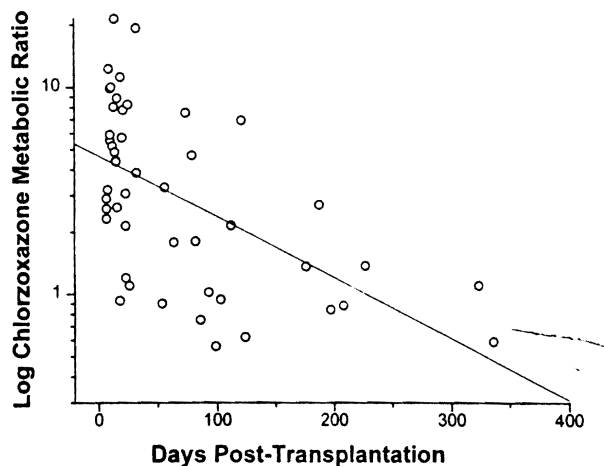


Fig. 2. The 4-hour chlorzoxazone metabolic ratio versus days after transplantation in the liver transplant patients ($r = -0.56$; $p < 0.001$).

DISCUSSION

The ratio of 6-hydroxychlorzoxazone to chlorzoxazone was markedly elevated in liver transplant patients in the first month after transplantation. The higher chlorzoxazone metabolic ratio implies that CYP2E1 activity is enhanced in these patients and its subsequent decline indicates that the enzyme activity returns to values comparable to those observed in healthy control subjects over time.

A number of factors that are altered after liver transplantation were examined in relation to the alteration of the chlorzoxazone metabolic ratio. The fact that the chlorzoxazone metabolic ratio is significantly depressed in the patients with liver disease compared with the normal healthy subjects indicates that hepatocellular or biliary disease by itself does not produce an elevation in the chlorzoxazone metabolic ratio. The operative procedure probably did not produce this elevation in CYP2E1 activity, and biliary ligation in an animal model leads to a down-regulation of CYP2E1 activity.¹⁹ No elevation in the chlorzoxazone metabolic ratio was observed in patients who had not received liver transplants who were also given the same immunosuppressant agents. Although the anesthetic agent routinely used in transplant patients, a fluorinated hydrocarbon, is a substrate for CYP2E1, the patients who had not received liver transplants also received this agent but did not have an increased chlorzoxazone metabolic ratio.

Cytokine induction during the early posttrans-

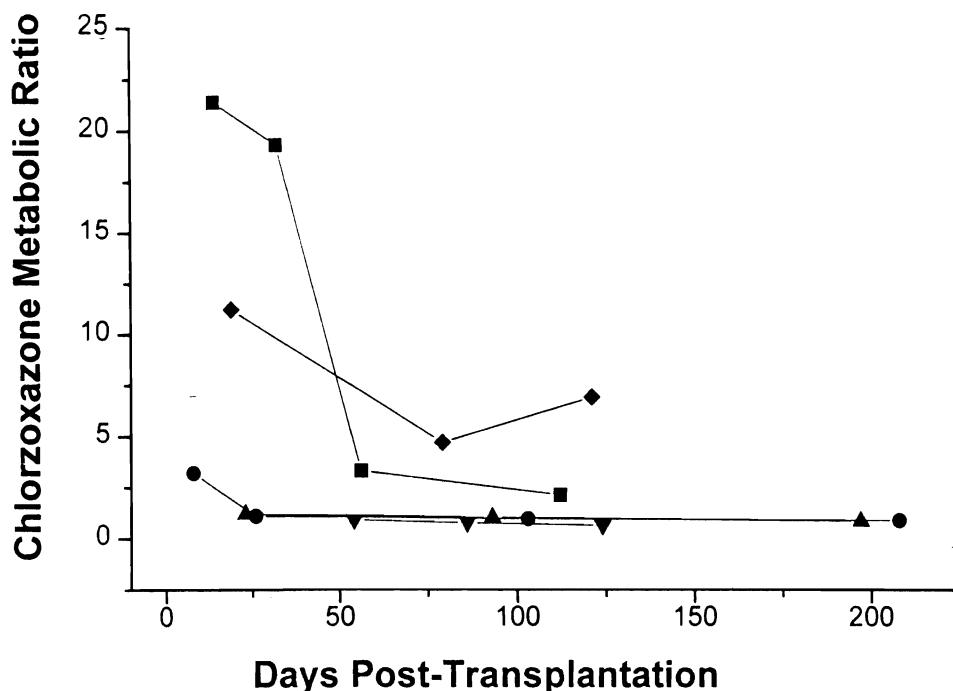


Fig. 3. The 4-hour chlorzoxazone metabolic ratio versus days after transplantation in the five liver transplant subjects who were studied at least three times during their follow-up. Each patient is described by a separate set of symbols.

plantation period is pronounced in liver transplant patients because of reperfusion injury, rejection, infection, and the inflammatory responses that accompany these pathologic processes. Recent studies have provided direct evidence for the induction of CYP2E1 by cytokines. Abdel-Razzak et al.,²⁰ studied the effects of cytokines on the CYP isozyme messenger ribonucleic acid (mRNA) expression in human hepatocyte cultures and found that the only isozyme that was induced in the presence of interleukin-4 was CYP2E1. Tindberg et al.,²¹ also found that CYP2E1 mRNA was induced up to sevenfold in rat brain cortical glial cell cultures that were exposed to lipopolysaccharide or interleukin-1 β . Therefore the induction of CYP2E1 activity in liver transplant patients exposed to high levels of cytokines is a viable explanation for the results observed in this study.

Another possible cause of chlorzoxazone metabolic ratio elevation could be the slower elimination of the 6-hydroxychlorzoxazone metabolite in the liver transplant patients.²² To exclude this variable, patients with diminished renal function who might have reduced renal elimination of the 6-hydroxy-

chlorzoxazone conjugate were excluded from analysis. Because a large portion of the administered chlorzoxazone dose is not recovered in the urine, one could speculate that the 6-hydroxychlorzoxazone metabolite may be secreted in bile. If biliary dysfunction reduced the amount of metabolite eliminated in the bile, thereby increasing plasma concentrations of 6-hydroxychlorzoxazone, we would have expected a higher urinary metabolite recovery when the chlorzoxazone metabolic ratio was higher. However, the urinary excretion of 6-hydroxychlorzoxazone did not significantly correlate with chlorzoxazone metabolic ratio, number of days after transplant in the liver transplant patients, or serum bilirubin. In addition to the lack of association between chlorzoxazone metabolic ratio and 6-hydroxychlorzoxazone urinary recovery, we did not observe a significant change over time in the 8-hour urinary recovery of 6-hydroxychlorzoxazone in the liver transplant patients.

The findings of this study are significant both to the understanding of the regulation of CYP-mediated enzymatic degradation of endogenous and exogenous substrates and for the practical

Table II. Chlorzoxazone and 6-hydroxychlorzoxazone pharmacokinetic parameters in liver transplant patients within the first postoperative month and in healthy control subjects after single-dose administration of 250 mg chlorzoxazone

| Parameters | Liver transplant patients (n = 7) | Healthy control subjects (n = 16) |
|---------------------------------|-----------------------------------|-----------------------------------|
| <i>Chlorzoxazone</i> | | |
| Plasma C _{max} (ng/ml) | 1440.1 ± 912.7* | 5321.5 ± 1439.8 |
| Plasma t _{1/2} (hr) | 1.7 ± 1.0 | 1.1 ± 0.2 |
| CL/F (ml/min) | 1181.7 ± 908.3* | 407.4 ± 220.1 |
| <i>6-Hydroxychlorzoxazone</i> | | |
| Urinary recovery (mg) | 172.6 ± 21.0 | 158.6 ± 37.1 |
| Plasma C _{max} (ng/ml) | 3046.4 ± 1848.5* | 1617.5 ± 319.9 |
| Plasma t _{1/2} (hr) | 2.1 ± 0.5* | 1.4 ± 0.4 |
| CL _m (ml/min) | 1018.3 ± 913.3* | 263.1 ± 163.1 |

C_{max}, Maximum concentration; t_{1/2}, half-life; CL/F, apparent oral clearance (in which F is the fraction absorbed); C_m, formation clearance.

Data are mean values ± SD.

*p < 0.05 versus healthy control subjects.

applicability of this information to the management of liver transplant patients. This study shows that CYP2E1 activity, as measured by the 6-hydroxylation of chlorzoxazone, can be markedly elevated soon after liver transplantation. Other commonly studied isozymes of the CYP family are either depressed or unaltered during the early postoperative period.²³⁻²⁴ The practical application of this study to liver transplant patients is that increased metabolic degradation of administered drugs that are metabolized by CYP2E1 may lead to either a diminished effect of the agent or to increased drug toxicity from a metabolite. Several of the fluorinated anesthetic agents, such as enflurane and sevoflurane, are metabolized by CYP2E1, and some dosage alteration may be necessary in a liver transplant patient who requires additional surgery in the early posttransplant period. CYP2E1 is also involved in the metabolism of acetaminophen, but our previous observations in 10 liver transplant patients did not find any change in drug elimination or conjugation compared with normal subjects.²⁵

In conclusion, this study has documented a

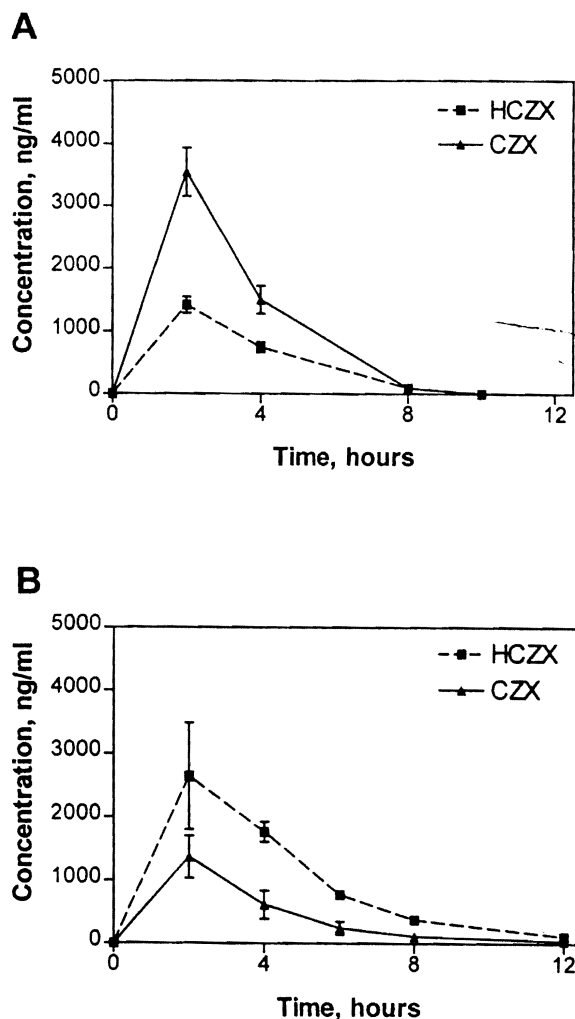


Fig. 4. The plasma concentration versus time profiles for the 16 healthy control subjects (A) and the seven liver transplant patients (B). The concentrations of 6-hydroxychlorzoxazone (HCZX; broken line) and of the parent chlorzoxazone (CZX; solid line) are shown. The maximum observed concentrations and oral clearances for chlorzoxazone and 6-hydroxychlorzoxazone were significantly different in the two groups.

markedly increased activity of CYP2E1 in the early postoperative period for liver transplant patients, as measured by the metabolic ratio of 6-hydroxychlorzoxazone to chlorzoxazone in plasma at 4 hours after an oral dose of 250 mg chlorzoxazone. The chlorzoxazone metabolic ratio returned to values that were observed in normal subjects and the patients who had not received liver trans-

plants between 1 month and 1 year after transplantation. The definitive cause for this induction in CYP2E1 activity is currently unknown. The metabolic capacity of the individual CYP isozymes cannot be assumed to be uniformly depressed in the postoperative period for liver transplant patients, and alterations in drug regimens for substrates of CYP2E1 may be necessary for these patients.

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