Galactose Elimination Capacity as a Prognostic Marker in Patients With Severe Acetaminophen-Induced Hepatotoxicity: 10 Years' Experience

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Background & Aims: **Patients with acetaminophen-induced fulminant hepatic failure may have the capacity for recovery if sufficient liver cell mass remains to allow regeneration. We investigated the prognostic potential of the galactose elimination capacity (GEC) as a noninvasive measurement of functioning liver cell mass in severe acetaminophen-induced hepatotoxicity.** ***Methods:*** **All patients admitted with acetaminophen poisoning during a 10-year period were studied retrospectively. A total of 220 patients who had at least one GEC performed were included in the study.** ***Results:*** **The GEC was lower in patients with than without hepatic encephalopathy (14.5 ± 5.6 μmol/min/kg vs. 23.2 ± 6.7 μmol/min/kg; $P < 0.0001$). Among patients with hepatic encephalopathy, the GEC was significantly higher in spontaneous survivors than in nonsurvivors (16.8 ± 5.6 μmol/min/kg vs. 12.2 ± 4.7 μmol/min/kg; $P < 0.0001$). In a logistic regression analysis, GEC was associated independently with mortality (odds ratio: 1.28 per 1 μmol/min/kg decrease in GEC; 95% confidence interval: 1.14–1.45). A threshold GEC of 16.5 μmol/min/kg to identify nonsurvivors had a sensitivity of 90%, a specificity of 72%, a positive predictive value of 49%, and a negative predictive value of 96%. None of 14 patients with hepatic encephalopathy and a GEC less than 10 μmol/min/kg survived.** ***Conclusions:*** **The GEC was strongly associated with development of hepatic encephalopathy and death from acetaminophen-induced fulminant hepatic failure. The GEC was too unspecific to be used alone for identification of transplantation candidates, but it may be useful as a supplement to other selection criteria.**

The only treatment option that radically improves the outcome of fulminant hepatic failure (FHF) is emergency liver transplantation.[1] However, some patients with FHF, acetaminophen-induced in particular, may have the capacity for spontaneous recovery. Thus, it is of central importance in the management of patients with FHF to identify a subgroup of patients who are unlikely to survive without liver transplantation.

Different selection criteria for urgent liver transplantation have been proposed, and among these the King's College Hospital (KCH) criteria have gained considerable acceptance.[2,3] Problems with the KCH criteria mainly have been ascribed to their limited sensitivity and to the length of time that may pass until a patient fulfills the criteria.[4–6] A possible reason for these shortcomings may be that the KCH criteria, which are based on pH, prothrombin, and creatinine levels, mainly reflect the degree of multiorgan dysfunction associated with FHF and only to a minor degree reflect hepatic dysfunction or the capacity for recovery.

Several tolerance tests have been proposed for quantitative assessment of dynamic liver function.[7] The galactose elimination capacity (GEC) test determines the disappearance rate of galactose owing to phosphorylation by hepatic galalactokinase, which is taken as a measure of functioning liver cell mass.[8–10] The GEC has been studied extensively in patients with chronic liver disease, and it has been identified as a prognostic indicator of mortality in cirrhosis.[11–17] A few studies have shown that GEC is lower in nonsurvivors than in survivors from FHF.[9,18] However, these previous studies only included one case of acetaminophen-induced FHF, and otherwise only case reports and animal studies of GEC in acetaminophen-induced hepatotoxicity have been reported.[18–20]

The objective of this study was to evaluate the GEC test as a prognostic marker in patients with severe acetaminophen-induced hepatotoxicity. In particular, the capability of the GEC to identify appropriate candidates for liver transplantation was examined.

Patients and Methods

The medical records of all patients admitted to Rigshospitalet, Copenhagen, Denmark, with acetaminophen poi-

Abbreviations used in this paper: FHF, fulminant hepatic failure; GEC, galactose elimination capacity; HE, hepatic encephalopathy; INR, international normalized ratio; KCH, King's College Hospital; NAC, N-acetylcysteine; NS, not significant; ROC, receiver operating characteristic.

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Table 1. Anamnestic, Biochemical, and Clinical Data in the 220 Patients Who Had a GEC Test Performed Compared With 651 Patients Who Had Not

	GEC performed (n = 220)	GEC not performed (n = 651)
Age (*yr*)	39 [26–48][a]	31 [21–45]
Sex (*M/F*)	77 (35%)/143 (65%)	223 (34%)/428 (66%)
Intentional/accidental overdose	175 (80%)/45 (20%)[a]	565 (87%)/86 (13%)
Quantity of acetaminophen (*g*)	35 [22–50][a]	25 [15–50]
Time to NAC (*hr*)	24 [16–88][a]	13 [4–26]
Acute co-ingestion of alcohol	37 (17%)	146 (22%)
Regular alcohol abuse	80 (36%)[a]	148 (23%)
INR	4.7 [3.4–6.5][a]	2.1 [1.4–3.4]
Bilirubin level (μ*mol/L*)	107 [55–262][a]	26 [12–52]
Alanine transaminase level (*U/L*)	8900 [5170–12,645][a]	1260 [24–7854]
Creatinine level (μ*mol/L*)	218 [93–520][a]	85 [74–106]
Hepatic encephalopathy	102 (46%)[a]	44 (6.8%)
Liver transplantation	12 (5.5%)[a]	0 (0%)
Death	38 (17%)[a]	24 (3.7%)

NOTE. Values are given as median [1st quartile–3rd quartile].
[a]$P < 0.05$ (χ^2 test or Mann–Whitney test).

soning between 1992 and 2001 were reviewed. Patients who had at least one GEC performed were included in the study. The following information was recorded for each case: age, sex, quantity of acetaminophen ingested, time from acetaminophen ingestion to initiation of N-acetylcysteine (NAC) treatment (time to NAC), regular alcohol abuse, acute co-ingestion of alcohol, biochemistry including international normalized ratio (INR), bilirubin level, alanine transaminase level, creatinine level, GEC and time of GEC, hepatic encephalopathy (HE) grade II–IV, orthotopic liver transplantation performed, death/survival, and cause of death. Regular abuse of alcohol was defined as an excess of 14 U weekly for women and 21 U for men (1 U = 10 g of ethanol). HE was graded according to the Fogarty criteria, and FHF was defined as the development of HE grade II–IV.[21]

All patients were treated immediately with a standard regimen of intravenous NAC for a minimum of 20 hours even on suspicion of acetaminophen poisoning regardless of severity.[22] The majority of patients with severe acetaminophen-induced hepatotoxicity defined by an INR greater than 1.7 were transferred from other hospitals.

The GEC Test

The GEC test was performed preferentially in patients who had developed or were considered at high risk for developing FHF. However, the decision of whether to perform a GEC test was made by the managing physician, and strict criteria were not formulated. The GEC was determined after a single injection of galactose essentially as described by Tygstrup.[8] In short, 25 g of galactose was injected intravenously over a maximum of 5 minutes. Arterial or capillary blood samples were drawn at 5-minute intervals from 25 to 60 minutes after the injection.[23] Galactose concentrations were determined enzymatically, and the GEC was computed according to Tygstrup's[8,24] method with a correction for urinary excretion and uneven distribution of galactose. Normal range of the GEC at our laboratory is 25–55 μmol/kg/min.

Statistics

GEC values are presented as mean ± SD. The Mann–Whitney test was used for the comparison of a variable between 2 subgroups, the Fisher exact test was used for the comparison of frequencies, and Spearman's test was used for correlations. For multivariate analysis a backward, stepwise multiple or logistic regression analysis was applied. Receiver operating characteristic (ROC) analysis was used to identify the optimum threshold value of GEC to discriminate nonsurvivors. Different ROC curves were compared by comparing the area under the ROC curve with estimation of SE according to Hanley and McNeill.[25,26] Data were analyzed using Statistica 6.0 statistical software (StatSoft Inc., Tulsa, OK). $P < 0.05$ was considered statistically significant.

Results

During the 10-year study period, 871 patients were admitted with acetaminophen poisoning. A total of 288 GECs were performed in the 220 patients (25%) who were included in the study. Table 1 shows the anamnestic, biochemical, and clinical data of the 220 included patients in comparison with the 651 patients who were not included. A GEC was performed in 70% of patients (102 of 146) who developed HE and in 68% of patients (50 of 74) who died or were transplanted, showing the select nature of the study population. Of the 24 patients who died without having a GEC performed, one was dead on arrival, 3 died from cardiac arrest shortly after arrival, and 9 were considered terminal at arrival; in 6 patients a GEC was prescribed but never performed,

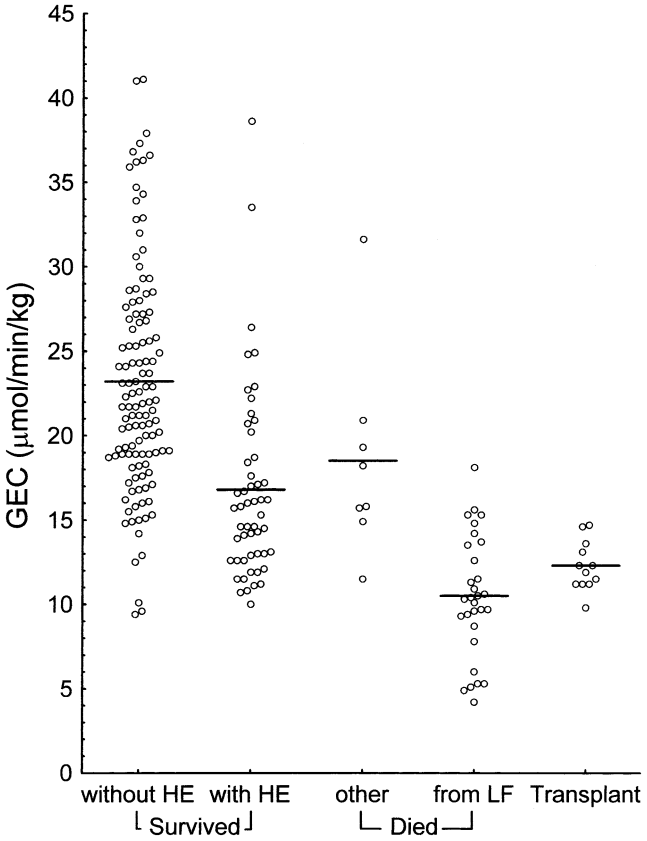

Figure 1. The distribution of initial GEC values in patients who survived with or without HE, in patients who died directly from liver failure (LF) or from other causes, and in patients who were transplanted. Mean is indicated by horizontal lines.

and in the remaining 5 patients a GEC was never prescribed.

In 182 patients, a single GEC was performed. The GEC was performed twice in 24 patients and more than 2 times in the remaining 14 patients.

GECs

GECs (first value only) ranged from 4.2 to 41.1 μmol/min/kg with a mean of 19.2 ± 7.6 μmol/min/kg (Figure 1). The GEC was significantly lower in the 102 patients with HE than in the 118 patients without HE (14.5 ± 5.6 μmol/min/kg vs. 23.2 ± 6.7 μmol/min/kg, respectively; Mann–Whitney: $P < 0.0001$). Among patients with HE, the GEC was significantly higher in the 52 spontaneous survivors than in the 50 patients who died or were transplanted (16.8 ± 5.6 μmol/min/kg vs. 12.2 ± 4.7 μmol/min/kg, respectively; Mann–Whitney: $P < 0.0001$). No difference in GEC was shown between the 38 patients who died without orthotopic liver transplantation and the 12 who were transplanted (12.1 ± 5.3 μmol/min/kg vs. 12.3 ± 1.5 μmol/min/kg, respectively). In the 38 patients who died without orthotopic liver transplantation, death was related directly to liver failure in 30 patients, whereas 8 patients died from complications (infection in 3 patients, cardiac failure in 2 patients, surgical complications in 2 patients, intestinal ischemia in 1 patient) after an improvement in liver function. The GEC was significantly lower in the 30 patients who died directly from liver failure than in the 8 patients who died from complications (10.5 ± 3.6 μmol/min/kg vs. 18.5 ± 6.0 μmol/min/kg, respectively; Mann–Whitney: $P < 0.001$). Figure 1 shows the distribution of GEC values for each of the described outcomes. A considerable overlap between survivors and nonsurvivors was noticed. However, patients with a GEC greater than 16.5 μmol/min/kg were unlikely to die from liver failure, whereas a GEC less than 10 μmol/min/kg in a patient with liver failure appeared to be incompatible with survival.

Factors Associated With GEC

The GEC showed a strong inverse correlation with routine biochemical markers of liver failure such as INR (Spearman: $R = -0.64$; $P < 0.0001$), bilirubin (Spearman: $R = -0.65$; $P < 0.0001$), and creatinine (Spearman: $R = -0.48$; $P < 0.0001$), but not with alanine transaminase (Spearman: $R = -0.12$; P = NS).

The GEC was correlated inversely with age (Spearman: $R = -0.27$; $P < 0.0001$) and with time to NAC (Spearman: $R = -0.23$; $P < 0.001$), but not with quantity of acetaminophen ingested (Spearman: $R = -0.004$; NS). The GEC was significantly lower in patients with than without regular abuse of alcohol (16.8 ± 7.0 μmol/min/kg vs. 20.5 ± 7.6 μmol/min/kg, respectively; Mann–Whitney: $P < 0.0001$), whereas no differences were observed between patients with and without acute co-ingestion of alcohol (20.1 ± 7.2 μmol/min/kg vs. 19.0 ± 7.6 μmol/min/kg; Mann–Whitney: NS) or between men and women (19.2 ± 7.3 μmol/min/kg vs. 19.1 ± 7.7 μmol/min/kg, respectively; Mann–Whitney: NS). In a multiple regression analysis, a high age, a long time to NAC, and regular alcohol abuse were confirmed as independent risk factors of a low GEC, whereas quantity of acetaminophen, acute alcohol co-ingestion, and sex all were eliminated from the analysis.

Effect of Time on GEC

In Figure 2, GEC values are plotted against the time between acetaminophen ingestion (known in 202 cases) and performance of the GEC test. The absolute difference in GEC between survivors and nonsurvivors decreased with increasing time of the GEC (covariate analysis: $P < 0.01$). Thus, for GECs performed no later than 72 hours after acetaminophen ingestion, the GEC

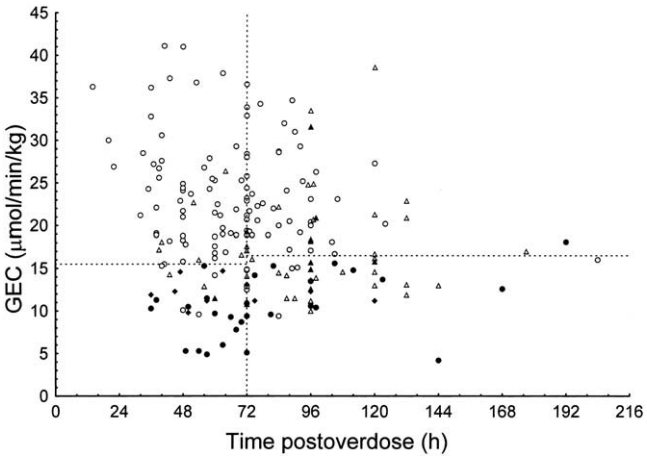

Figure 2. Initial GEC values plotted against time since acetaminophen ingestion (○) in patients without hepatic encephalopathy, (△) in survivors with hepatic encephalopathy, (▲) in patients who died after an improvement in liver function, (●) in patients who died from liver failure, (◆) or patients who were transplanted. Dotted lines depict the discriminative thresholds identified by ROC analysis (see text).

was 22.6 ± 7.3 μmol/min/kg in survivors vs. 10.4 ± 3.5 μmol/min/kg in nonsurvivors, whereas for GECs performed later than 72 hours after acetaminophen ingestion, the corresponding values were 20.0 ± 6.5 μmol/min/kg and 14.5 ± 5.2 μmol/min/kg, respectively.

Figure 3 shows the time course of GEC in patients with repeated measurements. Again, GEC values tended initially to be lower in nonsurvivors than in survivors, but with increasing time the values approximated between the 2 groups.

Prognostic Implications of the GEC

In a logistic regression analysis using GEC together with each of the 3 biochemical components of the KCH criteria (INR > 6.5, creatinine > 300 μmol/L, pH < 7.30) as independent variables, the GEC was associated independently with mortality (odds ratio: 1.28 per 1 μmol/min/kg decrease in GEC; 95% confidence interval: 1.14–1.45; $P < 0.0001$). In Table 2, the prognostic value of different cut-off levels of the GEC was calculated and compared with that of the KCH criteria. In Table 2, both death and orthotopic liver transplantation are considered nonsurvival, but exclusion of the transplanted patients (not shown) did not change the findings substantially. ROC analysis identified a GEC less than 16.5 μmol/min/kg as the optimum threshold to discriminate nonsurvivors (not shown). A GEC less than 16.5 μmol/min/kg was a sensitive but rather unspecific marker of nonsurvival when compared with the KCH criteria. Thus, 45 of 92 patients (49%) with a GEC less than 16.5 μmol/min/kg died in comparison with 5 of 128 patients (4%) with a GEC greater than 16.5 μmol/min/kg (Fisher test: $P < 0.0001$). By comparative ROC analysis (Figure 4), a GEC performed within 72 hours after acetaminophen ingestion provided more prognostic information than a GEC performed later than 72 hours (area under the ROC curve 96.0% [SE 2.2%] vs. 80.2% [SE 3.4%], respectively; $P < 0.01$). However, both were inferior to the KCH criteria with regard to specificity, positive prognostic value, and accuracy (Table 2).

When only the 102 patients with hepatic encephalopathy were included, ROC analysis identified a GEC less than 12 μmol/min/kg as a specific but rather insensitive threshold to discriminate nonsurvivors. A GEC less than 12 μmol/min/kg identified death directly from liver failure significantly better than death from subsequent complications (21 of 30 patients [70%] vs. 1 of 8 deaths [13%], respectively; Fisher test: $P < 0.01$). In contrast, the KCH criteria identified death from liver failure or from subsequent complications equally well (24 of 30 deaths [80%] vs. 6 of 8 deaths [75%]; Fisher test: nonsignificant).

By selecting an even stricter cut-off GEC value at 10 μmol/min/kg, the specificity could be increased to 100% because 14 patients who eventually died were identified exclusively. Of these 14 patients, only 10 also fulfilled the KCH criteria, showing that a GEC less than 10 μmol/min/kg identified patients who were overlooked by the KCH criteria despite having a liver function below the survival limit. Thus, when adding a GEC less than 10 μmol/min/kg to the KCH criteria, their sensitivity and negative predictive value increased at no cost to the specificity (Table 2). In patients with hepatic encephalopathy and a GEC between 10 and 16.5 μmol/min/kg,

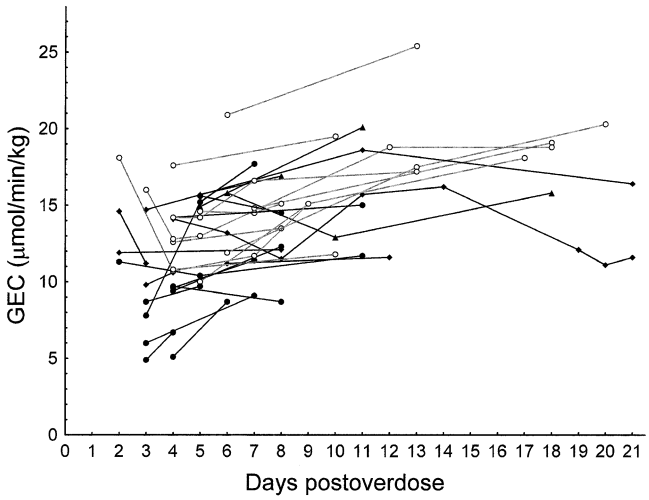

Figure 3. The time course of GEC (○) in survivors, (▲) in individual patients who died after an improvement in liver function, (●) in patients who died from liver failure, or (◆) patients who were transplanted.

Table 2. Assessment of the GEC and the KCH Criteria as Prognostic Indicators in 220 Patients With Severe Acetaminophen-Induced Hepatotoxicity

Indicator	n	Nonsurvivor	Sensitivity	Specificity	Positive predictive value	Negative predictive value
All patients (n = 220)						
GEC < 16.5 μmol/min/kg	92	45	90	72	49	96
KCH criteria	52	37	82	91	71	92
Time to GEC ≤ 72 h (n = 113)						
GEC < 15.5 μmol/min/kg	37	24	96	85	65	99
KCH criteria	25	20	80	94	80	94
Time to GEC > 72 h (n = 89)						
GEC < 16.5 μmol/min/kg	41	16	82	66	44	92
KCH criteria	22	18	73	91	73	91
Patients with hepatic encephalopathy (n = 102)						
GEC < 12 μmol/min/kg	36	28	56	85	78	67
GEC < 10 μmol/min/kg	14	14	28	100	100	59
KCH criteria	52	37	74	71	71	74
KCH criteria *or* GEC < 10 μmol/min/kg	56	41	82	71	73	80

23 of 34 patients (68%) who fulfilled the KCH criteria died in comparison with 8 of 28 patients (29%) who did not (Fisher test: $P = 0.005$).

Discussion

Spontaneous recovery from FHF may occur, provided that the remaining liver cell mass is sufficient to allow time for hepatic regeneration, that the patient has the capacity for regeneration, and that fatal nonhepatic complications are avoided. Thus, a measure of functioning liver cell mass would be expected to identify a subgroup of patients without chance of spontaneous recovery despite supportive treatment. Functioning liver cell mass can be estimated directly from determination of hepatocyte volume in biopsy specimens; however, liver biopsy examination is contraindicated or impractical in most patients with FHF.[27,28] The GEC, which is correlated to liver weight, has been suggested as a noninvasive measure of functioning liver mass.[9,29] In our study, a GEC less than 10 μmol/min/kg appeared to correspond to a remaining liver cell mass below the critical mass required for regeneration, and liver transplantation should be considered strongly. Previous studies in non–acetaminophen-induced FHF have found a similar survival limit.[9,18] A GEC between 10 and 16.5 μmol/min/kg was associated with a high rate of HE, which might result in survival as well as death from liver failure. Thus, the outcome in this middle subgroup must depend on additional factors such as the patient's regenerative capacity, comorbidity, or the development of extrahepatic complications. Patients with a GEC within this interval would be appropriate candidates for liver-assist treatment and should by other means be evaluated for emergency liver transplantation. Finally, a GEC greater than 16.5 μmol/min/kg was associated with an excellent prognosis with a high recovery rate of liver function. Because these observations were from a highly specialized liver intensive care unit, these limits and the prognostic implications may not apply directly in a less specialized setting.

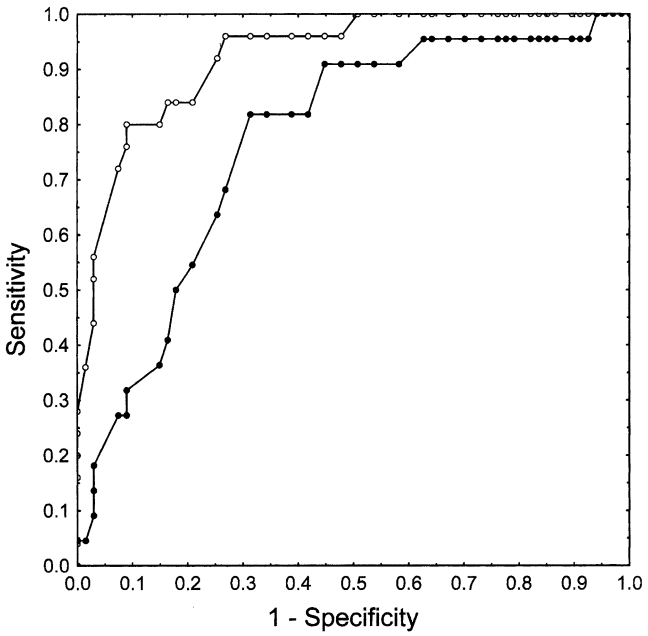

Figure 4. ROC curve plotting sensitivity vs. one specificity for different cut-off values of GEC performed (○) within 72 hours of and (●) later than 72 hours after acetaminophen ingestion.

The GEC was correlated with routine biochemical markers associated with liver failure such as INR and bilirubin. However, no upper limit incompatible with survival has been identified for any of these traditional

markers, which probably reflects that they are not specific measures of liver function.

High age, a long time to NAC, and regular alcohol abuse were all risk factors of a low GEC. Because all 3 factors are also risk factors of hepatotoxicity from an acetaminophen overdose, this simply may reflect an association between severe hepatotoxicity and a low GEC.[30] However, the GEC has been shown to decrease with age in parallel with a decrease in liver volume.[29] Also, the GEC is decreased in patients with alcohol-induced liver disease.[17] Thus, it cannot be excluded that older patients and alcohol abusers had relatively lower GECs even before the overdose; however, this does not change the prognostic value of a low GEC.

The study suggests that the time course of the GEC is different in nonsurvivors and survivors because the difference between the 2 groups decreases with time (Figure 2). Survivors appear to reach nadir GEC on day 4 (Figure 3), which is consistent with the findings of a previous study.[19] Thereafter, the GEC value slowly increases, which probably reflects an increase in liver cell mass owing to regeneration. In nonsurvivors, the initial GEC value is significantly lower, but then also increases. The cause of this increase is more elusive, but improved hepatic circulation owing to rehydration and NAC treatment as well as insufficient regeneration may contribute. Consequently, a GEC should be performed as early after admission as possible to provide the maximum prognostic information, and successive measurements are unlikely to provide any further information.

The prognostic significance of the GEC test lies in its ability to identify a small subgroup of patients with no or very little chance of survival (GEC $<$ 10 μmol/min/kg) and a larger subgroup of patients with a high chance of survival (GEC $>$ 16.5 μmol/min/kg). Unfortunately, the majority of the fatalities fell into the middle subgroup (GEC of 10–16.5 μmol/min/kg) in which GEC values overlapped between survivors and nonsurvivors (Figure 1). Thereby, a GEC less than 10 μmol/min/kg would be too insensitive to be used as the only criterion to identify liver transplantation candidates. However, the GEC may be useful as a supplement to the KCH criteria because it identified some of the patients who were misclassified by the KCH criteria. Another noticeable difference between the GEC and the KCH criteria was that the GEC specifically identified death directly from liver failure, whereas the KCH identified death from liver failure or from subsequent complications equally well. The reason probably is that the GEC specifically measures liver function, whereas the parameters used in the KCH criteria mainly reflect the degree of multiorgan dysfunction. This distinction between death from liver failure and death from subsequent complications may be relevant because it is not obvious that patients who die from complications despite improvement in liver function would have benefited from liver transplantation.

In conclusion, the GEC was associated strongly with development of HE and death from acetaminophen-induced FHF. Patients with a GEC greater than 16.5 μmol/min/kg were highly unlikely to die from liver failure, whereas a GEC less than 10 μmol/min/kg appeared incompatible with survival.

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