The value of plasma acetaminophen half-life in antidote-treated acetaminophen overdosage

Background: **A plasma acetaminophen (INN, paracetamol) half-life of more than 4 hours has been correlated with hepatotoxicity in acetaminophen overdosing not treated with an antidote. Acetaminophen half-life has not been studied in patients receiving the antidote *N*-acetylcysteine.**

Methods: **Prospectively, 112 patients with acetaminophen overdosage all treated with intravenous *N*-acetylcysteine were studied. A minimum of 2 plasma acetaminophen values >20 μmol/L were available for calculation of acetaminophen half-life, assuming first-order kinetics.**

Results: **Overall, the median acetaminophen half-life was 5.4 hours (range, 0.8-119.7 hours). Forty-eight patients with no or little hepatotoxicity (ALT <1000 U/L), 43 patients with hepatotoxicity without encephalopathy, and 21 patients with hepatotoxicity and encephalopathy had acetaminophen half-lives of 3.0 hours (range, 0.8-10.0 hours), 6.4 hours (range, 1.3-19.0 hours), and 18.4 hours (range, 4.6-119.7 hours), respectively ($P < .001$). An acetaminophen half-life >4 hours was observed in 71 patients, and 56 of those (79%) had hepatotoxicity (ALT >1000 U/L or coma). Thirty-three of 41 patients (81%) with an acetaminophen half-life <4 hours had no hepatotoxicity. A receiver operating characteristic curve analysis showed that an acetaminophen half-life of 5.5 hours provided better discrimination; hepatotoxicity was therefore present in 49 of 54 patients with an acetaminophen half-life >5.5 hours (positive predictive value, 91%) and in 15 of 58 patients with a half-life below this limit (negative predictive value, 74%) despite treatment with *N*-acetylcysteine.**

Conclusions: **Acetaminophen half-life correlates well with the degree of liver damage in patients treated with the antidote *N*-acetylcysteine. Longer half-lives reflect a greater toxic effect on the liver. (Clin Pharmacol Ther 2002;71:221-5.)**

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Acetaminophen (INN, paracetamol) overdosage is increasingly common in many Western countries.[1-3] Although many of the cellular and molecular mechanisms that lead to liver damage have been elucidated in animal models of acetaminophen overdosage,[4-8] there is still a need for better understanding of the clinical course and prognosis of each individual patient. Why severe hepatotoxicity—and often multiorgan failure—develops in some patients and why only transient or no increases in aminotransferase occur in other patients is not completely understood. The length of the interval from ingestion of the overdosage to initiation of antidote treatment with *N*-acetylcysteine is a very important prognostic marker for the development of hepatotoxicity.[9] In addition, long-term alcohol intake seems to potentiate the deleterious effects of acetaminophen,[10-14] although this remains a matter of debate.[15]

In normal subjects, acetaminophen half-life is approximately 2 to 2.5 hours.[16] Three decades ago, Prescott et al[17] examined the value of acetaminophen

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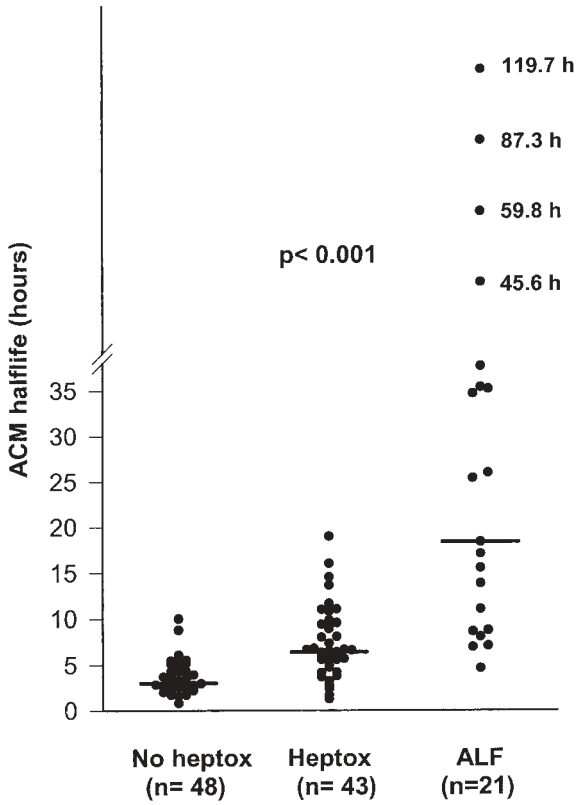

Fig 1. Acetaminophen (ACM) half-life in all patients. *Lines* indicate median for each group. No heptox, Maximum ALT <1000 U/L; Heptox, maximum ALT >1000 U/L but no acute liver failure (ALF).

half-life in 30 patients with acetaminophen overdosage; a half-life of 4 hours or more predicted severe hepatotoxicity, and all patients with an acetaminophen half-life greater than 4 hours were characterized as having significant hepatotoxicity. However, hepatotoxicity was not clearly defined in that study, which was performed before the era of antidote treatment with *N*-acetylcysteine. The use of an antidote such as *N*-acetylcysteine may well influence acetaminophen metabolism and possibly alter the usefulness of the previously observed cutoff level of 4 hours. The aim of this prospective study was to determine the value of acetaminophen half-life in patients treated with *N*-acetylcysteine in relation to the development of hepatotoxicity and hepatic encephalopathy. We also wanted to determine whether 4 hours was still an optimal discriminatory value in *N*-acetylcysteine–treated patients for these purposes.

METHODS

Acetaminophen half-life was determined in 112 patients (70 women and 42 men; median age, 29.5 years; age range, 13-65 years) with acetaminophen overdose (intake of 10 g or greater) who had at least 2 measurements of plasma acetaminophen concentrations above 20 μmol/L, excluding the first 4 hours after acetaminophen ingestion. The concentrations were plotted on a semilogarithmic scale (the *y*-axis), with hours after intake on the *x*-axis. Acetaminophen half-life was calculated, assuming first-order kinetics[17] from the slope of the fitted line (linear regression) through the data points. Biochemical values, including acetaminophen concentrations, were determined at the Department of Biochemistry, Rigshospitalet (Copenhagen, Denmark).

All patients were treated with intravenous *N*-acetylcysteine according to established guidelines.[18-20] Patients with hepatic encephalopathy and therefore acute liver failure were observed in the specialized liver intensive care unit and were treated according to international standards.[21]

Data are summarized as medians and ranges. The Mann-Whitney test was used for comparisons between two groups, whereas ANOVA on ranks was used for comparisons among 3 groups. The Spearman rank correlation was used to estimate the association between groups. A *P* value of .05 was considered to be significant.

RESULTS

Hepatic encephalopathy developed in 21 patients—3 patients with grade II, 6 with grade III, and 12 with grade IV—and they composed the acute liver failure group. Thirteen of these patients died, and 2 underwent liver transplantation. All patients with acute liver failure had ALT levels greater than 1000 U/L. ALT levels above 1000 U/L (median, 9000 U/L; range, 1020-21,500 U/L) developed in 43 patients without hepatic encephalopathy (the hepatotoxicity group),[1] whereas 48 patients had maximum ALT levels below 1000 U/L (median, 25 U/L; range, 8-850) and no encephalopathy (the nonhepatotoxicity group).

Forty-five patients had 2 plasma acetaminophen measurements, 36 patients had 3 measurements, 13 patients had 4 measurements, and 18 patients had 5 or more measurements. The linearity of the semilogarithmic plot was determined for the 67 patients with 3 or more plasma acetaminophen measurements; the median r^2 determined by linear regression analyses was 0.99 (range, 0.41-1.00; mean $r^2 = 0.95$).

Overall, the median acetaminophen half-life was 5.4 hours (range, 0.8-119.7 hours). The acetaminophen half-life was 3.0 hours (range, 0.8-10.0 hours) in the

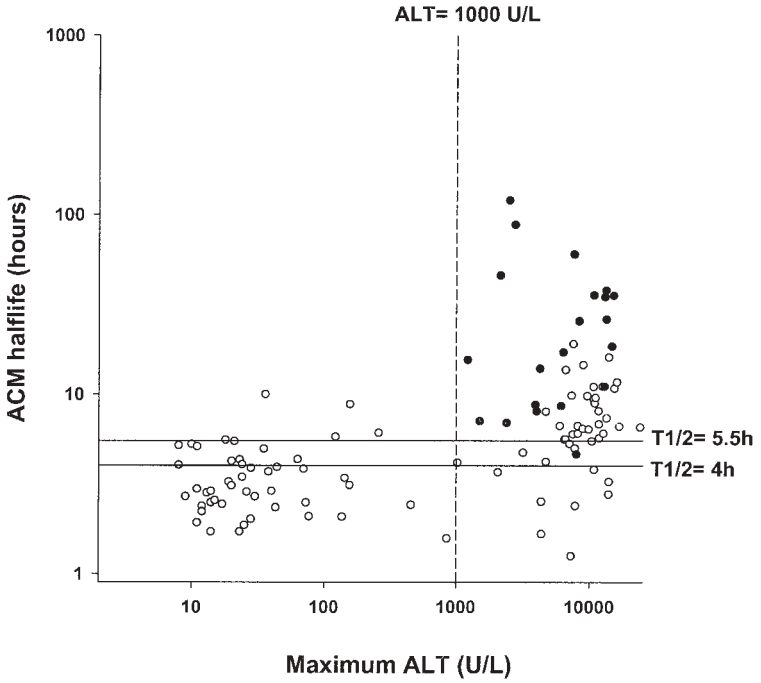

Fig 2. Acetaminophen (ACM) half-life as a function of peak ALT for all patients. *Horizontal lines* mark proposed acetaminophen half-life cutoff values of 4.0 and 5.5 hours, whereas *broken vertical line* is limit for defined hepatotoxicity (ALT >1000 U/L). *Solid circles* are patients with acute liver failure. Note that both axes are logarithmic.

nonhepatotoxicity group, 6.4 hours (range, 1.3-19.0 hours) in the hepatotoxicity group, and 18.4 hours (range, 4.6-119.7 hours) in the group of patients with acute liver failure, respectively ($P < .001$, ANOVA on ranks, pairwise comparisons; Fig 1). In the patient group with acute liver failure, acetaminophen half-life was 11.2 hours (range, 6.9-119.7 hours) in 8 survivors versus 26.0 hours (range, 4.6-87.3 hours) in 13 nonsurvivors (difference not significant).

Fig 2 shows acetaminophen half-lives in all patients as a function of peak ALT. An acetaminophen half-life of more than 4 hours was observed in 71 patients. Fifty-six of those (79%) were from the hepatotoxicity or acute liver failure groups. Thirty-three of 41 patients (81%) with an acetaminophen half-life of less than 4 hours had no hepatotoxicity. A receiver operating characteristic curve analysis that included the comparison of sensitivity versus 1 minus specificity for all possible cutoff levels was done (Fig 3), and the apex of the curve was the point at which the sum of sensitivity and 1 minus specificity was greatest. The apex corresponded with the 5.5-hour half-life, and an acetaminophen half-life cutoff value of 5.5 hours had a slightly higher accuracy for discriminating between hepatotoxicity and no hepatotoxicity than the cutoff value of 4 hours; κ values were .65 and .57, respectively. Therefore an acetaminophen half-life >5.5 hours was observed in 54 patients, and 49 of those had hepatotoxicity (positive predictive value, 91%), whereas 43 of 58 patients with a half-life <5.5 hours had hepatotoxicity (negative predictive value, 74%).

Median acetaminophen half-life increased with increasing delay from acetaminophen intake to initiation of antidote treatment (Fig 4). Acetaminophen half-life correlated with the delay from acetaminophen intake to antidote treatment (Spearman rank order correlation coefficient, 0.61; $P < .0001$). Acetaminophen half-life correlated with age (correlation coefficient, 0.20; $P = .03$) but not with the acetaminophen dose ingested ($P = .42$).

DISCUSSION

This study shows that acetaminophen half-life increased in proportion to the severity of hepatotoxicity in acetaminophen overdosage in patients treated with the antidote *N*-acetylcysteine in a manner similar to that observed before *N*-acetylcysteine was used. The acetaminophen half-life increased with increasing

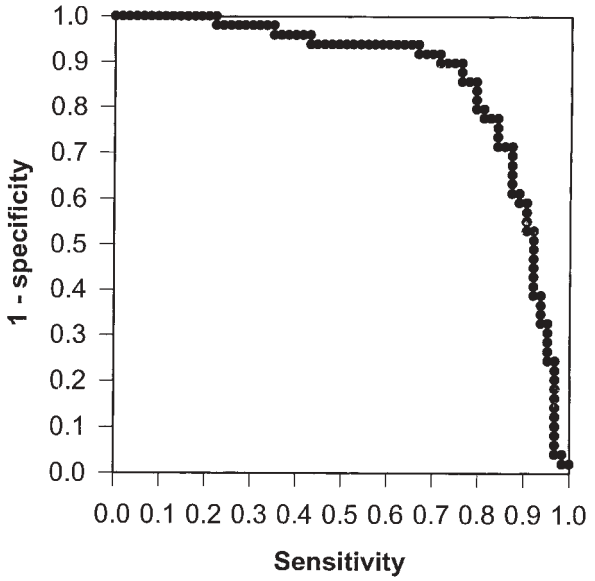

Fig 3. Receiver operating characteristic curve for cutoff levels that discriminate between hepatotoxicity and no hepatotoxicity.

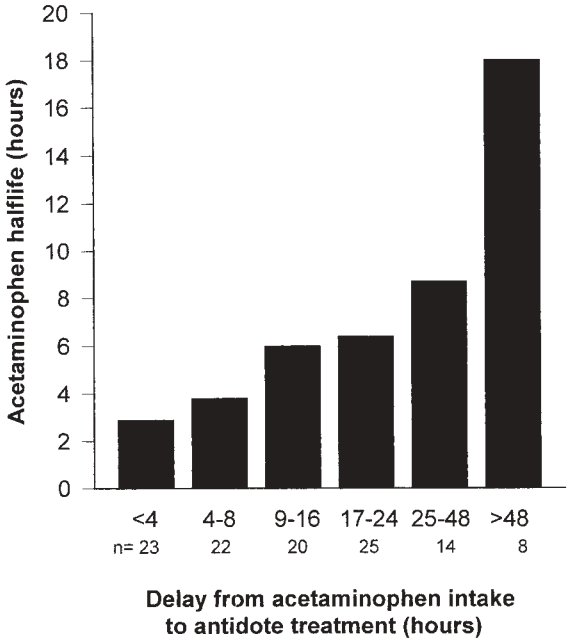

Fig 4. Acetaminophen half-life as a function of delay from acetaminophen ingestion to the start of treatment with the antidote (*N*-acetylcysteine).

degrees of hepatotoxicity, reflecting a limited hepatic capacity for acetaminophen metabolism and clearance. Acetaminophen half-life was dramatically prolonged in patients with acute liver failure—up to several days, which was much longer than the increase in half-life observed in patients with severe chronic liver disease.[22,23]

The major hepatic pathways of acetaminophen include glucuronidation or sulfation, yielding nontoxic conjugates excreted by the kidney.[1] A secondary pathway involves the cytochrome P450 (CYP) system, especially CYP2E1, by which acetaminophen is metabolized to the highly reactive metabolite *N*-acetyl-*p*-benzoquinoneimine, which may bind covalently with hepatic proteins[4] causing cellular necrosis. The toxic effect of *N*-acetyl-*p*-benzoquinoneimine is ameliorated by the natural antidote glutathione.[7] *N*-Acetylcysteine replenishes the limited hepatic contents of glutathione and thereby protects against hepatic glutathione depletion attributable to the acetaminophen metabolism.[24]

It was important to assess whether plasma acetaminophen metabolism could be explained by first-order kinetics, which is the established kinetic model in healthy subjects.[1] In patients with 3 or more plasma acetaminophen measurements, the linearity in a semilogarithmic plot was very close to 1.00, and we concluded that first-order kinetics seems also to be valid for acetaminophen overdosage. Therefore *N*-acetylcysteine did not seem to alter the basic kinetics of acetaminophen.

Prescott et al[17] have reported an acetaminophen half-life of 4 hours to be an important marker of severe liver damage. As shown in Figs 1 and 2, there was no complete discrimination between the group with hepatotoxicity and the group with no hepatotoxicity for the 4-hour cutoff level or for any other level, and a considerable overlap was observed. Still, the 4-hour cutoff level has worked well; however, this study suggests that the 5.5-hour acetaminophen half-life cutoff is probably more accurate in antidote-treated patients. A larger future study that compares the discriminatory value of the 4- and 5.5-hour cutoff half-lives may determine this more precisely. It is possible that antidote treatment reduces the hepatotoxicity for any given intoxication or overdosage, which could explain why a discriminatory half-life is greater in antidote-treated patients (5.5 hours) than in those who did not receive an antidote (4 hours). Therefore the majority of patients with acetaminophen half-life values between 4 and 5.5 hours may now avoid hepatotoxicity because of antidote treatment.

A major advantage of the use of acetaminophen half-life as a marker of severity of liver damage in acetaminophen overdosage is that the test can be used at any given time in the clinical course, as long as detectable

acetaminophen is present in the blood. The physician does not have to know the exact time since acetaminophen ingestion to perform this test because the test requires only 2 or more plasma acetaminophen concentrations, at separate time points. The test can probably be performed at most hospitals.

Acetaminophen half-life was highly influenced by the delay to initiation of antidote treatment. This observation is in keeping with the previously reported importance of the "delay to antidote" with regard to severity of liver damage,[9] although a possible spurious history on the exact time of ingestion should always be taken into account.

In conclusion, our study showed that the acetaminophen half-life is well correlated with the degree of liver damage in patients treated with *N*-acetylcysteine and that the most prolonged half-lives were observed in patients with acute liver failure. The previously suggested cutoff half-life of 4 hours is still valid; however, an acetaminophen half-life of >5.5 hours seems to work even better as a marker of severe hepatotoxicity.

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