Acetaminophen and the U.S. Acute Liver Failure Study Group: Lowering the Risks of Hepatic Failure

William M. Lee

Acetaminophen overdose is the leading cause for calls to Poison Control Centers (>100,000/year) and accounts for more than 56,000 emergency room visits, 2,600 hospitalizations, and an estimated 458 deaths due to acute liver failure each year. Data from the U.S. Acute Liver Failure Study Group registry of more than 700 patients with acute liver failure across the United States implicates acetaminophen poisoning in nearly 50% of all acute liver failure in this country. Available in many single or combination products, acetaminophen produces more than $1 billion dollars in annual sales for Tylenol products alone. It is heavily marketed for its safety compared to nonsteroidal analgesics. By enabling self-diagnosis and treatment of minor aches and pains, its benefits are said by the Food and Drug Administration to outweigh its risks. It still must be asked: Is this amount of injury and death really acceptable for an over-the-counter pain reliever? (HEPATOLOGY 2004;40:6–9.)

Although acetaminophen was approved for use in the 1950s, hepatotoxicity leading to liver failure was not recognized in significant numbers in the United States prior to 1980. At that time, acetaminophen was well recognized as a significant hepatotoxin in the United Kingdom. With the discovery linking aspirin to Reye's syndrome in children reported between 1982 and 1987, Americans turned to acetaminophen as a safer alternative for children and adults (even though Reye's is extremely rare in the adult population). Cases of fatal acetaminophen hepatotoxicity were reported during the mid 1980s, dubbed "therapeutic misadventures," and the association of acetaminophen poisoning with alcohol was explored for the first time.[1–6] Although true incidence studies were (and are) not available, no systematic case series of acute liver failure (ALF) patients included acetaminophen prior to 1999, when 20% of cases were related to acetaminophen in a retrospective study from the ALF Study Group covering the period 1994–1996.[7] Similar data were reported in 2000, in which 20% of cases were believed to be related to acetaminophen during a 13-year retrospective study (1983–1995) from the University of Pittsburgh.[8] Both of these studies may have underestimated the number of cases, since they were largely drawn from transplant databases. However, the U.S. ALF Study, in a prospective study including patients not considered for transplantation, recorded that 39% of all ALF cases were considered due to acetaminophen between 1998 and 2001.[9] More recently, 49% were deemed acetaminophen-related in 2003 (unpublished data, ALF Study Group). These figures cannot be equated to actual incidence figures. Nevertheless, the increases are striking.

It is important to distinguish between examining all cases entering the hospital with presumed acetaminophen overdose and only those with acute liver failure, a much smaller group. Of 71 acetaminophen overdose patients admitted to Parkland Memorial hospital over a 39-month period, only 7 patients developed acute hepatic failure and succumbed to their illness. Fifty were considered suicidal, with only 1 death resulting, whereas 6 deaths occurred among 21 unintentional overdoses.[10] In fact, only10 of 50 suicidal patients even demonstrated aminotransferase levels ≥1,000 IU/L. These data confirmed that most suicidal patients receive medical care within 4 hours of ingestion and are therefore reliably protected by the acetaminophen antidote, *N*-acetylcysteine. By contrast, overdoses that are called accidental or, more accurately, unintentional are associated with ingestion over several days, a specific cause of pain, and suicidal intent is denied. Late presentation is characteristic of the unintentional group, since there is no understanding of possible

Abbreviations: ALF, acute liver failure; FDA, Food and Drug Administration.

From the Division of Digestive and Liver Diseases, University of Texas, Southwestern Medical Center, Dallas, TX.

Address reprint requests to: William M. Lee, M.D., F.A.C.P., Division of Digestive and Liver Diseases, University of Texas, Southwestern Medical Center, 5323 Harry Hines Blvd., Dallas, TX 75390-9151. E-mail: William.Lee@utsouthwestern.edu; fax: 214-648-3715.

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harm; medical attention is sought only after symptoms of toxicity have developed, and a poorer prognosis is found, as observed in this study. Previous studies have suggested a strong association with excess alcohol in this group; however, this association remains controversial.[6] It is important to note that data from the ALF Study Group differ from data from the Parkland study described above, because the group admits only those patients developing coagulopathy and encephalopathy and is thus not the whole spectrum of potential or actual hepatotoxicity.

Unintentional Acetaminophen-Related Acute Liver Failure: U.S. ALF Study Group Data

The U.S. ALF Study has provided a more detailed snapshot of the unintentional cases.[3] Fifteen percent involve the simultaneous and unrecognized use of multiple acetaminophen-containing preparations. More frequent than the unwitting use of two products is impulsive overdosing when pain relief is not forthcoming. Unintentional overdoses are larger overall than suicidal ones, the median dose being 34 gm versus 20 gm for suicidal patients, but these large doses are consumed over an average of 3 days. In many instances, individuals are using alcohol, hypnotics, or illicit drugs in combination, undoubtedly clouding judgment and often delaying hospitalization. More than 60% of unintentional cases in our study used a narcotic combination, such as hydrocodone and acetaminophen (Vicodin and others). Excessive use (up to 40 or more tablets per day) appears to occur over weeks prior to onset of liver injury, suggesting addiction to the narcotic component and the development of tolerance to the narcotic and to the acetaminophen.[11] The events prior to presentation are often unclear, but the biochemical picture in these "chronic" patients is just as acute, suggesting that patients may build up tolerance for both drugs for a time, then experience "breakthrough," resulting in severe and often fatal liver injury. It is possible that fasting due to an intercurrent illness or simply increasing the dose once too often brings about this effect.[12] Because patients with unintentional toxicity frequently exhibit signs of polysubstance abuse, they may be less likely to be referred for or to receive a liver transplant.

Suicidal Acetaminophen Ingestions

As might be expected, suicidal ingestions that lead to acute liver failure are associated with late presentation, alcohol, or other concomitant drugs that may cloud the sensorium, delaying presentation, and larger total doses possibly indicate more serious intent rather than a gesture. Even with late presentation, *N*-acetylcysteine orally (and recently approved by the Food and Drug Administration (FDA) in an intravenous preparation, Acetadote) may provide some protection against fatal injury and undoubtedly prevents a large number of deaths.[13]

Although suicidal cases are more prevalent in the emergency room, unintentional overdoses are more frequent among those with severe liver failure in the ALF Study. Unlike the Parkland study, the difference in numbers of suicidal and unintentional cases reaching hepatic failure is small. These data do not tally with those of the FDA, in which fatal suicidal cases are said to exceed unintentional cases by 3:1. I am not certain of the reasons for this discrepancy, but it is likely that many suicidal patients do not get referred to transplant centers and so would not be evaluated by the ALF Study Group or may even die at home. Traditionally, acetaminophen poisoning has a very good prognosis, even if hepatic failure has developed. The survival of the acetaminophen patients who develop encephalopathy (67%) exceeds that for most other forms of acute liver failure, such as idiosyncratic drug toxicity, where survival without transplantation is only 20%.[3] However, nearly one third of those reaching the threshold of encephalopathy die, and only 7% undergo transplantation.[7] Because of the sheer number of cases, deaths due to acetaminophen toxicity constitute the most frequent deaths in the study. Suicidal intent, a history of previous suicide attempts, or evidence of substance abuse will preclude transplant consideration. Once acute liver failure develops, the outcome for either type of overdose, suicidal or unintentional, is similar.[3]

Other Issues: Indeterminate and Viral Hepatitis

Recent studies from the ALF Study Group highlight more subtle issues surrounding acetaminophen. With a recently developed assay that reliably detects acetaminophen-containing protein adducts released into the plasma by dying hepatocytes, 20% of ALF patients with indeterminate etiology (no cause discerned after extensive investigation) were found to be due to unrecognized acetaminophen poisoning.[14] The acetaminophen adducts assay provides the "smoking gun," compelling evidence of specific hepatocyte damage due to acetaminophen, and may be particularly helpful when historical data is lacking. Lack of a clear history of ingestion typically results from patient obtundation, the physician's failure to ask the right questions, or possibly denial, whether innocent or purposeful.

Likewise, in patients with viral hepatitis, acetaminophen use for symptoms of fever or right upper-quadrant pain may lead to acute liver failure: 20% of patients with established viral hepatitis admitted to the ALF Study had

detectable acetaminophen drug levels (not adducts); these patients had median alanine aminotransferase levels of 5,400 IU/L as compared to 1,367 IU/L for those in whom acetaminophen could not be detected, suggesting an acetaminophen-type injury.[15] Acute liver failure in acute hepatitis A patients was significantly associated with acetaminophen use in a recent study from France.[16] Whether acetaminophen is more toxic or doses should be limited in the presence of chronic liver disease or cirrhosis remains unclear. Prudent management would suggest that doses within a 24-hour period in any patient with acute or chronic liver disease be limited to around 2 gm, half the suggested maximum of 4 gm; however, this figure is arbitrary.

The FDA's Role

A report of acetaminophen-related data from the first three years of the ALF Study prompted a one-day meeting of the FDA's Non-prescription Drugs Advisory Committee, devoted to unintentional acetaminophen overdoses, held in Bethesda, MD, on September 19, 2002.[4] Efforts to limit suicidal overdoses was declared not to be the purpose of the meeting, despite their greater number. The committee was asked to determine whether package labeling should be changed. Current package labeling requirements do not compel manufacturers to list ingredients on the front of the package. A weak warning regarding alcohol, stating that those who drink more than three drinks per day should contact their doctor concerning use of the product, is given. It seems highly unlikely that an active drinker will call his physician specifically to inquire about how much over-the-counter pain reliever he should take for his hangover.

Also, there is no mention of liver toxicity on the current package labels. After a day of testimony, the FDA committee agreed unanimously that package labeling should include a prominent warning that excess quantities of acetaminophen might lead to liver injury, and that the generic name, acetaminophen, must be displayed in a suitably large font on the front of the package, to avoid the mistaken use of more than one acetaminophen-containing preparation. An education program was also suggested and has recently been announced by the FDA. But the agency has yet to act on the main recommendation of its advisory committee, made 21 months ago, to change the labeling requirements "immediately."

In the United Kingdom, acetaminophen (paracetamol) has been a serious problem since the 1970s, and it accounted for 73% of all acute liver failure in a study from Kings College Hospital.[17] Most overdoses in Great Britain are suicide attempts, and the average citizen seems to know that the drug is toxic. Successful legislative efforts there in 1998 resulted in a more aggressive approach toward limiting overdosing, making over the counter paracetamol available only in limited quantities (typically 16 tablets or capsules) and requiring blister packaging, thus making the impulsive large overdose less likely.[18] Paracetamol may be prescribed in larger quantities. Studies from Great Britain comparing the incidence of serious events related to paracetamol prior to these laws, with comparable periods since the legislation, indicate a decline in hospital admissions (10%), deaths (19%), and liver transplants (56%), although a few studies are less clear.[19–21] One large referral hospital in London, however, saw a 74% decline in paracetamol-related deaths or transplants comparing the prelegislation and postlegislation periods.[20] The FDA's Advisory Committee did not address the problem of suicidal overdoses, the question of whether limited package size or use of blister packs might help either form of overdose, or other ways to limit the sometimes disastrous abuse of narcotic-acetaminophen combinations.[22]

These issues are complex. Acetaminophen is safe but has a narrow therapeutic window for such a popular over-the-counter drug. Excess dosing occurs in a significant number of individuals for a variety of reasons that may involve substance abuse, but the clinical and laboratory signature is clearly that of acetaminophen toxicity. Impulsive behavior seems common in the United States. No FDA sanction short of withdrawal from the market would prevent all cases resulting from such risky behavior. However, if another pain reliever were to be developed that was uniformly safe and effective, acetaminophen would rapidly disappear: Prescription of barbiturate hypnotics, the No. 1 choice for suicide in the 1960s, rapidly declined once the safer benzodiazepines became available. A limit to package size and the use of blister packaging could prevent a significant number of cases. Changing more than the package label would also send the message that this medicine, like most others, is *not* globally safe, as its marketers claim. For a pain reliever with only mild-to-moderate efficacy, it would seem prudent to move toward limiting these needless deaths. The ALF Study Group in the coming years would happily witness a decline in incidence of these tragic cases. A more vigorous and multipronged approach from the FDA would be refreshing, as the number of cases appears to be increasing.

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