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HIGHLIGHTS FROM MEDICAL GRAND ROUNDS

MANAGING ACETAMINOPHEN OVERDOSE

An overdose of acetaminophen carries a potentially dismal prognosis because of the liver damage that may result. Given that acetaminophen is the most widely prescribed analgesic in the United States, and that alcohol and certain drugs potentiate its action, clinicians need to know when to intervene, what tests to order, and what treatments are available in case of an overdose. This overview offers an approach to preventing and treating acetaminophen hepatotoxicity.

THE TOXIC METABOLITE

In healthy people, 98% of acetaminophen is conjugated into a glucuronide or sulfate that is safely excreted. The other 2% is metabolized via the cytochrome P-450 enzyme system into highly toxic intermediate metabolites, chief of which is N-acetyl-P-benzoquinone imine (NAPQI), which then must conjugate with glutathione to form mercapturic acid in order to be safely excreted. NAPQI presents no problems provided there is enough glutathione. Most people have enough to protect against an excess of the toxic metabolite for as long as 36 hours. However, when the body's store of glutathione is depleted, the toxic metabolite recirculates freely, binding covalently to tissue macromolecules in zone 3 of the liver, causing irreversible necrosis of the liver.

POTENTIATORS OF ACETAMINOPHEN

Concurrent alcohol use exacerbates the problem. Alcohol induces the cytochrome P-450 enzyme sys-

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tem to produce more of the toxic metabolite. In addition, since many alcoholics are chronically malnourished, their baseline glutathione levels may be inadequate if subjected to excessive amounts of acetaminophen's toxic metabolite. As a result, the "incubation period" before acetaminophen-related liver damage occurs in alcoholics is much shorter, perhaps only 18 hours.

Certain drugs such as isoniazid (used in tuberculosis prophylaxis) may also induce cytochrome P-450 system activity and enhance the hepatotoxic effects of acetaminophen.

PROGNOSIS

In assessing the extent of liver damage in a patient who has taken an acetaminophen overdose, the bilirubin level, the prothrombin time, and the presence of lactic acidosis are the best indicators at present. A bilirubin level greater than 4 mg/dL or a prothrombin time more than 2.2 times the normal value herald a poor prognosis, as does severe acidosis.

The nomogram (*Figure*) relating plasma acetaminophen concentrations to likely severity of liver damage can be used to guide decisions such as whether vigorous therapy is necessary. In addition, plasma acetaminophen concentrations may help to predict the outcome. The cutoff levels are 200 µg/mL at 4 hours after acetaminophen ingestion, and 50 µg/mL at 12 hours—higher levels predict hepatotoxicity.

Patients who take alcohol concurrently with acetaminophen have a much greater tendency toward hepatotoxicity. In fact, in these patients the acetaminophen cutoff levels are lower, ie, 100 µg/mL at 4 hours and 25 µg/mL at 12 hours. Binge drinkers are at greater risk of acute acetaminophen hepatotoxicity than chronic drinkers.

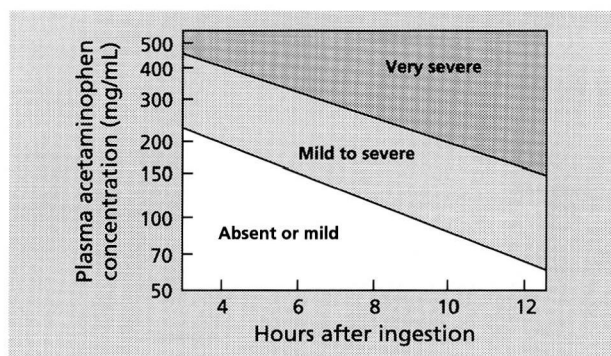


FIGURE. Likely degree of liver damage according to plasma acetaminophen concentration. Patients with values in the lowest zone will likely have only mild liver damage or none at all, and do not need specific therapy. Values in the highest zone are predictive of very serious liver damage and mandate treatment with acetylcysteine or other agents; values in the middle zone are less predictive but mandate similar treatment. From Zimmerman JH. Hepatotoxicity. New York: Appleton-Century-Crofts, 1978.

TREATMENT OPTIONS

For patients with severe hepatic damage, the only treatment is liver transplantation. In patients with a less severe condition, acetylcysteine is the treatment approved by the US Food and Drug Administration (FDA). Acetylcysteine, which is thought to help replenish glutathione, thereby neutralizing the toxic metabolite, is given orally in a loading dose of 140 mg/kg, then 70 mg/kg at 2-hour intervals for at least 72 hours. The drug is effective when given early, but the later it is given the less likely it will be successful. A major drawback is nausea and vomiting. Parenteral administration may circumvent this, but a parenteral form is not yet approved by the FDA.

Although not an FDA-approved treatment for acetaminophen overdose, cimetidine seems to offer some protection: it blocks the cytochrome P-450 enzyme system, inhibiting production of the toxic metabolite. Rabbits receiving cimetidine before or after acetaminophen overdose, or acetylcysteine before overdose, had significantly higher survival rates when compared with no treatment. Intravenous cimetidine (50 mg/hour) can be used in addition to acetylcysteine for 72 hours.

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SUGGESTED READING

Bonkovsky HL, Kane RE, Jones DP, et al. Acute hepatic and renal toxicity from low doses of acetaminophen in the absence of alcohol abuse or malnutrition: evidence for increased susceptibility to drug toxicity due to cardiopulmonary and renal insufficiency. *Hepatology* 1994; 19:1141-1148.

Crippin JS. Acetaminophen hepatotoxicity: potentiation by isoniazid. *Am J Gastroenterol* 1993; 88:590-592.

IDENTIFYING EARLY MARKERS OF TYPE II DIABETES

THE PATH TO non-insulin-dependent diabetes (NIDDM) begins long before the blood glucose concentration rises above normal limits, perhaps as early as adolescence. Treating established NIDDM can curb complications of hyperglycemia that affect the eyes, kidneys, and nerves, but it will not halt the complications caused by hyperinsulinemia (ie, hyperlipidemia, hypertension, and accelerated atherosclerosis). Earlier identification of those at risk for NIDDM may permit earlier dietary and exercise intervention.

FROM 'FEAST OR FAMINE' TO 'FEAST OR FEAST'

The tendency toward NIDDM may have had some benefit for our ancestors, who lived in times of "feast or famine," by making it easier to store ingested glucose as fat. This would have helped them survive lean times, but it has no use in our modern, overfed society.

People destined to acquire NIDDM cannot use glucose effectively because of insulin resistance. Muscle glucose disposal can be shown to be impaired in individuals with a propensity to develop NIDDM well before the circulating blood glucose value is elevated. Among a number of postreceptor events triggered by the binding of insulin to its receptor, a defect in glycogen synthase activity has been documented to be present in some such individuals. They also have a high number of type 2 muscle fibers, which are relatively avascular, highly glycolytic, and insulin-insensitive.

After a glucose load, the blood sugar level rises, and the beta cells compensate by secreting more insulin, in turn causing down-regulation of cell-surface insulin receptors in susceptible people. Thus, the beta cells, to maintain euglycemia, must secrete even more insulin—until they manifest their genetically weak insulin secretory capacity and cannot pro-