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Acetaminophen Liver Injury

SUMMARY

Acetaminophen can produce potentially fatal liver necrosis, via an intermediate toxic metabolite. Hepatic injury usually requires acute ingestion of at least 10-15 g of the drug. The patient typically feels well for one to three days before evidence of liver damage appears. Striking elevation of aminotransferases is characteristic, reflecting acute hepatocellular necrosis. In non-fatal cases, recovery is usually rapid. Liver damage can be completely prevented by oral or IV N-acetylcysteine (Mucomyst), which blocks the effect of the toxic metabolite. However, treatment is effective only if given within eight to 12 hours of acetaminophen ingestion. Hence, prompt action by the physician can prevent acetaminophen liver necrosis. (Can Fam Physician 1985; 31:2155-2158)

SOMMAIRE

L'acétaminophène, via un métabolite intermédiaire toxique, peut engendrer une nécrose hépatique potentiellement mortelle. Il faut habituellement ingérer entre 10 et 15 g de ce produit pour provoquer la réaction hépatique. Typiquement, le patient se sent bien pendant 24 à 72 heures avant que ne se manifestent les signes de dommage hépatique. La caractéristique est l'élévation marquée des aminotransférases signifiant une nécrose hépatocellulaire aigue. Dans les cas non mortels, la récupération est habituellement rapide. Il est possible de prévenir complètement de dommage hépatique si l'on donne de la N-acétylcystéine (Mucomyst) par voie orale ou I.V.; elle bloque les effets du métabolite toxique. Ce traitement n'est toutefois efficace que si on l'administre moins de 8 à 12 heures après l'ingestion d'acétaminophène. Il est donc important que le médecin agisse rapidement s'il veut prévenir la nécrose hépatique par intoxication à l'acétaminophène.

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CANADIANS OFTEN reach for acetaminophen (Tylenol, Panadol, Anacin-3, Tempra, etc.) to relieve minor aches and pains. This mild analgesic/antipyretic was introduced in the 1890s, but achieved widespread use only within the past 20 years.[1] It's a remarkably safe drug in recommended amounts, but acute overdosage can cause liver damage—sometimes fatal.[1,2] Reports of hepatic toxicity began to appear in the mid-1960s, and by the early 1970s acetaminophen was a major cause of fulminant liver failure in the U.K. (where it's called paracetamol).[2,3] Overdosage has become a problem in North America only more recently, coincident with a marketing blitz lauding acetaminophen as an over-the-counter alternative to acetylsalicylic acid.[1]

Pathophysiology

Mitchell et al.[4] established the disorder's pathogenesis. Neither acetaminophen itself nor its major metabolites are hepatotoxic. A small fraction (about 5%), however, is converted by the hepatic cytochrome P-450 system to a potentially harmful 'reactive intermediate' metabolite, which is normally rendered harmless by conjugation with hepatic glutathione (G-SH). The liver contains enough G-SH to handle several times the therapeutic dose of acetaminophen, but a massive overdose will eventually deplete G-SH levels. Once this occurs, the reactive metabolite binds to liver cytoplasmic proteins, which in turn leads to cell necrosis.[4] The chemical structure of the toxic intermediate(s) is still debated, as is the exact mechanism by which binding induces cell injury.[1]

Important clinical corollaries follow. First, liver injury occurs only after threshold G-SH depletion. In practice, this means that acetaminophen has a very wide safety margin before liver damage need be feared. The threshold injurious dose in adults is usually at least 10-15 g[1,2]—about 30-45 standard 325 mg tablets or 20-30 extra strength 500 mg tablets. Ingestion of such doses is usually a suicidal gesture, and only rarely accidental. Children tolerate the drug even better than adults, possibly because of different pathways of metabolism and enhanced G-SH turnover.[5] The toxic threshold is at least 150 mg/kg for children under age 12, and liver damage is uncommon even with higher doses.[5]

Second, once threshold dosage is reached, liver injury reflects direct

dose-related drug toxicity rather than a hypersensitivity phenomenon. This is clinically important, because plasma acetaminophen concentrations can be used to predict whether liver damage is likely. Simple nomograms are available relating plasma drug levels, the time after ingestion, and the likelihood of hepatic necrosis.[2, 6] Many community hospitals can now measure blood acetaminophen concentrations with a turnaround time of only an hour or so.[7]

Third, because the toxic metabolite arises via the hepatic P-450 system, other drugs which influence this system can modify acetaminophen toxicity. For example, phenobarbital is a P-450 stimulant and cimetidine inhibits the P-450 pathway; in experimental animals these drugs will therefore respectively enhance or inhibit acetaminophen toxicity.[4, 8] Insufficient data are available to be confident of a similar effect in human beings, although it appears likely.[9] The most important interaction occurs with ethanol, but the effects are complex and unpredictable.[1, 10, 11] Nevertheless, in clinical practice it's not uncommon to see acetaminophen overdosage in alcohol abusers—partly because alcoholics are more likely to take a drug overdose, although a pharmacologic interaction also contributes. The presence of underlying liver disease per se does not appear to enhance susceptibility to acetaminophen toxicity;[12] thus, the therapeutic dose of the drug need not be modified in patients with cirrhosis.

Finally, if hepatic G-SH depletion can be prevented, liver injury will not develop, even after doses which otherwise would be fatal. This concept is fundamental to the therapy of acetaminophen overdosage.

Clinical and Laboratory Features

There are two important clinical points about acetaminophen hepatotoxicity. First, evidence of liver injury is characteristically delayed for one to three days. Second, when illness does appear its features reflect acute hepatocellular necrosis rather than a cholestatic (obstructive) drug reaction.

Even after fatal doses, for the first 36-72 hours patients usually feel well except for transient nausea and vomiting.[2, 3, 6] Physicians seeing such patients at home or in the emergency department therefore should not ignore a story of massive ingestion just because the patient does not appear ill. A careful history from the patient or relatives is essential, with pill counts if possible, in order to establish the dose of acetaminophen taken. Impaired consciousness suggests the concomitant ingestion of other drugs.

Symptoms of liver damage develop after the initial lag phase. Anorexia, nausea and vomiting, dark urine, and jaundice typically develop in rapid sequence. Physical examination is usually unremarkable except for the presence of variable jaundice. In severe cases a bleeding tendency may develop and the patient may lapse into hepatic encephalopathy; these signs usually portend a poor prognosis.[2, 3] Patients with fatal liver necrosis develop frank hepatic coma; functional renal failure (hepatorenal syndrome) may supervene as a terminal event.[2]

Biochemical evidence of hepatocellular necrosis usually precedes clinical symptoms by a day or so. Strikingly elevated aminotransferase (transaminase) levels are the hallmark of the disorder; values begin to rise about 24-36 hours after drug ingestion and peak at about 72-96 hours.[2, 3, 6] Levels are typically in the 1000-2000 U/L range, but in severe cases may reach several thousand units. Bilirubin is variable, and alkaline phosphatase is only mildly or modestly increased. A rising prothrombin time reflects extensive hepatocellular damage and often presages a poor outcome.[2, 3]

Unlike viral hepatitis, which typically produces ongoing necrosis for several weeks, acetaminophen damage is a 'one-shot' injury. Thus clinical and biochemical derangements rapidly regress; in the typical patient with nonfatal necrosis, recovery is usually complete within a week or two of the peak illness,[3, 6] and spontaneous relapses do not occur. Occasionally, patients with extensive injury develop post-necrotic liver scarring, but this is unusual.[3, 13, 14]

Differential Diagnosis

The symptoms and high aminotransferase levels closely simulate acute viral hepatitis;[3] hence the drug history is critical in differentiation. Measurement of plasma acetaminophen concentration can be crucial if overdosage is suspected despite a patient's denials. Serologic tests for hepatitis antigens should not be relied upon, as results take too long to return and patients with non-A, non-B viral hepatitis will have negative results anyway. Liver biopsy can distinguish the two disorders but is not normally needed; unlike viral hepatitis, acetaminophen characteristically causes confluent centrolobular necrosis with relatively little inflammatory infiltrate.[14]

In the alcoholic, acetaminophen toxicity may be misdiagnosed as alcoholic hepatitis, especially if the patient is known to have cirrhosis or has physical signs of chronic liver disease.[1, 15] Here, too, the history of ingestion is critical. An additional important clue is the height of the aminotransferase elevation. Even in severe alcoholic hepatitis, levels are usually under 300 U/L;[16] values over 500 U/L almost always reflect a superimposed process, including drug injury. Aminotransferase levels may reach several thousand units in alcoholics with acetaminophen toxicity;[15, 17] in a few such patients a peculiar metabolic acidosis has also been reported[17] and may be a clue to the diagnosis.

Patients who attempt suicide with acetaminophen have often taken other drugs concomitantly, especially benzodiazepines or other psychotropic agents. These drugs can complicate the clinical picture, especially with neurologic signs, but are only rarely responsible for hepatic injury. In such cases liver damage should be assumed due to the acetaminophen.

Scattered reports of chronic acetaminophen hepatotoxicity have appeared, most commonly in alcoholics who ingest three grams or more of the drug daily.[12, 18] These patients have a chronic active hepatitis-like illness with progressive liver damage and fluctuating aminotransferase elevations. Chronic liver damage from acetaminophen needs further study, but it seems appropriate to inquire about heavy, ongoing use of the drug in patients with otherwise unexplained chronic hepatitis, especially if the course fluctuates unpredictably.

Management

Acetaminophen overdosage is unique in that liver damage can be aborted by early prevention of hepatic G-SH depletion.[2, 6] This principle, based on the pathogenesis of injury, enables even potentially fatal overdoses to be rendered harmless. However *treatment must be started within*

eight to 12 hours of drug ingestion,[2, 11] before irreversible binding of the toxic metabolite has occurred. Once liver damage develops there is no specific therapy.

Several sulfhydryl compounds can prevent G-SH depletion[2] but N-acetylcysteine (Mucomyst) is the generally preferred agent.[2, 6, 11] Its mechanism of action is complex, but efficacy is probably due primarily to enhanced G-SH synthesis.[19] The preferred method of administration is debated—the intravenous route is favored in the U.K.,[2] the oral route in North America.[6] The usual oral dose is 140 mg/kg initially followed by 70 mg/kg every four hours for three days. Intravenous N-acetylcysteine is usually infused over 20 hours, with half of the total 300 mg/kg dose given in the first 15 minutes. Both regimens were arbitrarily devised but are totally effective if given early enough. However, no protection occurs after about 16 hours.[2, 11]

N-acetylcysteine is remarkably safe; vomiting and diarrhea after oral usage are the only frequent side effects.[20] An anaphylactoid reaction has rarely been reported after IV infusion.[21] Because treatment is safe but critically time-dependent, in cases of doubt it's best to start therapy while awaiting further clarification.

Theoretically, treatment could alternatively be aimed at inhibiting the hepatic P-450 pathway, thereby blocking the formation of the toxic intermediate metabolite(s). Successful studies have been undertaken along these lines, for example with cimetidine,[8, 9] but are still experimental.

Based on the above principles, physicians faced with a potentially serious overdosage of acetaminophen should promptly take the following steps:

1. Establish as accurately as possible the amount and time of acetaminophen ingestion.
2. If the dose was clearly less than the toxic threshold, no further action is needed.
3. If a clearly toxic dose was ingested within the preceding eight to 12 hours, blood should promptly be taken for baseline liver function tests, complete blood count, etc., and for plasma acetaminophen concentration if available. Treatment with N-acetylcysteine should be started immediately, using either of the regimens noted above. Gastric lavage may be useful if the patient is seen within four hours of ingestion, but activated charcoal should not be given as it may interfere with the absorption of N-acetylcysteine.[11] The patient should be admitted to hospital, but treatment must not be delayed for admission formalities. Observation with serial liver function tests should continue until the danger period—usually three to five days—has passed.
4. If drug ingestion occurred more than 16 hours before the patient is first seen, therapy will be of no benefit. Patients who took a clearly toxic dose should be hospitalized and observed. If progressive liver failure develops an internist or gastroenterologist should be consulted to assist in managing specific complications (hepatic encephalopathy, coagulopathy, etc.).
5. If there is doubt about the amount or timing of the overdose, it's best to treat, preferably after obtaining blood for plasma acetaminophen concentration. Treatment can then be aborted if blood levels are clearly in the safe range.

Conclusion

Canadian family physicians will likely see acetaminophen overdosage with increasing frequency during the next few years. Although most cases will not result in liver damage, the potential for fatal hepatic necrosis demands knowledge of a few basic principles about the disorder. The most important of these are the concept of the threshold toxic dose; the lag period before hepatic damage appears; the ability of N-acetylcysteine to abort liver necrosis; and the 'window' of only a few hours during which therapy will be effective. Physicians who are aware of these principles can help minimize the dangers of acetaminophen overdosage. ◉

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