Therapeutic Review

Treatment of acetaminophen poisoning

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Acetaminophen is an analgesic that is frequently used in Canada, and the occurrence of overdoses with this drug seems to be increasing. The most serious complication of acetaminophen overdose is hepatic failure. Because pathophysiologic effects of acetaminophen poisoning and the mechanisms of its toxic effects are now better understood, a rational approach to treatment is possible. Seveal precursors of glutathione, acetylcysteine in particular, are effective in preventing liver damage if administered within 10 hours of acetaminophen ingestion. Plasma acetaminophen levels are a helpful guide to therapy.

L'acétaminophène est un analgésique d'usage fréquent au Canada, et le nombre de surdosages à ce médicament semble être en augmentation. L'insuffisance hépatique représente la complication la plus sérieuse du surdosage à l'acétaminophène. Comme les effets pathophysiologiques de l'empoisonnement à l'acétaminophène et les mécanismes responsables de ses effets toxiques sont maintenant mieux connus, une démarche de traitement rationnelle est possible. Plusieurs précurseurs du glutathion, l'acétylcystéine en particulier, sont efficaces pour prévenir les dommages hépatiques quand ils sont administrés moins de 10 heures après l'ingestion d'acétaminophène. Les taux plasmatiques d'acétaminophène orientent utilement le traitement.

The principles for the management of drug overdose are generally well recognized.[1] For most overdoses in adults medical management consists of good supportive care to restore or maintain adequate ventilation and circulation. With such care, deaths due to drug overdose should be rare as long as the patient reaches hospital before irreversible organ damage has occurred. In contrast to this, the management of some drug overdoses or poisonings involves administering specific drugs. In these cases the exact nature of the problem must be recognized early and followed by the appropriate treatment to ensure an optimal outcome.[1-5]

Acetaminophen (Tylenol) is a commonly taken analgesic drug. In the United Kingdom overdoses of this drug alone or with other analgesics are relatively frequent.[1,4,5] The number of such overdoses seems to be increasing in Canada although precise figures are not available. A recent inquest highlighted the fact that little information on the management of this treatable overdose has been published in Canadian medical journals and that physicians therefore may not be sufficiently aware of the appropriate treatment problem (*Toronto Sun*, Dec. 21, 1978: 29).

There is a wide variation between individuals in susceptibility to the toxic effects of acetaminophen, but in an adult a seriously toxic state typically may result after the ingestion of about 20 to 30 tablets (325 mg each). The most serious complication of acute acetaminophen overdose is hepatic failure;[1,6] before effective treatment was available hepatic necrosis developed in approximately 20% of patients.[1,6-8]

The clinically deceptive aspect of acetaminophen poisoning is that patients present without neurologic effects from the drug and in apparent good health. However, 12 to 24 hours later the hepatic damage caused by the drug becomes apparent, and it may cause death within 3 to 5 days.[1,3,7,8]

The most important step in recognizing this problem is to obtain a detailed history or corroborating evidence, or both, of what and how much was taken. Contrary to common belief, patients actually have taken what they allege to have taken in at least 80% of cases.[9] No effort should be spared in obtaining information from friends, relatives, police, pharmacists and physicians to establish what drug has been taken.

Pathophysiologic effects

Acetaminophen is rapidly absorbed from the stomach and upper gastrointestinal tract and then is metabolized in the liver by hydroxylation and conjugation.

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Only 4% is excreted unchanged in the urine.[1] In normal therapeutic doses approximately 7% is excreted as the product of hydroxylation, a step involving the creation of a toxic metabolite. This metabolite is normally conjugated with glutathione. However, in the presence of increased levels of acetaminophen in the plasma the glutathione in the liver is depleted, allowing the level of the hydroxylation metabolite to increase.[10] This compound binds irreversibly to macromolecules in hepatic cells, causing centrilobular hepatic necrosis.[11,12] Patients who already have a liver disease and are taking enzyme-inducing drugs (such as ethanol or barbiturates) seem to be at increased risk of this necrosis.[3]

Treatment

Various forms of therapy for acetaminophen overdose have been advocated, but until recently none had proved effective in preventing the hepatic necrosis.[1] After the biochemical mechanisms of the hepatotoxic effects of acetaminophen were established, the first specific, rational and successful treatment of severe acetaminophen poisoning was described by Prescott and associates[14] in 1974. Although it has not been possible to conduct controlled clinical trials of this treatment, other reports have confirmed its efficacy.[13-15]

The aim of the treatment is to decrease the amount of free toxic metabolite by increasing the level of hepatic glutathione. Glutathione itself does not penetrate hepatic cells and is ineffective therapeutically. However, its precursors, such as cysteamine, methionine and acetylcysteine have been shown to prevent or reduce acetaminophen-induced hepatic necrosis.[12] Although cysteamine hydrochloride and L-methionine may cause unpleasant side effects, some clinicians, considering the dangers of acetaminophen overdose, view these effects as acceptable. Acetylcysteine (Mucomyst) seems to be the agent most readily available and is now the choice for preventing acetaminophen-induced hepatic necrosis. When it is taken orally in the recommended dosage no serious toxicity has been reported.[3] To be effective, therapy with acetylcysteine must be started within 10 hours of the ingestion of acetaminophen. After 10 to 12 hours it is of no proven value, and there is the theoretical possibility of hepatotoxic effects from the antidote itself if the patient has liver damage from the acetaminophen. When acetylcysteine is being administered the patient *should not be given charcoal or a cathartic* orally, as this will interfere with absorption of the antidote.

An important aspect of treating acetaminophen intoxication is knowing when to begin treatment. It is essential for clinicians to be aware of the potential dangers of this overdose and to make an early and accurate assessment of the situation. Except for mild nausea and vomiting and some mild abdominal discomfort, these patients are usually asymptomatic, and the appearance of clinical signs or symptoms of hepatotoxic effects may be delayed by up to 5 days, although biochemical changes can occur within 12 hours. The dosage associated with toxic effects is quite variable. In general, patients who have ingested 6 g or more should be considered at risk, although in typical cases serious hepatic damage is more likely in those who take 12 to 15 g. The patient's serum acetaminophen level is the best, albeit imperfect, guide to therapy. Although the half-life of acetaminophen in the plasma has been shown to be the best method of predicting hepatic failure,[16] the difficulties related to obtaining multiple blood samples and other practical considerations can make this method of limited value.

The first measure of the concentration of acetaminophen in the plasma can provide both a guide to treat-

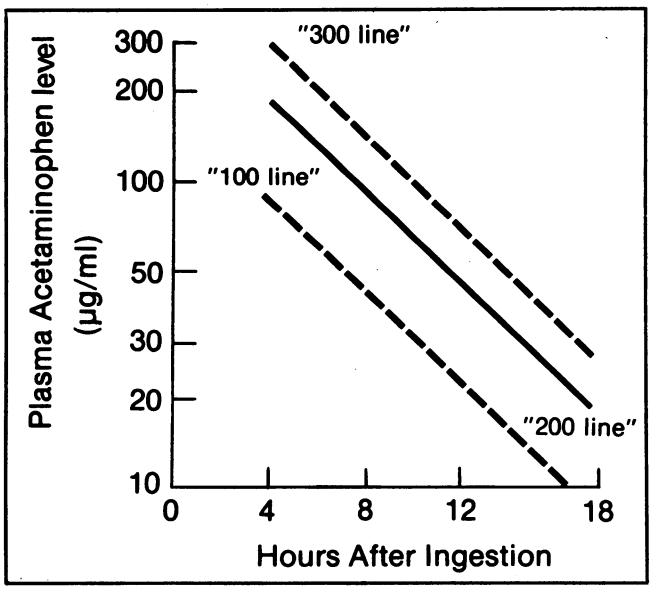

FIG. 1—Plasma acetaminophen levels related to time elapsed since ingestion of overdose, as a guide to treatment and an indication of prognosis.[3] A level of 300 μg/ml 4 hours after ingestion is represented by the "300 line", 200 μg/ml by the "200 line" and 100 μg/ml by the "100 line".

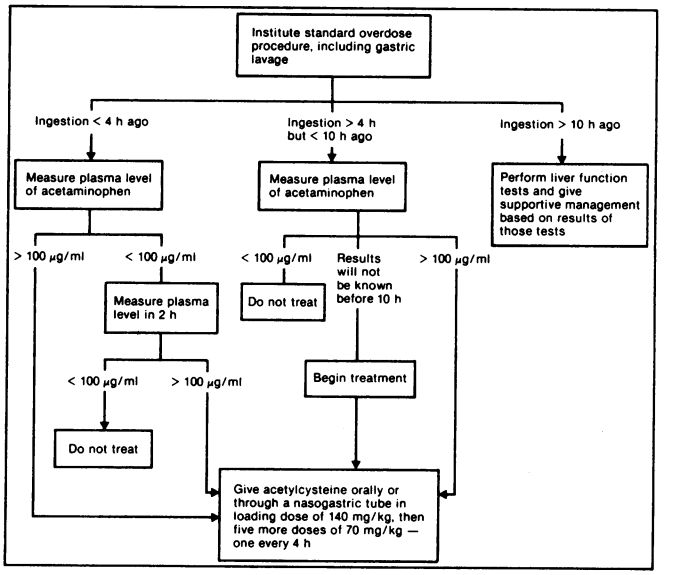

FIG. 2—Flow chart for management of an acetaminophen overdose.

ment and an indication of prognosis. Fig. 1 shows a semilogarithmic graph relating levels of acetaminophen in the plasma to time since ingestion. In patients with a plasma concentration below 100 μg/ml 4 hours after ingestion (below the "100 line") the risk of serious hepatic damage is negligible. For those with a plasma concentration above 200 μg/ml the risk is approximately 20%.[1,3] Virtually all patients with plasma concentrations greater than 300 μg/ml (above the "300 line") can be expected to suffer serious liver damage. All patients whose plasma levels of acetaminophen are above 100 μg/ml should be given acetylcysteine orally or through a nasogastric tube in an initial dose of 140 mg per kg of body weight, followed by five doses of 70 mg/kg at 4-hour intervals (Fig. 2). The drug should be diluted in juice or a flavoured beverage, such as ginger ale, if given orally. In rare cases acetylcysteine may have to be given intravenously. Although no intravenous formulation has been approved, in an emergency situation a sterile (not pyrogen-tested) 20% aqueous solution of acetylcysteine could be used. An initial dose of 150 mg/kg diluted in 200 ml of dextrose could be given intravenously over 15 minutes, followed by 50 mg/kg in 500 ml of 5% dextrose over the next 4 hours and a further 100 mg/kg in 1 litre of 5% dextrose over the next 16 hours (total dose 300 mg/kg in 20 hours.)[1,3] Nasogastric, rather than intravenous, administration is preferred by far.

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