Cold Remedies and Acetaminophen Poisoning

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Abstract: Ingestion of large amounts of acetaminophen, the principal ingredient found in over-the-counter cold remedies, results in serious damage to liver cells. Even if the dose is only several times higher than the recommended dose, poisoning with this drug may occur when it is taken for a number of consecutive days, after heavy drinking, or in combination with other drugs. If acetaminophen poisoning is suspected, treatment with acetylcysteine is necessary before the clinical manifestations of poisoning are apparent.

Key words: Acetaminophen poisoning; Acetylcysteine; Drug-induced hepatopathy; Cold remedy

Introduction

In 1999, the owner of a restaurant in Honjo City, Saitama Prefecture, was arrested on suspicion of poisoning one of his customers by giving him a high dose of a cold remedy, which he explained was a nutrient preparation, after taking out a large life insurance policy on the customer. This incident is still fresh in the memory of people in Japan.

The restaurant owner was thought to have been familiar with the lethal action of high-dose acetaminophen, the principal ingredient in over-the-counter (OTC) cold remedies, and to have killed the customer by giving him a large amount of a cold remedy to collect the insurance money.

In Western countries, acetaminophen has been used in suicide attempts, and many cases of acetaminophen poisoning have been reported. Death from acetaminophen poisoning, although not frequent, has also been reported in Japan.

Pharmacological Action of Acetaminophen

Acetaminophen is an antipyretic analgesic aniline compound that acts on the thermoregulatory center of the hypothalamus, causing dilation of the blood vessels in the skin and thereby increasing heat radiation and revers-
ing the increase in body temperature. It also exerts an analgesic effect by increasing the threshold of pain in the thalamus and cerebral cortex. A cetaminophen has an antipyretic effect comparable to that of aspirin, but has no ability to suppress inflammation. Unlike the anti-inflammatory drug aspirin, acetaminophen does not cause any gastrointestinal bleeding and is considered a safe, low-toxicity antipyretic analgesic.

Phenacetin, often used in analgesic formulations, is hydrolyzed to acetaminophen in the body. However, unlike acetaminophen, it often causes serious adverse effects such as nephropathy, hemolytic anemia, and methemoglobinemia. Therefore, the use of phenacetin is prohibited in the U.S., Canada, Scotland, Finland, and other countries. In Japan, phenacetin is still used as a formulating element in non-OTC antipyretic analgesic preparations such as Saridon® and Sedes G®, a situation that calls for precaution in prescribing antipyretic analgesics.

**Acetaminophen as an Active Ingredient in Cold Remedies**

In Japan, active ingredients used in the formulation of OTC cold remedies are regulated by law, and all cold remedies are required to contain 1–3 of the following 7 agents: aspirin, aspirin aluminum, acetaminophen, ethenzamide, sasapyrine, salicylamide, and lactylphenetidine. It is also stipulated that antipyretic analgesics contain 1–3 of 8 agents, i.e., sodium salicylate in addition to the above 7 agents.

A maximum of 300 mg of acetaminophen per dose, or a maximum of 1 g per daily dose, is permitted in cold remedy formulations. A cetaminophen may on rare occasions cause an allergic reaction at the recommended dose, but toxicity is seldom seen. Therefore, acetaminophen is considered safe except in those who have a history of allergic reaction to cold remedies, pregnant women, the elderly, and the feeble. A cetaminophen is thus contained in most OTC cold remedies and antipyretic analgesic drugs, which number in the several hundreds.

**Acetaminophen Toxicity**

Although about 5% of the acetaminophen taken into the body is excreted into urine without any metabolic change, most of it forms nontoxic compounds conjugated by glucuronic acid or sulfuric acid in the liver and is excreted into urine. However, some is converted to highly toxic N-acetyl-p-benzoquinone under the action of cytochrome P450, a drug-metabolizing enzyme present in the microsomes of liver cells. The N-acetyl-p-benzoquinone that is produced immediately conjugates with glutathione to become nontoxic mercapturic acid, which is then excreted into urine.

If acetaminophen is ingested at a dose that exceeds the processing capacity of glucuronic acid and sulfuric acid in the liver, the cytochrome P450-produced metabolite N-acetyl-p-benzoquinone increases, and all the glutathione molecules in liver cells are fully consumed through the conjugate reaction. If no glutathione is available, N-acetyl-p-benzoquinone binds to proteins and nucleic acids in liver cells, resulting in damage to these cells. Therefore, when a large amount of acetaminophen is ingested, centrilobular necrosis occurs in the liver, resulting in death due to acute liver failure. Since the toxic metabolite N-acetyl-p-benzoquinone is also produced in the kidney, acute renal tubular necrosis can occur as well.

According to reports from Western countries, the use of 10 g or more of acetaminophen (or 140 mg or more per kg of body weight) may cause intoxication, and 15 g or more may cause death. However, lesser amounts of this agent may cause intoxication in patients (1) who have decreased capacity for glucuronic acid conjugation in the liver, (2) who have increased cytochrome P450 activity because of habitual heavy drinking or the use of drugs such as phenobarbital, or (3) who have low levels of glutathione in liver cells because of undernutrition or regular use of acetaminophen.
In the case of the homicide in Honjo City, the victim was a habitual drinker. Therefore, it is not surprising that he developed acetaminophen poisoning after consuming a large amount of a cold remedy for a number of consecutive days.

In Japan, death from just 2.4 g of acetaminophen has been reported. This amount is only eight times more than the usual amount of acetaminophen contained in a single dose of cold remedy. There are several other cases of death in Japan from obviously lower doses of acetaminophen than those in cases in Western counties. This may be explained by (1) possible ethnic differences in the activity of drug-metabolizing enzymes in the liver, (2) the effects of other ingredients in the cold remedy (ethenzamide, bromovalerylurea, etc.), and/or (3) an insufficient amount of the antidote acetylcysteine.

Symptoms of Acetaminophen Poisoning

When acetaminophen is ingested orally, it is absorbed promptly from the gastrointestinal tract, and the peak blood concentration of the drug is achieved 30–60 min after ingestion. After a therapeutic dose has been taken, the half-life of acetaminophen in blood is 2–3 h, resulting in almost no effect on renal function. However, when a large dose is taken, or when there is liver injury, the time to peak blood concentration increases, and the half-life is more than doubled. If the half-life exceeds 4 h, hepatopathy will develop.

When a toxic dose of acetaminophen is ingested, nausea, vomiting, diarrhea, abdominal pain, and perspiration occur within 24 h. Abnormalities in liver function test parameters become apparent 12 h or more after ingestion. First, there is an increase in AST and ALT, which is followed by an increase in bilirubin and prolongation of prothrombin time. If there is increased activity of serum transaminases alone, without an accompanying increase in bilirubin, the hepatopathy will improve spontaneously if use of the drug is discontinued.

Hepatopathy is most severe 3 or 4 days after ingestion of the drug, with symptoms of vomiting, jaundice, right hypochondrial pain, and disturbance of consciousness. In cases of severe poisoning, nephropathy also occurs. Nephropathy manifests in low back pain, hematuria, and proteinuria 24–72 h after ingestion of the drug, but seldom progresses to renal failure. In rare cases, nephropathy alone, without concomitant liver injury, may occur. These symptoms usually begin to improve 5 days after ingestion of the drug.

The prognosis of acetaminophen poisoning is favorable when the total bilirubin level is under 4 mg/dl and the prothrombin time is within 24 s. The severity of liver injury should be assessed by liver function test before therapy and up to 5 days after the beginning of therapy.

Treatment of Acetaminophen Poisoning

When it is certain that a patient has ingested a large amount of acetaminophen, gastric lavage is performed after inducing vomiting in the patient. Since acetaminophen is promptly absorbed, it is desirable to perform gastric lavage within 30 min after ingestion of the drug. However, when an anticholinergic agent or central nervous system depressant is used concomitantly, absorption of acetaminophen is slowed. In such cases, gastric lavage should be employed even up to 6 h after ingestion of the drug, because the procedure is expected to still be effective.

When gastric lavage has been performed soon after the ingestion of acetaminophen, activated charcoal should be given orally to adsorb and remove any acetaminophen remaining in the gastrointestinal tract. However, if more than an hour has passed since the ingestion of acetaminophen, the drug may have been largely absorbed, and activated charcoal may not be
sufficiently effective or may interfere with the action of the oral antidote by adsorbing it. Activated charcoal, therefore, should not be used in this case.

In acetaminophen poisoning, the toxicity of its metabolite appears because of glutathione depletion in liver cells. Glutathione administration, however, is ineffective because glutathione is not taken up by liver cells. Therefore, acetylcysteine, a precursor of glutathione, is used for detoxication.

Acetylcysteine should be administered within 8 h after acetaminophen ingestion. It is reported that as long as it is administered within 8 h, the incidence of liver injury is similar regardless of whether it is within 4 h or later. Acetylcysteine does not prevent liver injury if administered more than 16 h after the ingestion of acetaminophen. However, the use of acetylcysteine even within 24 h is valid because it reduces the severity of hepatic coma and may lead to a better vital prognosis.

In Western countries, it is recommended that, if acetaminophen poisoning is suspected, acetylcysteine be administered after confirming that the patient’s blood concentration of acetaminophen is within the range of liver injury-inducing levels, by comparing the blood concentration of the drug determined 4 or more hours after ingestion with the nomogram (Figure). However, the relationship between the blood concentration of acetaminophen and its toxicity as seen in the figure is observed when acetaminophen alone is ingested.

In Japan, it is rare for acetaminophen to be used as a monotherapy. Instead, it is usually ingested as one component of cold remedies or antipyretic analgesics. Therefore, because of the effects of other ingredients contained in these preparations, acetaminophen poisoning may occur even if the blood concentration of acetaminophen is not high. Disturbance of consciousness may develop due to the actions of other formulating agents. In such cases, respiratory care is required.

If acetaminophen is the only offending agent, plasmapheresis is not effective and should not be used. However, if another or other offending agents are suspected, if the blood concentration of acetaminophen is extremely high, exceeding 1,000 μg/ml, or if there is acute liver failure, plasmapheresis should be used. If there is renal failure, hemodialysis should also be employed.

Usage of Antidote Acetylcysteine

A acetylcysteine, an antidote for acetaminophen poisoning, is commercially available as an expectorating inhalant in the form of 20% solution (A cetein® liquid, A.R.B.®, M ucofilin®).

To detoxify acetaminophen poisoning, a 1/4
dilution of the 20% acetylcysteine solution, i.e., 5% acetylcysteine solution, at a dose of 140 mg per kg of body weight should be ingested orally or administered via a gastric tube. Thereafter, 5% acetylcysteine solution at half the initial dose should be given every 4 h until 72 h after the beginning of therapy.

Since this drug is likely to induce vomiting at a high concentration and is thus difficult to drink, it may be helpful to dilute the drug about fourfold with orange juice or cola. If the patient vomits within 1 h after administration, re-administration is necessary. If vomiting is too severe, the patient should be allowed to ingest the drug slowly over 30-60 min, or the drug should be administered via a gastric tube inserted up to the duodenum, followed by inhibition of vomiting by intramuscular or intravenous injection of an antiemetic.

Antibiotics should not be used concomitantly in acetaminophen poisoning because they inactivate acetylcysteine.

Conclusion

Acetaminophen is widely used as an active ingredient of OTC cold remedies and antipyretic analgesics. Although it is safe at the recommended dose, its use for a number of consecutive days or in combination with other drugs may induce intoxication even when the amount ingested is not very large. If acetaminophen poisoning is suspected, proper treatment should be initiated promptly.