REVIEW ARTICLE

Update: the clinical importance of acetaminophen hepatotoxicity in non-alcoholic and alcoholic subjects

E. Tanaka, K. Yamazaki* and S. Misawa
Institute of Community Medicine, University of Tsukuba, Tsukuba-shi, Ibaraki-ken 305-8575, Japan and *Tsukuba Medical Examiner’s Office, Tsukuba-shi, Ibaraki-ken 305-8558, Japan

SUMMARY

Acetaminophen (paracetamol) is one of the most commonly used over-the-counter medications. Taken in doses greater than 150 mg/kg/day (>10 g), it usually causes acute liver failure. The authors review mainly the management of acetaminophen toxicity in both users and nonusers of alcohol. Chronic alcoholics are a special subgroup, who risk serious toxicity when taking acetaminophen, even in therapeutic doses. The acetaminophen–alcohol interaction is complex, because acute and chronic ethanol have opposite effects. This review also considers physiological and clinical changes, as well as the diagnosis and treatment of acetaminophen poisoning.

Keywords: acetaminophen, cytochrome P450 2E1, ethanol, hepatotoxicity, human, overdose, therapeutic use, toxicological effects

INTRODUCTION

Acetaminophen (paracetamol) is one of the most widely used antipyretic and analgesic drugs in the world because of its efficacy and relative safety. However, there are many papers showing that it can lead to severe hepatic necrosis and fatal hepatic failure after lower (therapeutic) doses, and regular alcohol intake (absence of alcohol abuse) (1–3) or co-administration of alcohol (1) with acetaminophen in humans.

There have been a number of reviews of acetaminophen hepatotoxicity and its treatment over the period 1984–2000 (2–40). Black (2), in his review of seven non-alcoholic and 13 alcoholic subjects (patients) suffering from acetaminophen hepatotoxicity, begins with a history of the drug and considers the scope of its use from 1977 to 1983. The molecular basis for hepatotoxicity is also discussed and this serves as a background for outlining its clinical manifestations and treatment. In 1995, Zimmerman and Maddrey (41) described about 67 cases of acetaminophen hepatotoxicity associated with a regular intake of alcohol. In 1997, Jonston et al. (24) also reported enhanced acetaminophen hepatotoxicity in 53 alcoholic subjects from 1966 to 1995 (Medline database). More recently, Mofredj et al. (42) also reported 21 cases of acetaminophen intoxication.

In general, therapeutic doses of acetaminophen are in the range 3–6 g/day (40) and it is widely recognized that an overdose of acetaminophen (10–15 g) may result in serious hepatotoxicity.

We have already reported that acetaminophen metabolized by cytochrome (CYP) P450 2E1 is clinically and toxicologically important and this enzyme is constitutively expressed in the liver and many other tissues (43). This article mainly reviews recent reports on acetaminophen hepatotoxicity in both non-alcoholic and alcoholic subjects.

MECHANISM OF TOXICITY AND METABOLISM OF ACETAMINOPHEN

As shown in Fig. 1, acetaminophen is metabolized extensively in the liver via three main pathways: glucuronidation, sulphation and oxidation after oral doses (44, 45). Human CYP2E1, as well as CYP1A2 and CYP3A4, can convert acetaminophen to reactive metabolites which form covalent protein adducts and, hence, cause toxicity (28, 46–49). The mechanism of the hepatotoxicity of acetaminophen is cell death by N-acetyl-p-benzoquinone imine (NAPQI), which can bind to cellular macromolecules (50). This metabolite is a highly reactive free radical intermediate which binds to reduced...
glutathione (GSH). Normally, the small amount of NAPQI formed after the ingestion of a therapeutic dose of acetaminophen is promptly detoxified by conjugation with glutathione. However, when high doses (>10 g) of acetaminophen are ingested, large amounts of NAPQI are formed, and the glutathione stores in the body are rapidly exhausted. As a consequence, unconjugated NAPQI then causes hepatic injury.

Recent articles have also described simple and useful techniques (liver slices or primary cultured hepatocytes, etc.) to investigate the underlying mechanisms associated with acetaminophen-induced cell injury (51–55). In cases of acute heavy alcohol ingestion, alcohol competes with acetaminophen for interaction with CYP2E1. With chronic alcohol use, a combination of CYP2E1 induction and glutathione depletion results in an increased accumulation of NAPQI, leading to enhanced acetaminophen hepatotoxicity from doses generally considered to be nontoxic. The syndrome of liver injury is distinctive, marked only by elevated levels of aspartate aminotransferase (AST), and poses a significant threat. The depletion associated with chronic use of acetaminophen and impaired glucuronidation is perhaps exacerbated by fasting.

**ACETAMINOPHEN HEPATOTOXICITY IN NON-ALCOHOLIC (REGULAR INTAKE) SUBJECTS**

Table 1 shows recent data in patients with acetaminophen hepatotoxicity. Black (2) has reported acetaminophen hepatotoxicity following therapeutic dosing in seven non-alcoholic subjects. The patients ranged from 16 to 67 years of age. The amount of acetaminophen ingested daily was between 3 and 6 g, which translates into 10–20 regular-strength tablets. The duration of acetaminophen ingestion varied from a few weeks to a year or more. Although all subjects recovered, he does not report any changes in biochemical parameters.

Zimmerman and Maddrey (41), more recently, reported 67 patients (male 42, female 25) who developed hepatic injury after ingestion of acetaminophen for therapeutic purposes. The patients ranged from 23 to 88 years of age. All were regular users of alcohol. Sixty-four percent of the patients were considered to be ‘alcoholic’, or reported intakes greater than 80 g/day, 35% took 60 g/day or less, and the remainder were vague in reporting their alcohol intake. Doses of acetaminophen were...
in the ‘nontoxic’ range (<6 g/day) in 60% of the group, within the recommended range (<4 g/day) in 40%, and 4-6 g/day in 20%. A characteristic feature was the very high level of AST, with figures in the range 3000–48 000 IU/l in more than 90% of cases. Almost 20% of the patients died.

**ACETAMINOPHEN HEPATOTOXICITY IN ALCOHOLIC SUBJECTS**

In long-term alcohol users, the syndrome of hepatotoxicity from acetaminophen taken in therapeutic or modestly excessive doses is distinctive. It is characterized by marked elevation of transaminase levels and a risk of acute liver failure with high morbidity and mortality rates (Table 2).

Black (2) has reported acetaminophen hepatotoxicity in 13 alcoholic subjects. The patients ranged from 27 to 63 years of age. The amounts of acetaminophen ingested ranged from as little as 2-6 g to greater than 10 g. As many as five alcoholic patients suffered severe hepatic injury following ingestion of 6-4 g of acetaminophen or less and these five cases all died. He does not report any biochemical parameters. Jonston and Pelletier (24) have also reported enhanced acetaminophen hepatotoxicity in 53 alcoholic subjects (male 32, female 21). The patients ranged from 27 to 66 years of age. The amount of acetaminophen ingested daily was 1-5–17 g (average 6-62 g/day). The duration of acetaminophen ingestion varied from one to 30 days (average 4-6 days). The peak AST was 850–30 000 IU/l (normal range: 8–40 IU/l). The plasma acetaminophen level in one reported case was 237 μg/ml (at 17 h) (normal range: 10–20 μg/ml). A total of 16 of the patients died.

**Table 1. Recent data in patients with acetaminophen hepatotoxicity**

<table>
<thead>
<tr>
<th>Age (yr)/Sex</th>
<th>Amount ingested (g/day)</th>
<th>Days of use</th>
<th>Plasma level [μg/ml, (hr*)]</th>
<th>Peak AST (IU/l)</th>
<th>Alcohol ingestion</th>
<th>Outcome</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. 67/M</td>
<td>1–3</td>
<td>3</td>
<td>27.5</td>
<td>3125</td>
<td>Regular</td>
<td>Survived</td>
<td>(1)</td>
</tr>
<tr>
<td>2. 33/M</td>
<td>6</td>
<td>1</td>
<td>–</td>
<td>15 730</td>
<td>Yes**</td>
<td>Survived</td>
<td>(56)</td>
</tr>
<tr>
<td>3. 16/M</td>
<td>3–5</td>
<td>3</td>
<td>330</td>
<td>11 270</td>
<td>–</td>
<td>Died</td>
<td>(58)</td>
</tr>
<tr>
<td>4. 29/F</td>
<td>75 (total)</td>
<td>–</td>
<td>1072</td>
<td>–</td>
<td>–</td>
<td>Survived</td>
<td>(57)</td>
</tr>
<tr>
<td>5. 50/M</td>
<td>2</td>
<td>30</td>
<td>2.5 (24)</td>
<td>467</td>
<td>Yes***</td>
<td>Died</td>
<td>(42)</td>
</tr>
<tr>
<td>6. 56/M</td>
<td>3</td>
<td>14</td>
<td>21</td>
<td>10 000</td>
<td>–</td>
<td>Died</td>
<td>(42)</td>
</tr>
</tbody>
</table>

AST: aspartate aminotransferase, ND: not available.
*: interval in h from admission to determination of acute blood level, **: 50 g/day for 8 years and recently 80 g/day for 2 months, ***: 80 g/day for 5 years.


**Table 2. Clinical features that help distinguish between acetaminophen hepatotoxicity and alcoholic hepatitis**

<table>
<thead>
<tr>
<th>Acetaminophen hepatotoxicity</th>
<th>Suicidal overdose</th>
<th>Alcoholic hepatitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>AST activity</td>
<td>Markedly increased</td>
<td>Normal initially, later may be markedly increased</td>
</tr>
<tr>
<td>ALT activity</td>
<td>Increased, but less than AST</td>
<td>Normal initially, later may be markedly increased</td>
</tr>
<tr>
<td>AST to ALT ratio</td>
<td>2&gt;</td>
<td>2&lt;</td>
</tr>
<tr>
<td>Prothrombin time</td>
<td>Increased to markedly</td>
<td>Normal initially, later may be markedly increased</td>
</tr>
<tr>
<td>Blood acetaminophen</td>
<td>Normal or slightly</td>
<td>Increased</td>
</tr>
</tbody>
</table>

AST: aspartate aminotransferase, ALT: alanine aminotransferase, *: IU/l.
Modified from Kumar and Rex (80).
PHYSIOLOGICAL AND CLINICAL CHANGES

Ingestion of a large amount of acetaminophen leads first to nausea, vomiting, sweating and anorexia, and there may be mild confusion. This is especially true if the analgesic is combined with a sedative agent in one of the numerous proprietary acetaminophen mixtures or taken together with sedative drugs. These physical changes are not usually apparent for 2–3 days (56–59). However, in a relatively short time the serum transaminase is dramatically elevated after ingestion of acetaminophen (60, 61). Hypoprothrombinemia, hypoglycemia, visual hallucinations, metabolic acidosis and leucocytosis can also occur. The degree of hypoprothrombinemia is relatively modest (24, 62).

Histopathological findings at autopsy (5) or following a biopsy (1, 24, 63) revealed confluent centrilobular (zone 3) liver cell necrosis definitely characteristic of acetaminophen hepatotoxicity. After ingestion of a low dose, these changes are already underway.

DIAGNOSIS AND TREATMENT

Several recent review articles have been published on the treatment of acetaminophen hepatotoxicity (27, 36). Rumack–Matthew nomograms have been published that relate blood levels of acetaminophen, charted according to the estimated time after ingestion, to the likelihood that liver injury will develop (64). The basic risk category was determined on the basis of serum acetaminophen levels. The study design nomogram was used as a tool to determine risk. For the purposes of risk classification, patients with acetaminophen concentrations between the treatment line defined by 150 µg/ml at 4 h and 37.5 µg/ml at 12 h, and by 200 µg/ml at 4 h and 50 µg/ml at 12 h, are considered at possible risk. Patients with concentrations between the treatment line defined by 200 µg/ml at 4 h and 50 µg/ml at 12 h, and by 300 µg/ml at 4 h and 75 µg/ml at 12 h, are considered at probable risk. Those with concentrations exceeding 300 µg/ml at 4 h and 75 µg/ml at 12 h are classified as being at high risk (36, 65). The lowest treatment line is defined by 150 µg/ml at 4 h and 37.5 µg/ml at 12 h (36, 65). However, there are several factors that have to be taken into account as far as these blood levels are concerned, e.g. no pre-existing liver dysfunction (64, 66, 67).

Rumack et al. (68) evaluated 662 consecutive patients admitted with acetaminophen overdoses. Those at risk on the basis of their acetaminophen blood levels, as plotted on the study nomogram, were treated with oral acetylcysteine. Statistically significant differences in the severity of hepatic toxicity were observed between patients treated within 16 h of ingestion and those treated between 16 and 24 h of ingestion. No deaths occurred among patients treated within 24 h of ingestion, except for one patient who was an alleged gunshot homicide. Seven percent of patients with plasma acetaminophen levels in the potentially toxic range, and treated with acetylcysteine within 10 h of ingestion, showed transient AST level elevations, whereas 29% of those treated between 10 and 16 h of ingestion and 62% of those treated between 16 and 24 h of ingestion showed similar transient toxicity. No consistent difference in hepatotoxicity could be demonstrated between alcoholic patients and non-alcoholic patients. Acute alcohol use resulted in less severe toxic reactions than in those patients not acutely using alcohol.

The main treatments for acetaminophen intoxication are activated charcoal and oral N-acetylcysteine, as an antidote (36, 69–73). N-acetylcysteine increases glutathione stores, acts as a glutathione substrate, and promotes conjugation via the nontoxic sulphation pathway (11–36). The oral administration of activated charcoal does not impair the absorption of orally administered N-acetylcysteine (74–76) However, there is no effect on acetaminophen poisoning (77). The standard treatment protocol for an acetaminophen overdose has been approved by many clinicians (36, 69–73). Zed and Krenzelok (36), for example, have minutely described the treatment of acetaminophen overdose. They recommend that a single dose of activated charcoal should be administered within 1 h of the acetaminophen overdose and acetylcysteine should be given if the acetaminophen concentration exceeds the treatment line in the nomogram. If a patient is treated within 10 h of acetaminophen ingestion, the risk of hepatotoxicity is low. In patients treated 10–24 h after ingestion, a 72-h oral or 48-h i.v. acetylcysteine regimen should be used. In patients with fulminant hepatic failure, acetylcysteine should be
given until recovery or death occurs. In patients who have taken extended-release acetaminophen, the acetaminophen concentration should be measured at 4 h and, if this level exceeds the treatment line, acetylcysteine should be started immediately. If the concentration is below the treatment line, a second acetaminophen concentration should be determined 4-6 h later. If this level is above the treatment line, acetylcysteine therapy should be started.

Woo et al. (73) have recently evaluated the safety and efficacy of a shorter N-acetylcysteine regimen in the treatment of acute acetaminophen overdose in the toxic range according to the Rumack–Matthew nomogram, and oral N-acetylcysteine treatment initiated within 24 h of ingestion in 75 patients. Their regional poison control centre recommended oral treatment with N-acetylcysteine 140 mg/kg, followed by a maintenance dose of 70 mg/kg every 4 h until the serum acetaminophen level was no longer detectable, rather than the standard 72-h treatment regimen. As far as the results were concerned, 25 (33.3%) patients were treated for a period of less than 24 h, 25 (33.3%) were treated for 24–36 h, and 25 (33.3%) were treated for 37–64 h; the mean and median duration of treatment was 31 h. None of the patients treated for less than 24 h had evidence of hepatotoxicity or an AST or alanine aminotransferase (ALT) level >1000 IU/l; hepatotoxicity developed in two (8%) patients treated for 24–36 h and four (16%) patients treated for 37–64 h. There were no deaths, and no patients required liver transplantation.

CONCLUSIONS

Acetaminophen poisoning is common in Japan (78) and the U.S.A. (79). Acetaminophen is a widely used drug, as it is an effective analgesic and antipyretic. Because of the absence of gastro-intestinal side-effects, it has been used as the analgesic of choice for alcoholic patients.

As shown in Fig. 1, alcohol intake is one of the very important factors associated with acetaminophen hepatotoxicity. Alcohol affects acetaminophen liver metabolism in the following ways: first, it lowers hepatic glutathione levels, causing a decreased capacity to detoxify NAPQI and second, it mainly induces liver CYP2E1, thus increasing the proportion of acetaminophen that is converted to NAPQI. Therefore, patients with alcoholic liver disease because of excessive alcohol intake may experience potentiation of the hepatotoxic effect of acetaminophen.

The interactions between acetaminophen and alcohol are complex and many questions remain to be answered. Heightened awareness of this preventable and treatable condition is required by healthcare providers and acetaminophen users alike. Because the minimum safe dose of acetaminophen is not known in the setting of chronic alcohol use, it seems prudent in such situations to avoid acetaminophen altogether, especially during brief periods of abstinence.

REFERENCES


71. Buckley NA, Whyte IM, O’Connell DL, Dawson AH. (1999) Oral or intravenous N-acetylcysteine: which is


