CASE REPORT

Mild hepatitis at recommended doses of acetaminophen in patients with evidence of constitutionally enhanced cytochrome P450 system activity

A. Grieco* MD, L. Miele* MD, A. Forgione* MD, E. Ragazzoni† MD, F. M. Vecchio‡ MD and G. Gasbarrini* MD

*Institute of Internal Medicine, †Institute of Pharmacology and ‡Institute of Pathology, Policlinico Universitario “A. Gemelli”, Università Cattolica del Sacro Cuore, Rome, Italy

SUMMARY

Acetaminophen (paracetamol) is used throughout the world for pain relief and antipyresis in both children and adults. In many countries, it can be purchased without a medical prescription and it is also a common component of a number of over-the-counter remedies for colds, influenza and the like. Fasting, malnutrition and use of alcohol and/or other drugs are thought to play causal roles in hepatotoxicity associated with recommended doses of acetaminophen although liver injury provoked by therapeutic doses has also been observed in the absence of these factors. We describe two patients who experienced subclinical hepatotoxic reactions after taking acetaminophen at therapeutic doses. The results of an antipyrine metabolism test suggest the presence of constitutional hyperactivity of the cytochrome P450-dependent mixed function oxidative system in both patients. We hypothesize that the latter contributed to the hepatotoxicity and that it may play a role in idiosyncratic reactions to this drug.

Keywords: acetaminophen, adverse drug reaction, antipyrine, cytochrome P450, danger hypothesis, drug-induced liver disease, idiosyncratic drug reaction, liver toxicity, paracetamol

INTRODUCTION

Acetaminophen (paracetamol) is used throughout the world for pain relief and antipyresis in both children and adults. In many countries, it can be purchased without a medical prescription and it is also a common component of a number of over-the-counter remedies for colds, influenza and the like. Its efficacy and relative safety are well known, but because of its widespread use and availability, it is also the most common cause of acute drug-related liver failure (1). Cases of the latter, which are often fatal, are generally associated with suicide-related or accidental overdoses (2, 3). Hepatotoxic effects have also been associated with the use of therapeutic doses, but these are rare occurrences, and in most cases, chronic alcohol use and/or malnutrition have been implicated as possible contributing factors (4). A recent single-blind, randomized, placebo-controlled study has demonstrated that therapeutic doses of acetaminophen may elevate transaminases even in the absence of other possible causes and after only a few days from start of consumption (5).

The present report describes two patients who developed mild hepatitis after treatment with acetaminophen at recommended doses. We suggest that both cases are examples of idiosyncratic drug reactions and discuss a possible contribution of a constitutional hyperactivity of the cytochrome P450 (CYP)-dependent mixed function oxidative system (MFOS).

CASE 1

A 37-year-old woman [weight: 57 kg, height: 158 cm, body mass index (BMI): 22.83 kg/m²] was
referred to our Outpatient Unit for Liver Disease for evaluation of hypertransaminasemia (ALT 200 IU/L; AST 100 IU/L), after taking acetaminophen (1 g/day for 3 days) to bring down a fever started 1 week earlier. The hypertransaminasemia had been unexpectedly diagnosed by her family physician during investigation of a persistent flu-like syndrome. The drug was discontinued and 1 week later the patient was seen by our staff. The physical examination was unremarkable. She was afebrile with normal heart rate (78 bpm) and blood pressure (140/70 mmHg). She denied all symptoms and there were no signs of pruritus, rash or jaundice. Alkaline phosphatase, gamma-glutamyl transferase (GGT), total bilirubin, creatinine phosphokinase and aldolase levels were all within normal limits and serum ALT and AST were, respectively, 180 and 98 IU/L (normal values 5–45 IU/L). The complete differential blood count was normal, with no signs of eosinophilia or neutrophilia, as were the platelet-count, total protein level and gamma globulin level. Serology was negative for hepatitis A, B, C and E, cytomegalovirus, Epstein–Barr virus infection and endomysial antibodies. She confirmed that she had taken no medications other than acetaminophen and had eaten normally throughout the flu-like episode. She denied all use of recreational drugs, herbal remedies and alcoholic beverages. During a routine check-up in June 1999, liver function parameters had all been within normal limits.

The next day the patient returned to our clinic for an antipyrine (AP) test (to evaluate CYP-dependent enzyme activity) and measurement of alpha-glutathione-transferase level (HEPKIT Alpha; Biotrin International. Dublin, Ireland).

At 8:00 AM antipyrine (18 mg/kg body weight) was administered orally with 200 mL of water. Venous blood samples were drawn 3 and 24 h after drug administration, and plasma antipyrine concentrations were measured spectrophotometrically. Pharmacokinetic parameters (plasma levels at 0 time, area under the concentration/time curve, half-life, volume of distribution, plasma clearance) were calculated as previously described (6). As shown in Table 1, AP clearance was considerably increased over normal values. The serum alpha-glutathione-transferase level was within normal limits. Fine-needle liver biopsy revealed enlargement of the portal tract with a mild inflammatory infiltrate. At higher magnification, foci of hepatocyte necrosis were also noted in the lobule (Fig. 1a,b).

No treatment was prescribed. Forty days after discontinuation of the acetaminophen, the patient’s serum aminotransferase levels had normalized (ALT 15 IU/L, AST 18 IU/L; normal: 5–45). They were still normal at a 6-month follow-up visit, but a repeat AP test performed at this time revealed that clearance was still significantly higher than normal (Table 1).

**CASE 2**

A 56-year-old man (weight: 75 kg, height: 178 cm, BMI: 23.67 kg/m²) was admitted to the orthopaedics department for persistent right knee pain, which he had been treating at home with acetaminophen (500–1000 mg b.i.d. for 5 days). He denied use of other drugs (including herbal preparations) and alcohol consumption. He was afebrile with no signs of jaundice or skin rash and denied myalgia and other systemic symptoms.

<table>
<thead>
<tr>
<th>Patient 1</th>
<th>Patient 2</th>
<th>Normal valuesa</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>6 months</td>
<td>Baseline 6 months</td>
</tr>
<tr>
<td>Clearance (mg/kg/min)</td>
<td>0.94 0.74</td>
<td>0.71 0.69</td>
</tr>
<tr>
<td>Volume distribution (L)</td>
<td>39.9 34.8</td>
<td>55.1 69.4</td>
</tr>
<tr>
<td>Half life T/2 (h)</td>
<td>8.8 9.7</td>
<td>11.7 15.5</td>
</tr>
</tbody>
</table>

aData from healthy controls, as previously reported (5).
Routine admission lab-work unexpectedly revealed signs of cholestatic hepatitis: ALT 281 IU/L, AST 133 IU/L (normal values 5–45 IU/L); GGT 168 IU/L (normal values 5–45 IU/L) and alkaline phosphatase 305 IU/L (normal >190 IU/L). The total bilirubin level, prothrombin activity and complete blood count were within normal limits and there was no sign of eosinophilia. Serology was negative for past or present infection with hepatitis virus A, B, C or E. Abdominal ultrasound imaging excluded biliary-tree obstruction. A fine-needle liver biopsy showed expansion of the portal space with inflammatory lymphoid infiltrate with a granulomatous component (Fig. 1c,d).

An AP-test administered on the fifth day of hospitalization revealed rapid clearance of the drug (0.62 mg/kg/min). The serum alpha-glutathione-transferase level (16.01 ng/mL) was within normal limits according to the range displayed in the manufacturer’s instructions (HEPKIT™ Alpha; Biotrin International). Acetaminophen was discontinued and the cholestatic indices and transaminase levels gradually decreased without any form of treatment. The patient was discharged and 3 months later, transaminases and cholestatic parameters were completely normal. The 6-month follow-up confirmed complete normalization of liver function parameters, but repeat AP testing revealed persistently increased clearance (Table 1).

**DISCUSSION**

Therapeutic doses of acetaminophen (<4 g/day) are metabolized mainly through glucuronidation and sulphation, but a small percentage undergoes oxidation by enzymes of the MFOs, primarily CYP2E1. This reaction gives rise to a highly reactive free-radical intermediate, N-acetyl-benzoquinone (NAPQI), which is normally inactivated through conjugation with reduced glutathione (GSH). When high doses of the drug (>10 g) are taken, however, the large amounts of NAPQI produced can rapidly exhaust GSH stores (7) (Fig. 2). Most cases of acetaminophen-induced hepatotoxicity have been attributed to dose-dependent mechanisms. Reports of acute liver injury caused by therapeutic doses of the drug are extremely rare but their true incidence may well be underestimated. Ascertainment is likely to be limited to patients with severe liver injury requiring medical support while diagnoses of ‘mild’ or silent toxicity are largely fortuitous. Nonetheless, rare instances of liver toxicity following use of recommended doses of acetaminophen have been described and they have been attributed to the presence of factors such as malnutrition, starvation, chronic alcohol exposure or use of other CYP450-inducing drugs, which diminish GSH levels. As a result, NAPQI covalently binds to nucleophilic macromolecules and causes hepatocyte necrosis (4, 8–10).
Pharmacokinetic studies indicate that depletion of hepatic GSH levels can occur with doses of acetaminophen as low as 0.5–3.0 g (6). In two recent studies, ingested doses of ≤4 g/day were reported for 7% (11) and 17.5% (3) of all patients hospitalized with acute acetaminophen-induced liver failure. Zimmerman et al. reported 67 cases of hepatotoxicity associated with therapeutic use of acetaminophen. Sixty per cent of these patients had used doses below the level considered to be toxic (6 g/day) and 40% were taking doses within the recommended (up to 4 g/day) (12).

The mechanisms underlying toxic reactions to therapeutic doses of acetaminophen remain to be defined, but chronic alcohol use seems to be a contributing factor in many cases associated with moderately excessive or therapeutic doses. Many reports show that acutely ingested alcohol competes with acetaminophen for the interaction with CYP2E1 whereas chronic alcohol abuse results in a combination of CYP2E1 induction and GSH depletion, which increases the fraction of acetaminophen that is converted to its toxic metabolite NAPQI (13). Indeed, all 67 patients studied by Zimmerman et al. (12) were regular alcohol users, while Schiodt et al. reported chronic ethanol use in well over half of all patients admitted to an urban county hospital in USA for acute liver failure due to accidental acetaminophen overdose (10).

There are few reports of seemingly idiosyncratic reactions to therapeutic doses of acetaminophen in patients without a history of alcohol intake, but in these cases other conditions, such as starvation or use of other drugs, may have contributed to the hepatic damage (4, 8, 9).

Recently, a case of hepatotoxicity provoked by recommended doses (4 g/day) of acetaminophen was described in a woman with concurrent squamous cell carcinoma of the anus and renal cell carcinoma (14). The authors suggested that the toxic reaction was in any case a dose-dependent phenomenon as subsequent (inadvertent) treatment with lower doses was well tolerated. Nevertheless, there are several factors that might have contributed to the liver damage in this case, including nutritional status, antibiotic therapy and general anaesthesia. Fabris reported two cases of acute hepatitis following administration of low doses of acetaminophen (0.5–1.5 g/day) (15). However, both patients had melanomas and were being treated with interferon and effects of other factors (e.g. poor nutritional status due to the presence of cancer, administration of other drugs including antibiotics and general anaesthetics) cannot be excluded.

The fact is that any factor that increases the production of NAPQI or reduces the availability of GSH will enhance the risk of a hepatotoxic reaction to acetaminophen. In addition to the factors discussed above, this list must also include interindividual variations, in the size of the hepatic GSH pool and/or in CYP activity (16). In our opinion, their role in adverse reactions to acetaminophen, which was first hypothesized almost 30 years ago by Johnson and Tolman (17), and recently reproposed by other authors (12, 15), cannot be...
excluded, particularly in those cases in which other risk factors cannot be readily identified. The two patients we observed are good examples. Both were in good health with no evidence of neoplastic disease or other systemic pathology. Both denied any use of alcohol as well as other drugs that might cause CYP enzyme induction. Neither had been fasting and malnutrition could be excluded on the basis of their BMIs. Their asymptomatic elevations of serum ALT and AST (>2 IU/mL) were similar to those reported by Tanaka et al. (18) but far lower than those observed in the alcohol-users reported by Zimmerman (12). According to recent understanding on drug-induced liver disease (DILD), both our cases fit the model of the idiosyncratic drug reaction recently reviewed (19).

Cases of acetaminophen toxicity associated with the use of recommended doses are currently considered to represent idiosyncratic reactions that do not occur in most patients regardless of the dose administered. Even if the allergic model should explain some cases of idiosyncratic reaction, as our cases had neither eosinophilia nor cutaneous rashes, we should suggest a non-allergic mechanism for idiosyncrasy. We believe that both these cases are consistent with a ‘danger model’ of idiosyncratic reaction (20). The mild hepatitis was caused by the toxicity of the reactive metabolite, NAPQI, which was probably present in larger amounts due to genetically determined upregulation of CYP activity. Under certain circumstances, the toxic hepatocyte injury provoked by NAPQ1 might also have resulted in a ‘danger signal’ capable of activating the immune system (20). The fact that acetaminophen was promptly discontinued as soon as the transaminase elevations were noted, together with the patients’ otherwise good health, may explain why the hepatic damage was so mild and why it never triggered an immune reaction.

We, therefore, feel that both cases were idiosyncratic and can be attributed to genetically determined enhancement of cytochrome-P450 enzyme activity and this hypothesis is also supported by the AP test results. The AP test has been widely used in clinical studies for global assessment of the in vivo activity of the MFOS (20). We have used it extensively in patients with chronic active hepatitis, liver cirrhosis and liver metastases, as well as in healthy subjects (5, 21, 22). Due to interindividual variations, however, AP is not a suitable probe for assessing the activity of distinct human CYP enzymes (23). Interestingly, the AP clearance values of both our patients were higher than the mean value observed among the healthy volunteers we have studied (6, 22) and these rates remained high when the test was repeated after a 6-month acetaminophen wash-out period.

These results support the hypothesis that constitutionally enhanced MFOS activity leading to overproduction of NAPQI can probably cause liver-cell necrosis even in the absence of GSH depletion. Genetically determined ‘abnormalities’ in an individual’s capacity for metabolizing drugs (e.g. rapid vs. slow acetylators) are thought to be one of the main causes of idiosyncratic drug reactions. This chain of events might explain toxic events that occur without drug overdosage (24, 25).

Considering the widespread use of acetaminophen, physicians and patients alike should be aware that even therapeutic doses of this drug can cause serious liver injury. This report supports the possibility that genetic and environmental factors may trigger an unexpected idiosyncratic reaction through the innate immune system regulation (downstream); in our cases acetaminophen liver toxicity (18).

In the future, pharmacogenomics and more accurate identification of ‘high-risk’ subjects may reduce the incidence of DILD, including those caused by drugs such as acetaminophen, which has characterized medical history in the 20th century.

REFERENCES


