Therapeutic Dose of Acetaminophen as a Possible Risk Factor for Acute Kidney Injury: Learning from Two Healthy Young Adult Cases

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Abstract

Acetaminophen overdose can lead to severe liver and kidney failure; however, the risk of therapeutic doses in healthy individuals causing acute kidney injury (AKI) is less clear. We herein describe the cases of two young adults with renal biopsy-proven acute tubular necrosis under a therapeutic dose of acetaminophen. The first patient exhibited mild reversible renal insufficiency, whereas, in the second case, the patient demonstrated a slightly increased serum creatinine level and enlarged kidneys and the administration of contrast media and antibiotics may have worsened the renal dysfunction, leading to the need for temporal hemodialysis. Physicians should be aware of the risk of acetaminophen causing AKI and avoid administering other nephrotoxic agents in such cases.

Key words: acetaminophen, acute kidney injury, acute tubular necrosis

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Introduction

Acetaminophen is widely used and incorporated in many over-the-counter drugs as an analgesic and antipyretic. Acetaminophen is a phenacetin metabolite (1). Phenacetin has been recognized to be one of the most nephrotoxic analgesics and was withdrawn from the market in most countries, including Japan (2). An acute acetaminophen overdose can cause potentially lethal liver and kidney failure, presenting with a histology of hepatic necrosis and acute tubular necrosis (ATN) (2). At therapeutic doses, acetaminophen can be toxic in patients who consume an excessive amount of alcohol or take drugs that stimulate P-450 microsomal oxidase enzymes (3-5). However, in healthy individuals with a normal renal function, the risk of therapeutic doses of acetaminophen causing acute kidney injury (AKI) is less clear. We herein describe the cases of two healthy adults with AKI possibly triggered by the ingestion of therapeutic doses of acetaminophen. One patient showed slight ATN, while the other developed severe ATN requiring hemodialysis. These cases highlight the risk of therapeutic doses of acetaminophen causing AKI.

Case Reports

Case 1

A 23-year-old woman was referred to our hospital due to renal insufficiency. She took one tablet (200 mg) of acetaminophen for a fever nine days before admission and mosapride citrate hydrate and kampo: daikenchuto for left lower abdominal pain five and three days before admission, respectively. There was no other drug intake, including diuretics or excessive amounts of acetaminophen. The patient had no psychological background. Her laboratory data

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A 26-year-old woman presented to the emergency room complaining of a fever, abdominal pain and backache. Seventeen days before the visit, she had received a rubella vaccine. From 14 to 10 days before the visit, she took two shin-sedes tablets (a popular over-the-counter headache medicine that is sold in Japan) three times (80 mg of acetaminophen, 200 mg of ethenzamide and 30 mg of allyliso-propylacetylsurea per tablet) for a slight fever and painful period. One day before the visit, her temperature increased to 39°C and she took one tablet of oseltamivir and kampo: mao-to. She presented to the emergency room complaining of a fever, abdominal pain and backache. Her blood pressure was 96/69 mmHg, which was nearly her usual level, with no significant physical signs of dehydration. A urinalysis was almost clear, the serum creatinine level was 1.06 mg/dL and the C-reactive protein level was 5.17 mg/dL. The serum total bilirubin level was 2.15 mg/dL, and the transaminase level was not elevated. There was no evidence of hemoconcentration on the blood or urinary examinations. Enhanced computed tomography performed to evaluate the patient’s abdominal pain revealed bilateral enlarged kidneys with no other significant abnormal findings. A urinary tract infection was suspected; thus, 1 g of cefazolin sodium salt was administered and oral cefaclor was prescribed. The next day, the patient consulted a urologist. Tazobactam/piperacillin sodium was substituted for cefazolin and cefaclor. The serum creatinine level increased to 4.72 mg/dL on the third day, and the patient was admitted to the nephrology ward of our hospital for a further evaluation of AKI. Her systolic blood pressure was consistently maintained around 100 mmHg after admission. Her body weight was 46 kg with no significant changes between the values obtained before and after admission. The calculated fractional excretion of sodium was 19.4%, and the renal function did not show any improvement upon an intravenous volume challenge, indicating that the possibility of prerenal acute renal failure was unlikely. A physical examination was unremarkable, except for the fever and upper abdominal pain. The urinary N-acetyl-β-D-glucosaminidase, alpha 1 microglobulin and beta 2 microglobulin levels were increased to 10.1 U/L, 82.9 mg/L and 31,450 μg/L, respectively. Ga-67 scintigraphy re-
vealed a bilateral renal uptake, suggesting acute interstitial nephritis. A urinalysis was almost clear, and eosinouria was absent. The serum creatinine level peaked at 10.68 mg/dL on the fifth day, and the patient developed anuria, at which time hemodialysis was introduced. After four sessions of hemodialysis, the patient’s urinary volume increased and her serum creatinine level decreased. Hemodialysis was discontinued on the 11th day. A renal biopsy was performed on the 12th day, which showed severe ATN with regenerating tubular epithelial cells, tubulointerstitial infiltration of inflammatory cells and slight tubulitis (Fig. 2A, B).

DLST results obtained 10 days after admission showed slightly positive findings for shin-sedes 8 (186 cpm, normal range: below 180 cpm), while other drugs used before admission were negative, including oseltamivir, mao-to, contrast media (iophexol), cefaclor, cefazolin sodium salt and the rubella vaccine.

The size of the patient’s kidneys decreased to a normal size, as judged on ultrasound, and her symptoms of abdominal pain and backache disappeared. Acute extension of the kidneys may have caused the backache and abdominal pain. The patient was discharged on the 23rd day with a serum creatinine level of 1.06 mg/dL without any symptoms or inflammatory signs. The latest serum creatinine measurement had returned to the normal range.

Discussion

It is well known that an acute overdose of acetaminophen can lead to severe liver and kidney failure. At therapeutic doses, acetaminophen is toxic in individuals who consume an excessive amount of alcohol or take drugs that stimulate P-450 microsomal oxidase enzymes (3). However, in healthy individuals with a normal renal function, it is less clear whether the regular use of therapeutic doses of acetaminophen carries a risk of renal failure.

Our first case strongly indicates that a therapeutic dose of acetaminophen can cause ATN, even in healthy individuals. Since it has been reported that a slight but significant level of apoptosis is induced by therapeutic doses of acetaminophen in cultured tubular cells (6), it is possible that AKI with slight ATN may occur in humans who consume a therapeutic dose of acetaminophen. This kind of reversible slight renal insufficiency may not be noticed unless the serum creatinine level is measured. Therefore, our first case provides a valuable example in which elevation of the serum creatinine level was actually detected and the presence of ATN was proven on a renal biopsy. It is now well known that some patients who recover from AKI may progress to chronic kidney disease (CKD) (7-9). Hence, some cases of CKD of unknown etiology after recovery from AKI may be explained by this kind of mechanism.

In the second case, on admission, the patient showed slight elevation of the serum creatinine level associated with enlarged bilateral kidneys, indicating that the AKI had existed before the introduction of contrast media for abdominal CT and the administration of cefaclor, cefazolin sodium salt and tazobactam/piperacillin, even though all of these drugs can potentially induce AKI. Therefore, it is possible that the additional administration of potentially nephrotoxic agents (contrast media and/or antibiotics) in this case exacerbated the progression of slight to severe AKI. There are a few reports of renal failure occurring after the use of oseltamivir; thus, the risk of AKI is described in the drug information for this medication. However, a deteriorated general status induced by the influenza virus itself or concomitantly used drugs, such as non-steroidal anti-inflammatory drugs (NSAIDs), is considered to be causative for renal failure; therefore, oseltamivir does not appear to be the primary cause of AKI in this case.
It has been reported that therapeutic doses of acetaminophen induce severe ATN (10) and that acetaminophen-induced renal failure becomes evident after hepatotoxicity in most cases (11). Therefore, our second case may be a rare case in which a therapeutic dose of acetaminophen caused severe ATN requiring hemodialysis with slight hepatic injury. Moreover, the patient exhibited increased urinary markers of acute tubulointerstitial damage and a positive Ga-67 uptake in the kidneys, thus suggesting acute tubulointerstitial nephritis. The renal histology also demonstrated ATN accompanied by tubulointerstitial inflammation and slight tubulitis. There is one case report of tubulointerstitial nephritis induced by the therapeutic use of acetaminophen in addition to alcohol intoxication; however, our patient did not consume alcohol (4). Although an allergic reaction to shingles^5 based on the positive DLST results may have contributed to the tubulointerstitial damage observed in the second case, the degree of tubulointerstitial inflammation can be explained as a secondary phenomenon associated with severe ATN. Both acetaminophen and ethenzamide are causative ingredients; however, there have been no English-language reports of ATN caused by ethenzamide. Therefore, the effects of ethenzamide on the development of AKI in this case remain unclear. One possible reason for the lack of any English literature on this topic is due to the fact that ethenzamide, an NSAID that is often contained in over-the-counter drugs together with other NSAIDs, is rarely prescribed in hospitals and its adverse renal effects may have been overlooked.

In summary, the incidence of renal failure induced by a therapeutic dose of acetaminophen is much less than that of other NSAIDs. However, physicians should be aware that the ingestion of therapeutic doses of over-the-counter drugs incorporating acetaminophen is a risk factor for AKI, even in healthy individuals, and avoid administering other nephrotoxic agents to patients with acetaminophen-induced renal damage.

The authors state that they have no Conflict of Interest (COI).

References


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