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Acetaminophen induced nephrotoxicity in an adolescent girl

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Summary

Acetaminophen induced nephrotoxicity is not a frequent consequence of acetaminophen overdose. The pathophysiology has been attributed to oxidative stress. Here, we report a 16-year-old female patient who developed non-oliguric acute renal failure without hepatotoxicity following ingestion of 14 tablets of 500 mg acetaminophen and recovered spontaneously in a week. *(Turk Arch Ped 2011; 46: 334-6)*

Key words: Acetaminophen, nephrotoxicity, tubulointerstitial nephritis

Introduction

Acetaminophen (AA) is a commonly used analgesic and antipyretic agent. Hepatotoxicity is an important result of AA overdose and the mechanisms of toxicity have been examined comprehensively. However, AA-related nephrotoxicity (AARN) is a less commonly seen side effect. Although oxidative stress is being thought to be involved in the pathophysiology, the effective pathways of tubular cell damage has not been fully elucidated (1-3).

It has been reported that the degree of renal damage is independent of hepatic damage and AARN can be observed without development of hepatotoxicity (2-4). Acetaminophen-related nephrotoxicity may or may not be oliguric and histopathology usually displays acute tubular necrosis (1). Here, we present a non-oliguric case of AARN with a clinical picture of tubulointersititial nephritis (TIN).

Case

A 16 year old girl presented to the emergency department with complaints of headache and vomiting one hour after taking 14 tablets of 500 mg acetaminophen (117mg/kg). There was no pathology in the patient's personal history. On physical examination, vital signs and blood pressure were within normal limits. A single dose of active charcoal (1g/kg) and N-acetylcysteine (140 mg/kg loading dose) were given to the patient whose AA blood level measured at presentation was found to be in the low-risk range (112 µg/mL). Transaminases of the patient were within the normal range at presentation and during follow-up. AA levels which were measured in four-hour intervals rapidly regressed to normal values in 24 hours (93-68-35-10-5 µg/mL). At the end of the 36th hour, monitoring was discontinued. Two days later the patient presented to the emergency department, when her vomiting recurred and blood urea nitrogen (BUN) was found to be 21 mg/d L and serum creatinine level was found to be 2.14 mg/dL. Urine output was found to be enough and urine density was found to be 1004. Urine microscopic examination revealed abundant erythrocytes and leucocytes. Fractioned sodium excretion (FENa) value was found to be 3.3% and 70% of the leucocytes were eosinophyles. Kidney dimensions and echogenicities were observed to be increased on ultrasonographic examination. AA-related TIN was considered in the patient. No biopsy was taken, since BUN and serum creatinine values regressed to 9 and 0.75 mg/dL, respectively at the end of the first week (Table 1).

Discussion

AARN which occurs in acetaminophen overdose is a known finding which has drawn little attention (5). Acetaminophen-related nephrotoxicity has been defined as

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Table 1. Laboratory findings in the days following ingestion of acetaminophen.

	1st day	2st day	3st day	4st day	5st day	11st day
BUN (mg/dL)	8	4	21	18	9	9
SCr (mg/dL)	0.68	0.69	2.14	1.38	1.11	0.75
ALT (IU/L)	12	15	13	11	10	30
AST (IU/L)	20	18	11	11	9	27

ALT: alanine aminotransferase, AST: aspartat aminotransferase, BUN: Blood Urea nitrogen, SCr: serum creatinine

the finding of a BUN value of >18 mg/dL and serum creatinine level of >1,1 mg/dL and the presence of at least one of the following findings: high blood pressure (systolic >140 mmHg, diastolic >85 mmHg), abnormal urinary findings (hematuria >2+, proteinuria >2+) (4). In acetaminophen overdose, the frequency of AARN is reported to be 8.9% in adolescent patients (4), while it is reported to be 1% in adult patients (1).

In acetaminophen–related nephrotoxicity, clinical course, laboratory findings and renal biopsy findings are generally compatible with acute tubular necrosis (5). Use in combination with other nephrotoxic drugs, dehydratation, underlying renal failure and chronic alcohol consumption increase the risk (5). Chronic AA-related TIN is observed as a result of chronic consumption of at least two types of antipyretic analgesic and drugs containing caffeine and/or codeine additionally (6). Although our patient had none of the risk factors mentioned above, she presented with acute non-oliguric renal failure, hypostenuria, increased FENa levels, marked tubular dysfunction, eosinophyluria, sterile pyuria and hematuria. Rash or joint swelling was not observed. Although the diagnosis of TIN could not be confirmed, the above mentioned findings especially eosinophyluria suggested AA-related TIN.

N-acetyl-benzo quinoneimine (NAPQI) is a toxic metabolite of AA and is generally detoxified by glutathione-S-transferase enzyme. This enzyme conjugates NAPQI with reduced glutathione and is present both in the liver and the kidney abundantly (1,3). When high amounts of AA are taken and glutation deposits in the kidney are decreased, hepatotoxicity and nephrotoxicity develop (3). When hepatotoxicity develops, the amount of NAPQI which should be conjugated in the kidneys increases and the risk of AARN increases in parallel (1). However, AARN can be observed without development of hepatotoxicity (2,4). Findings of renal failure were observed without accompanying hepatotoxicity findings in 5 of 17 cases who developed renal failure following acetaminophen intoxication and who had a mean age of 31.7±21.1 (7). Again, oliguria was found in 23 of 31 cases who developed AARN without hepatotoxicity and renal replacement treatment was required in 13 (8). In our patient, no increase was found in transaminases before or after the development of AARN.

In current guidelines related to AA toxicity, monitoring times are shorter than 48 hours, if transaminases and prothrombin time are normal (5,9). However, it is currently known that nephrotoxicity can easily be missed in patients who are discontinued to be followed up in 48 hours (5). Hence, in 8 adult patients who developed both hepatotoxicity and AARN, mean times to achieve peak values of serum alanine transferase and prothrombin time were the first 2.5 days and 2.2 days, respectively and mean times to achieve peak values of urea and creatinine levels were 5.3 and 5.5 days (5). In a study including 44 adult cases with AA overdose, it was observed that the highest abnormal renal laboratory findings occured 48-72 hours after ingestion of the drug and nephrotoxicity continued for 2-3 days in 3 cases who had no requirement of dialysis and who had mild AARN. In a case who had a requirement of dialysis, the highest levels occured in the 8th day and these levels returned to normal in 3 weeks. In these 4 patients, the highest mean BUN value was found to be 24.08 (15.96-45.08) mg/dL and the highset mean serum creatinine value was found to be 2.7 (1.4-6.2) mg/dL (4). In all cases, urine density was found to be low and hematuria and proteinuria were observed in 2 of them (4). In our adolescent patients, BUN and serum creatinine values increased to higher levels compared to the levels defined in the cirteria on the 4th day (21 mg/d Land 2.14 mg/dL, respectively) and proteinuria and hematuria were observed. Laboratory findings returned to normal levels in 2 days.

Hepatic damage can generally be improved with N-acetylcysteine (NAC). However, it has been reported that NAC treatment does not prevent renal damage and even may damage the kidneys (2,3,10). Nevertheless, NAC has been reported not to worsen nephrotoxicity (2). NAC treatment was administered to our patient, when she presented to our emergency department the first time. In the following days, hepatotoxicity did not develop, but nephrotoxicity was observed. Therefore, it can be stated at least that NAC did not have a protective effect on renal function.

Our patient who developed AA-related oliguric acute renal failure and who had findings of TIN was presented to draw attention to the significance of monitoring renal function and the fact that AARN may also be in the form of TIN in cases with AA overdose.

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