

## Acetaminophen-induced hepatotoxicity in a glutathione synthetase-deficient patient

Ayşegül Tokatlı<sup>1</sup>, H. Serap Kalkanoğlu-Sivri<sup>1</sup>, Aysel Yüce<sup>2</sup>, Turgay Coşkun<sup>1</sup>

Units of <sup>1</sup>Nutrition and Metabolism, and <sup>2</sup>Gastroenterology, Hepatology and Nutrition, Department of Pediatrics, Hacettepe University Faculty of Medicine, Ankara, Turkey

**SUMMARY:** Tokatlı A, Kalkanoğlu-Sivri HS, Yüce A, Coşkun T. Acetaminophen-induced hepatotoxicity in a glutathione synthetase-deficient patient. Turk J Pediatr 2007; 49: 75-76.

We report a patient with glutathione synthetase (GS) deficiency who developed acetaminophen-induced hepatotoxicity after a two-day treatment with regular doses of acetaminophen. A nine-month-old female was referred because of intractable metabolic acidosis. She was given acetaminophen at therapeutic doses over a 48-hour period. She was hospitalized because of confusion and metabolic acidosis. Liver function tests were abnormal with normal bilirubin levels. The urine gas chromatography-mass spectrometry (GC/MS) showed massive excretion of 5-oxoproline. She improved and liver function tests normalized in the next six days, but compensated metabolic acidosis and massive 5-oxoprolinuria persisted. The analysis of GS in erythrocytes revealed 5% of normal enzyme activity, and the patient had 491G>A mutation on both alleles in the GS gene. In this report it can be assumed that patients, even if heterozygous for a mutation of the GS gene, are at risk for acetaminophen toxicity.

*Key words:* acetaminophen, hepatotoxicity, glutathione synthetase deficiency.

Glutathione is one of the major antioxidants, which functions as a redox buffer by removing toxic peroxides. Glutathione is metabolized via the  $\gamma$ -glutamyl cycle. The synthesis of glutathione consists of two consecutive steps catalyzed by  $\gamma$ -glutamylcysteine synthetase and glutathione synthetase (EC 6.3.2.3) (GS). Glutathione normally regulates its own synthesis by feedback inhibition of  $\gamma$ -glutamylcysteine synthetase. Depletion of glutathione causes accumulation of  $\gamma$ -glutamylcysteine, which is metabolized to 5-oxoproline by an alternate pathway<sup>1</sup>. Massive excretion of 5-oxoproline is usually associated with genetic defects in  $\gamma$ -glutamyl cycle. But a number of conditions also lead to increased 5-oxoproline excretions at more modest concentrations. More recently, transient metabolic acidosis and 5-oxoprolinuria have been described in association with some medications such as acetaminophen<sup>2</sup>.

High levels of acetaminophen lead to depletion of sulphur-containing amino acids, including cysteine and glutathione, with subsequent disruption of the  $\gamma$ -glutamyl cycle, thus causing 5-oxoprolinuria.

The toxicity of acetaminophen is closely linked to its metabolism with therapeutic dosing. Acetaminophen is predominantly metabolized by conjugation with sulfate and glucuronide. Approximately 5%-10% of the drug is oxidized by cytochrome P450 dependent pathways to a toxic metabolite N-acetyl-p-benzoquinone imine (NAPQI). NAPQI is detoxified by glutathione and eliminated in the urine and bile. The NAPQI that is not detoxified may bind to hepatocytes and produce cellular necrosis. Individuals who are deficient or heterozygous for GS deficiency may have a limited capacity for detoxification of NAPQI through conjugation with glutathione. These people have an increased risk of developing a toxic reaction to acetaminophen even at therapeutic doses<sup>3</sup>.

We report here acetaminophen-induced hepatotoxicity in a GS-deficient patient.

### Case Report

A nine-month-old female was referred because of intractable metabolic acidosis. She was the product of a first-cousin marriage. Five

days previously, she developed malaise and vomiting, and she was given acetaminophen at therapeutic doses over a 48-hour period. Acetaminophen was discontinued thereafter. On the third day, she developed diarrhea requiring intravenous hydration in daily care. The next day, she was hospitalized because of confusion and metabolic acidosis (pH: 6.99, base excess: -25 mmol/L), but no cause was identified. She was treated with intravenous bicarbonate, but metabolic acidosis persisted (pH: 7.37, base excess: -10.6 mmol/L). After two days, the patient was referred to our hospital. At the time of admission, she had altered mental status, hepatomegaly (2 cm) and mild normocytic normochromic anemia (Hb: 8.9 g/dl) with mild reticulocytosis (2% of erythrocytes). A venous blood gas showed a pH: 7.23 and base excess: -17.6 mmol/L. Liver function tests were abnormal (aspartate aminotransferase-AST: 2689/3034 IU/L, alanine aminotransferase-ALT: 1037/1402 IU/L) with normal bilirubin levels.

Investigation for the common causes of metabolic acidosis proved fruitless, with only a mildly increased serum lactate. All viral hepatitis markers were negative. The urine gas chromatography-mass spectrometry (GC/MS) showed massive excretion of 5-oxoproline. Blood acetaminophen level was less than 1 µg/ml. She partially responded to bicarbonate treatment which was still continuing, with her blood gas revealing mild compensated metabolic acidosis (pH: 7.38, base excess:-7.6 mmol/L). Six days after the admission, she improved and liver function tests normalized, but compensated metabolic acidosis and massive 5-oxoprolineuria persisted. The analysis of GS in erythrocytes revealed 5% of normal enzyme activity and the patient had 491G>A mutation on both alleles in the GS gene. She was placed on vitamin C, vitamin E and alkaline (Shohl) solution therapy. At present, she is 15 months old and her latest developmental assessment was appropriate for her age. 5-oxoprolineuria in follow-up urine samples was a constant finding.

## Discussion

In this patient, hepatic dysfunction, metabolic acidosis and 5-oxoprolineuria were compatible with acetaminophen toxicity, but she had only been given acetaminophen at 15 mg/kg every six hours for the first two days. But the persistent 5-oxoprolineuria and metabolic acidosis were highly suggestive of a genetic defect in the  $\gamma$ -glutamyl cycle.

The safety and efficacy of acetaminophen in children are well established. In general, the risk of developing toxic reaction to acetaminophen appears to be lower in children. But a child with genetic defect in the  $\gamma$ -glutamyl cycle has a risk of developing a toxic reaction when taking acetaminophen, even if in therapeutic doses<sup>4</sup>.

In the literature, 491G>A mutation was associated with moderate GS deficiency<sup>5</sup>. According to her clinical phenotype and genotype, this patient had the moderate form of the disease. We believe that the dehydration requiring intravenous rehydration gave an additional risk for developing acetaminophen toxicity in the patient.

## Acknowledgements

The analysis of glutathione synthetase in erythrocytes and mutation analysis from the patient were performed by Ellinor Ristoff M.D, Ph.D. (Stockholm-Sweden). She and her group are gratefully acknowledged by the authors.

## REFERENCES

1. Njalsson R, Norgren S. Physiological and pathological aspects of GSH metabolism. *Acta Paediatr* 2005; 94: 132-137.
2. Mayatepek E. 5-oxoprolineuria in patients with and without defects in the  $\gamma$ -glutamyl cycle. *Eur J Pediatr* 1999; 158: 221-225.
3. American Academy of Pediatrics Committee on Drugs. Acetaminophen toxicity in children. *Pediatrics* 2001; 108: 1020-1024.
4. Morton NS, Arana A. Paracetamol-induced fulminant hepatic failure in a child after 5 days of therapeutic doses. *Paediatr Anaesth* 1999; 9: 463-465.
5. Njalsson R, Ristoff E, Carlsson K, Winkler A, Larsson A, Norgren S. Genotype, enzyme activity, glutathione level, and clinical phenotype in patients with glutathione synthetase deficiency. *Hum Genet* 2005; 116: 384-389.