Case Report

health science

LIVER FAILURE DEVELOPING SECONDARY TO OVERDOSE OF PARACETAMOL USE

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ABSTRACT

Paracetamol (acetaminophen, N-acetyl-P-aminophenol, APAP), which is found in many preparations in our country, is the most commonly used over-the-counter analgesic in the world. The drug, which is pregnancy category B, is widely used in pregnancy. Paracetamol is the most commonly reported drug poisoning agent. Paracetamol is metabolized via the liver. Paracetamol poisoning is the most common cause of liver failure. Liver toxicity is seen in single doses of 200mg/kg or 10gr, and repeated intakes of 100mg/kg or 4gr/day. Gastric lavage can be performed in patients who apply within the first 2 hours of oral intake, and activated charcoal should be given in the first 4 hours. N-acetyl cysteine (NAC) is given as an antidote. The mainstay of treatment in patients with hepatic failure is liver transplantation. In our case, the laboratory results of a 27-year-old patient with a 19-week pregnancy who had abdominal pain and had an oral intake of 3gr IV and 2gr in the first 48 hours, followed by an oral intake of more than 3gr per day for about 3 days after she came to the emergency room. Ph:7.32, lactate: 5.6mmol/lt (>2) in blood gas, AST:7283 U/L (0-40), ALT: 3540 U/L (0-49), ALP:162 U/L, GGT:43 U/L, total bilirubin:2.9mg/dL, D-dimer:19800 ng/mL, INR:4.54(0, 8-1,2), APTT: 37.1 sec, creatinine 1.44 mg/dL(<1.1), hepatitis markers were negative. Considering his history, laboratory results and clinic, the patient's paracetamol toxicity was evaluated as stage 3-4, and he was referred to the center where liver transplantation was performed with a preliminary diagnosis of fulminant liver, but the patient died without transplantation in the center she went to.

INTRODUCTION

Paracetamol (acetaminophen, N-acetyl-P-aminophenol, APAP) was introduced in 1955, which is found in many preparations in our country, is the most commonly used over-the-counter analgesic and antipyretic in the world1.The drug, which is pregnancy category B, is widely used in pregnancy,and used in children. Paracetamol is used alone in preparations or combined with many drugs. As of 2015, it is included in more than 300 drug preparations in Turkey alone 2. It is the most common form of voluntary or accidental drug poisoning because it is cheap and easily accessible.

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CASE

A 27-year-old female patient was brought to the emergency department with the complaint of abdominal pain. Her medical history included diabetes mellitus, familial Mediterranean fever (FMF), and pituitary adenoma. The patient, who was 19 weeks pregnant, had a history of hospitalization 2 days ago due to the increase in FMF attacks. General condition is moderate, conscious, cooperative, blood pressure 100/60 mm/Hg, saturation 99%, heart rate 104/min, fever 36.6 C, fingertip blood glucose 72mg/dl. EKG was in sinus rhythm. There was widespread tenderness in all quadrants on abdominal examination, and other systemic examinations were normal. Ph:7.32, lactate: 5.6mmol/lt (>2), in blood gas, AST:7283 U/L (0-40), ALT: 3540 U/L (0-49), ALP:162 U/L, GGT:43 U/L, total bilirubin: 2.9mg/dL, D-dimer:19800 ng/mL, INR:4.54(0, 8-1,2), APTT:37.1s, creatinine 1.44 mg/dL(<1.1), hepatitis markers were negative. In his history, the patient who used excessive amounts of paracetamol on the 2nd day of hospitalization and after discharge (3gr IV and 2gr oral intake in the first 48 hours and more than 3gr oral intake in the following day). Hydration was provided to the patient. Upon his application to us within the first 18 hours of taking paracetamol, the patient was given NAC (150mg/kg 200 cc 5% dextrose in 15 minutes, 50mg/kg 5% 500 cc dextrose in 4 hours, 100mg/kg 5% 1000 cc dextrose in 16 hours) iv planned. Liver failure due to paracetamol toxicity was considered and urgent referral was made to the liver transplant center.

DISCUSSION

Paracetamol is used in two forms as oral and intravenous (IV). Therapeutic dose is 10-15mg/kg in children; in adults, 325-1000mg every 4-6 hours for oral use. The maximum daily dose is 75/kg in children and 4g in adults. In children over 50 kg or adults, the intravenous dose is 650 mg every 4 hours or 1 g every 6 hours. The maximum dose for intravenous administration is 4g per day. For the toxicity of paracetamol, either high-dose acute intake or repeated high-dose intake is required. In acute single dose intake, >200mg/kg or 10gr in adults and children over 6 years of age, paracetamol toxicity in children younger than 6 years of age ≥200mg/kg. In adults and children over 6 years of age, repeated doses of >200mg/kg or more than 10g are taken, and if >100mg/kg or 4gr/day is taken for longer than 48 hours, toxicity occurs. Toxicity occurs as a result of repeated doses ≥200 mg/kg in children under 6 years of age, ≥150mg/kg in a 24-hour period, and ≥100mg/kg every 24 hours in a 48-hour period[2]. Unfortunately, no method has yet been developed for the potential toxicity that may occur after intravenous acetaminophen overdose[5].

Paracetamol is rapidly absorbed in the stomach and intestine after oral intake and is metabolized in the liver[2]. 90% of the paracetamol taken in the treatment dose range is conjugated with sulfate and glucuronide in the liver and metabolized, and the metabolites are excreted in the urine[3]. Almost 2% is excreted unchanged in the urine. The remaining about 8% is converted to a toxic and highly reactive compound known as N-acetyl p-benzokinoimine (NAPQI) by hepatic cytochrome p450 enzymes (CYP2E1, CYP1A2, CYP3A4)[3-4]. Under favorable conditions, NAPQI is rapidly converted to non-toxic metabolite by glutathione (GSH). In cases of GSH deficiency such as paracetamol poisoning, chronic alcoholism and malnutrition, NAPQI is not metabolized and causes liver damage[6,7,8]. Although it is not known exactly how NAPQI damages the liver, it is thought to cause mitochondrial damage by reacting with sulfhydryl groups, causing protein deformation, and as a result, cell death [6,7].

It was first shown to cause hepatic necrosis in a patient in Scotland in 1966[9]. The most common cause of liver failure in America and Europe is the use of paracetamol[10]. Paracetamol-related hepatic failure accounts for 42% of all hepatic failures in the United States and It causes more than 300,000 hospitalizations[6,11]. In an epidemiological study, which included 7 countries, it was seen that 20% of liver transplantations were caused by paracetamol poisoning. This rate is 52% in Ireland, 28%in the UK, 8% in the Netherlands, 1% in Italy[12].

Single-time high-dose intakes have a better prognosis than repeated intakes, and it has been shown that those who present 24 hours after intake have the worst prognosis[1, 13].

It can be evaluated in 4 clinical stages in paracetamol-related toxicity. Stage 1 is the period in the first 24 hours after ingestion of a toxic dose. Patients may be asymptomatic at this stage or show nonspecific signs of toxicity such as nausea,

anorexia, vomiting and malaise. Stage 2; Stage 1 symptoms regress on the second-third days of toxic dose intake, but signs of hepatotoxicity such as increased serum transaminases (aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels and right upper quadrant pain occur. In stage 2, most of the patients recover without sequelae. Stage 3 covers 3 to 4 days, some of the patients may go to fulminant liver failure, as well as characteristic metabolic acidosis, coagulopathy, kidney failure, encephalopathy and gastrointestinal symptoms. In stage 4, after day 5, either clinical improvement or multiple organ failure and death occurs. If the patient survives complications of fulminant liver failure, it starts to improve within two weeks and after 1-3 months the liver heals without sequelae[5]. Severe liver toxicity is defined as AST or ALT above 1000IU/L.[2]

Diagnosis is mostly made by anamnesis and blood paracetamol levels. Although it is a definite diagnosis to measure paracetamol level in the blood, it cannot be applied in every hospital[5].

Gastric lavage can be performed in patients who apply within the first 2 hours of oral intake, and activated charcoal should be given in the first 4 hours. N-acetyl cysteine (NAC) is given as an antidote. The mainstay of treatment in patients with hepatic failure is liver transplantation[5].

Acetylcysteine, the essential ingredient in the prevention and treatment of paracetamol toxicity. Although the mechanism of action of acetylcysteine is not known exactly, it is thought to have two important benefits. In the first 8 hours of paracetamol poisoning, acetylcysteine prevents toxicity by preventing NAPQI from binding to hepatic macromolecules. If there is toxicity for more than 24 hours, acetylcysteine reduces hepatic necrosis by acting as an antioxidant, reducing neutrophil infiltration, increasing microcirculation or increasing tissue oxygenation[5].

In paracetomal toxicity, the treatment approach should be the same in pregnant patient, acetylcysteine has been shown to be safe and effective in pregnant patients as well[5].

Intravenous acetylcysteine is preferred because of its easy use. Standard acetylcysteine therapy; a 150mg/kg loading dose is administered over 1 hour, followed by a first maintenance dose of 50mg/kg for 4 hours and a second maintenance dose of 100mg/kg for 16 hours. It can be given with 5% dextrose or 0.45% NACI[5].

Unfortunately, fulminant hepatic failure develops in a minority of patients who take an overdose of paracetamol. Especially in patients who do not receive acetylcysteine treatment, the mortality rate is more pronounced. Deaths are usually 3-5 days after drug intake. It occurs in days and is based on complications such as cerebral edema, hemorrhage, shock, acute lung injury, sepsis, and multiple organ failure. Acetylcysteine therapy in the treatment of fulminant liver failure due to paracetamol and treatments for complications and should be referred to a center for liver transplantation without delay[5]. The most common criterion used since 1989 for patients who may benefit from transplantation with paracetamol-induced liver elevation is the King's Collage criterion[14]. Markers of king's collage criteria (Table 1); despite fluid and hemodynamic resuscitation.metabolic acidosis (arterial pH<7.30) or coagulopathy (prothrombin time>100sec), renal failure (serum creatinine >3.3mg/dl or 292micromol/L) and grade 3 or 4 hepatic encephalopathy[14]. Some studies have shown that hypoglycemia and lactic acidosis are important indicators of mortality in liver failure[14].

CONCLUSION

Since paracetamol is easily accessible and cheap, its toxicity is very common. Although it is used in children, adults and pregnant women considering how safe it is, it harms patients if it is not taken in appropriate doses. Ingestion of paracetamol in high single doses or in consecutive high doses also causes toxicity. Paracetamol toxicity can result in asymptomatic, non-specific findings, fulminant liver failure and even death. Diagnosis is made by anamnesis and blood paracetamol level, and in patients whose paracetamol level cannot be measured, but who have high-dose paracetamol intake in the anamnesis, treatment should be started quickly. Since acetylcysteine, which is our main treatment, is easily accessible and applied, treatment should be started early, thus, liver damage should be reduced in patients. It should be kept in mind that fulminant liver failure, the need for transplantation and even death will occur in patients who present late or whose treatment is delayed. In cases where liver function tests are high, it should be kept in mind to question the use of paracetomol in patients.

Our patient did not meet the King's Collage criteria because of pH: 7.32, creatinine: 1.44 mg/dl, APTT: 37.1 seconds and he was conscious. However, lactate: 5.6 mmol and high, and 72 mg/dl fingertip glucose were considered as the poor prognostic factor of the patient.

Abbreviations

ALT: Alanine aminotransferase
ALP:Alkalen fosfataz
AST: Aspartate aminotransferase
ECG: Electrocardiography
FMF:Familial mediterranean fever
GGT:Gamma glutamyl transferase
GSH:Glutathione
IV:İntravenous
NAC: N-acetyl cysteine
NAPQI: N-acetyl p-benzokinoimine
UK:United Kingdom

Conflict of interest statement

The authors declare that they have no conflicts of interests.

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