Review

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Management of Paracetamol (Acetaminophen) Intoxication

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Abstract

Acetaminophen intoxication is one of the most frequent causes of poisoning caused by medical treatment and deaths. Acetaminophen intoxication happens when it is taken in a single high dose or several times above the treatment dose. The approach to the patient with acetaminophen intoxication includes stabilization, decontamination and n-acetyl cysteine (the specific antidot of acetaminophen). In this article, it is aimed to review the approach to patients with paracetamol poisoning in the emergency department with current medical literature.

Keywords: Paracetamol; acetaminophen; intoxication; emergency

Özet

Asetaminofen zehirlenmesi tedaviye bağlı zehirlenmeler ve ölümlerin en sık görülen nedenlerinden biridir. Asetaminofen zehirlenmesi tek doz fazla miktarda alım ya da tedavi dozunun üzerinde tekrarlayan alımlarla gerçekleşmektedir. Asetaminofen zehirlenmesi olan hastaya yaklaşım stabilizasyon, dekontaminasyon ve spesifik antidot olan N-asetilsistein tedavilerini içerir. Bu makalede parasetamol zehirlenmeli hastalara acil serviste yaklaşımın güncel tıbbi literatür bilgileri eşliğinde derlenmesi amaçlandı.

Anahtar Kelimeler: Parasetamol; asetaminofen; zehirlenme; acil

Introduction

Paracetamol is the most widely used analgesic agent because of its reliability, efficacy and inexpensiveness. Paracetamol intoxication is reported frequently, because it is used commonly and accessed easily. Acetaminophen is found solitarily or combined with different medications that produced in tablet, capsule, gel or liquid form. Poisonings often result from either the wrong belief that the drug is very safe, or the poisoned patients not knowing that the drug they are taking contains acetaminophen.

In this article, it is aimed to review the approach to patients with paracetamol poisoning in the emergency department with current medical literature.

Epidemiology

According to the report of the American Association of Poison Control Centers, above 100.000 cases of paracetamol intoxication reported, 50.000 cases admitted to the emergency service and 10.000 patients are hospitalized every year[1]. The number of hepatotoxicity because of overdosing of paracetamol and death rates are rising lately with the increasing frequency of drug use[2]. Paracetamol intoxication causes hepatocellular necrosis and thus responsible for 500 deaths annualy in the United States of America.

Mechanism of Action and Pharmacokinetics

Hepatotoxicty occurs frequently with paracetamol intoxication, however renal failure, metabolic acidosis, coagulopathy, encephalopathy and recurrent gastrointestinal symptoms are also seen. Oral paracetamol is converted to a toxic metabolite, N-acetyl-p-benzoquinonimine (NAB), by cytochrome p450 enzyme system in the liver and detoxified by endogenous glutathione. Glutathione storage is decreased when paracetamol is taken in high doses and hepatotoxicity occurs because of the lack of detoxification of toxic metabolites. N-Acetylcysteine (NAC) is a glutathione precursor. NAC prevents bonding between toxic metabolites and hepatic macro molecules thus renews reduced glutathione storage. NAC also decreases hepatic necrosis by

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antioxidant mechanisms. It is reported that administration of NAC in the first 8 hours of intake greatly prevents toxicity in acute paracetamol intoxication[1-4]. It is recommended that paracetamol be taken 10-15 mg/kg up to 4-6 times per day in children and 650-1000 mg up to 4-6 times per day in adults. The recommended maximum dose is 4 grams in adults and 10-15 mg/kg in children. Paracetamol after the oral intake is well absorped from the gastrointestinal tract and in serum it reaches its peak concentration in 2 hours. The time to reach the peak plasma concentration may last longer in delayed gastric emptying. It may take 4 hours to reach the peak plasma concentration in time-release tablets. The absorption rate depends on the mode of administration. The absorption rate in suppository form does not exceed 40% however the absorption rate is between 60-98% in oral intake. The extent of protein binding is between 10-30%[5].

After oral intake, paracetamol is metabolized by conjugation with sulphate and glucuronide 90% in the liver. Glutathione levels decreased in high dose intake and hepatotoxicity occurs because the metabolites can not be detoxified. Acetaminophen metabolism may vary depending on age thus in elderly patients the likelihood of developing hepatotoxicity is high. . Children under 5 years of age are more resilient to hepatotoxicity than adults. Besides hepatic necrosis, renal tubular necrosis and hypoglycemic coma are the other fatal effects. Conversion to toxic reactive metabolites occur when paracetamol is taken in excessive doses. This substance that excreted in urine is responsible for renal tubular acidosis[6].

Clinical Features

After the acute intake of acetaminophen, patients may be asymptomatic or they might have mild non-specific symptoms like nausea, vomiting, fatigue, sweating and loss of appetite in the early stage. Liver damage becomes significant by the increase of aspartate aminotransferase (AST) after 8-36 hours. Right upper quadrant pain (or tenderness), nausea and jaundice may develop once the liver damage starts. AST levels continue to rise rapidly and reaches the peak level in 2 to 4 days. Alanine aminotransferase (ALT), prothrombin time (PT) and bilirubin levels begin to rise typically and AST reaches the point within hours after those. All the AST, ALT and PT levels may rise within 24 hours with severe toxicity[7].

With maximum liver damage, signs and symptoms consistent with fulminant hepatic failure that includes metabolic acidosis, coagulopathy and hepatic encephalopathy may develop in patients. Death may occur due to hemorrhage, adult respiratory distress syndrome, sepsis, multiple organ failure or cerebral edema. Risk of renal damage (Hepato-renal syndrome) increases with the level of liver damage is seen less than 2% of patients with no hepatotoxicity and 25% of patients with severe hepatotoxicity. The aminotransferases get back to normal in 5-7 days during the recovery period however complete histological healing in liver might take months. Once histological recovery is made, long term hepatic sequelae is not seen in patients[7].

Four Stages of Acetaminophen Intoxication

The clinical presentation acetaminophen intoxication in humans can be examined in 4 phases. Patients may be asymptomatic or they may show minimal toxicity symptoms like loss of appetite, nausea, vomiting and fatigue or non-specific symptoms in the first 24 hours (Stage 1) of exposure. The symptoms seen in stage 1 resolve on the second and third days but hepatotoxicity findings including right upper quadrant pain and tenderness with the increase of serum transaminases might occur. Patients who have mild to moderate hepatotoxicity recover fully with no sequelae even without any treatment. However some patients progress to fulminant hepatic failure on the third and fourth day (Stage 3)[8,9]. Characteristic stage 3 features include metabolic acidosis, coagulopathy, renal failure, encephalopathy and recurrent gastrointestinal symptoms. Patients who survive the complications of fulminant hepatic failure begin to improve in 2 weeks (Stage 4) and by the end of 1-3 weeks, hepatic dysfunction completely disappears. Acetaminophen also causes acute, extrahepatic toxic effects. It's because the presence of CYP450 or similar enzymes (e.g. prostaglandin H synthase) in other organs. Isolated renal damage, cardiac toxicity and pancreatitis can be rarely observed in isolated cases[10,11].

Diagnosis

The diagnosis of paracetamol intoxication starts with clinical suspicion in the emergency room. Therefore serum paracetamol level should be measured in patients suspected of having intoxication to determine the correct and early diagnosis and treatment. The amount of medication, the purpose and the form of use, dosage time and the other medications taken together should be questioned in all patients with suspected paracetamol intoxication. Serum levels should be viewed again 4 hours later after taking the drug acutely. BUN and creatinine, serum total bilirubin level, INR, AST, ALT, amylase, urinalysis, prothrombin time and blood gas test may be ordered. Blood and urine tox screen should be performed in patients with a history of suicide and deliberate attempt[6].

Goals of patient evaluation after acetaminophen intake: determining the risk of patients, diagnostic testing and treating with the antidote, NAC when appropriate.

Acetaminophen exposure can be classified as an acute or a chronic exposure and all types of exposure require various tests and risk assessment. Acute intake is generally thought to be a single intake or self-administered drug intake within

an 8-hour period. Taking supratherapeutic doses accidentally and taking self-administered drugs longer than 8 hours are considered to be chronic intake[7].

Risk Assessment in Acute Acetaminophen Intake

First, patient's risk of acute acetaminophen exposure should be determined. Laboratory risk classification is required in patients with acute intentional intake of acetaminophen regardless of the amount told by the patient. More than 10 grams or 150 mg/kg or 25 tablets of 500 mg should be taken acutely for hepatotoxicity to occur in adult patients. Serum acetaminophen levels should be assessed in patients admitted with acetaminophen intake or in intentional overdose patients who has access to acetaminophen even if the patient denies taking it. Acetaminophen has been found in the blood of 8% of the patients who refuse taking medication. Unidentified acetaminophen toxicity prevalence (18%) is high in patients who admitted with liver failure with no apparent cause.

It should be determined whether there is a need for antidote treatment by measuring the serum acetaminophen level in the 4th hour after intake or Rumack-Matthew nomogram. If the serum acetaminophen level is at or above the treatment line, this indicates the treatment indication of NAC. If the serum acetaminophen level is below the treatment line and the strongest possible scenario for the time of intake is taken, the patient does not need an antidote[7].

Rumack-Matthew Nomogram

The measured acetaminophen level is evaluated by marking on the Rumack-Matthew nomogram (Figure 1). This nomogram was derived from retrospective analyzes of patients who overdose acetaminophen and their outcome. The original nomogram line separating possible toxicity from non-toxic one is based on being 200 micrograms/ml of acetaminophen in the 4th hour, however the acetaminophen level in the 4th hour was changed to 150 micrograms/mL in order to increase the safety of treatment decisions afterwards.

The nomogram can be applied to the acetaminophen level obtained after a single intake only, or to acetaminophen levels between 4 hours and 24 hours after ingestion of the drug. This nomogram is not used to predict patient outcome in acetaminophen levels measured outside of this window or in chronic conditions or recurrent exposures. In the absence of hepatotoxicity, more than one measurement of acetaminophen is rarely required in acute poisonings[7].

Considering the data obtained before the widespread use of antidote therapy, the risk of hepatotoxicity in patients with serum acetaminophen levels above the original threshold value was found to be 60%, renal failure risk 1% and mortality risk 5%. In addition, patients with extremely high serum acetaminophen levels have a 90% risk of developing hepatotoxicity. It has been confirmed that acetaminophen level below 150 microgram/mL in the 4th hour after drug intake predicts good outcome in patients not receiving antidote therapy. According to the nomogram, patients with acetaminophen levels below this value have a 1% risk of hepatotoxicity and these patients recover without complications[12,13].

Treatment

The basis of the treatment is the correction of vital signs, removal of the poisoning agent from the body and administration of a specific antidote, N-acetylcysteine (NAC). Antidotes used in paracetamol intoxication are NAC, cystamine, dimercaprol and methionine[6].

Decontamination

In paracetamol poisonings, absorption should be prevented primarily, and supportive treatment should be started as soon as possible by following the levels showing the clinical course. Gastric lavage and activated charcoal can be applied to prevent absorption within the first 4 hours after ingestion of high-dose paracetamol. Activated charcoal binds to paracetamol in the intestinal lumen and prevents its absorption. Oral administration of 1 g/kg (maximum dose 50 grams) is recommended[6].

Increased Elimination

Dialysis is not routinely applied in cases of excessive intake of acetaminophen, as there is a highly effective antidote with good clinical results when given within 8 hours of ingestion. However, hemodialysis may be beneficial if the load of absorbed acetaminophen is high enough to cause hepatotoxicity despite normal doses of NAC. Consultation with a poison control center or a medical toxicologist is recommended for the initiation of hemodialysis in patients with high acetaminophen levels, hepatorenal syndrome, metabolic acidosis, encephalopathy and high lactate levels within 4 hours after acute massive ingestion. There is no conclusive evidence for the effectiveness of hemodialysis, but removing excess acetaminophen can prevent toxicity by allowing NAC to deal effectively with the reduced toxin load[7].

Antidote Treatment

When indicated, NAC should be administered as soon as possible. Delay of NAC for more than 8 hours after ingestion increases the risk of hepatotoxicity. When administered early (<8 hours), NAC's main role is to prevent hepatotoxicity by detoxifying NAPQI and reducing NAPQI production. In patients treated with NAC within 8 hours, the risk of liver damage is less than 4% and the death rate approaches zero. Although they can not tolerate the oral formulation due to vomiting and hepatic encephalopathy, both po and iv formulations of NAC are equally effective in patients admitted 8-24 hours after ingestion.

Once hepatic failure has occurred, NAC is only given intravenously. In acetaminophen-related liver failure, iv

NAC reduces the risk of hypotension, cerebral edema and death. Oral NAC should only be used if iv NAC is not available. The loading dose of oral NAC is 140 mg/kg. The maintenance dose consists of 70 mg/kg every 4 hours for a total of 72 hours of treatment.

The standard regimen of intravenous acetylcysteine is a 21-hour treatment protocol consisting of a 150 mg/kg loading dose for 1 hour, followed by an initial maintenance treatment at 50 mg/kg for 4 hours, and a second maintenance treatment at 100 mg/kg for 16 hours. IV Acetylcysteine is available as a 20% commercial solution and must be diluted to a 2% solution for administration through a peripheral vein. For this, 5% dextrose or 0.45% NaCl can be used. Due to the volume and hypotonicity of the required fluid, children and adults <40 kg should be monitored closely during the treatment to prevent fluid overload and hyponatremia[14,15].

Treatment guidelines according to the time of admission to the emergency department

Admissions within the first 4 hours after intake; Treatment begins with gastrointestinal contamination and acetaminophen level is monitored in the blood 4 hours after taking the drug. The result is placed on the nomogram. If acetaminophen level cannot be determined within 8 hours after intake, empirical acetylcysteine treatment is started without waiting for the result[16,17].

Admissions <4 hours and >24 hours after intake; The serum acetaminophen level should be determined as soon as possible. Especially if additional drug intake is suspected, GI decontamination can be applied, but its effectiveness may be limited due to the delay in admission. The need for acetylcysteine treatment should be determined by placing the acetaminophen level on the nomogram. Otherwise, empirical acetylcysteine treatment is started[11].

Admissions >24 hours or unknown time of intake; Serum acetaminophen level, transaminase, bilirubin and prothrombin time tests should be determined for patients with clinical findings suggestive of acetaminophen poisoning and whose time of intake is unknown. Acetylcysteine treatment should be started as soon as possible while the results are awaited. A detectable acetaminophen level (>10 micrograms/mL or >66 micromol/L) suggests that the patient is at risk of developing hepatotoxicity. Increased serum transaminases are markers of ongoing hepatic toxicity. Continuation of acetylcysteine therapy is required. If serum acetaminophen level is <10 microgram/mL or <66 micromol/L, and serum transaminases are not high, acetylcysteine treatment can be discontinued[16,17].

Other treatments

Cimetidine: Many studies have shown that some drugs show additional benefit in preventing acetaminophen-induced liver damage. The most important of these is cimetidine, which plays an inhibitory role in the metabolism of acetaminophen[18-20]. This treatment was found to be beneficial in animal studies, but it was observed that it did not provide additional benefits in patients treated with N-acetylcysteine[18,21]. Earlier studies investigated the benefits of methionine, dimercaprol, and cysteamine, but these studies were terminated due to side effects[18,22].

Dialysis: Although acetaminophen can be removed by dialysis, it is not included in the standard treatment protocol due to the safety and efficacy of N-acetylcysteine. Extracorporeal removal can be used to lower serum acetaminophen in patients unsuitable for N-acetylcysteine, but there are no systematic studies of the efficacy of this treatment[18,23]. Hemodialysis should not be considered as an alternative to N-acetylcysteine therapy.

Discharge

Asymptomatic patients who meet the treatment criteria should be treated with NAC. This treatment can be applied in the medical inpatient unit or the emergency room observation unit. The motivation behind any intake should be evaluated and psychiatric consultation should be ordered when necessary. Patients showing signs of severe hepatotoxicity and those at risk of fulminant hepatic failure should be hospitalized in a monitorized bed or intensive care unit. Frequent neurological checks, monitoring of vital signs, and repeated laboratory studies are required in these patients. If patients present with significant hepatotoxicity, transfer to a 3rd level care center, which specialized in the management of patients with liver failure and liver transplantation, is recommended[7].

Conclusion

1. As in all poisonings, the basic approach in paracetamol intoxication is to check the airway, respiration and circulation first.
2. Patients who admitted in the first 24 hours after an acute ingestion of paracetamol poisoning generally have no complaints or symptoms. Patients admitting later show signs of hepatic and renal damage. Signs and symptoms that may be caused by liver damage or failure such as nausea, vomiting, weakness, abdominal pain, renal damage, coagulopathy (eg, gastrointestinal bleeding), hepaticencephalopathy, cerebral edema or hypotension may be found in patients admitting late.
3. There are no early signs of toxicity and severity of intoxication in acute ingestion can be measured by showing the serum paracetamol level on the Rumack-Matthew nomogram. It is potentially serious if the dose taken is greater than 150 mg/kg.

Table 1: Acetylcysteine dosing regimens[17].

	PO	Adults iv	Children iv (21-40 kg)	Children iv (5-20 kg)
Preparation	Available in 10% and 20% solutions. Dilute to 5% solution for PO application	Available in 20% solutions. Dilution is required.	Available in 20% solutions. Dilution is required.	Available in 20% solutions. Dilution is required.
Loading dose	140 miligram/kg	150 mg/kg infused in 200 milliliters of 5% dextrose in 60 minutes	150 mg/kg infused in 100 milliliters of 5% dextrose in 60 minutes	150 mg/kg infusion in 60 minutes in 3 ml/kg 5% dextrose
Maintenance dose	17 doses of 70 milligrams/kg every 4 hours	50 mg/kg in 500 ml 5% dextrose followed by infusion in 4 hours 100 mg/kg infusion in 16 hours in 1000 ml 5% dextrose	50 mg/kg infusion in 4 hours in 250 ml 5% dextrose 100 mg/kg infusion in 16 hours in 500 ml 5% dextrose	Following infusion in 4 hours in 50 mg/kg, 7 ml/kg 5% dextrose 100 mg/kg, 14 ml/kg infusion in 16 hours in 5% dextrose
Treatment time	72 hours	21 hours	21 hours	21 hours
Recommendations	Dilute with powdered drink mix, juice or soda	Monitor for drug-related side effects or anaphylactoid reactions	Monitor for drug-related side effects or anaphylactoid reactions	Monitor for drug-related side effects or anaphylactoid reactions

4. After ingestion of a potentially toxic dose of paracetamol (single dose >7.5 grams), patients benefit from gastrointestinal decontamination and oral activated charcoal is recommended within the first 4 hours after ingestion.
5. Treatment includes stabilization, decontamination and application of the specific antidote, acetylcysteine.
6. There are 2 treatment protocols for acetylcysteine administration, 21-hour intravenous and 72-hour oral.
7. The 21-hour IV protocol includes a 150 mg/kg IV 15-60 minute loading dose followed by a 4-hour IV infusion of 12.5 mg/kg/h and a 16-hour 6.25 mg/kg/h IV infusion.
8. The 72-hour oral protocol includes a loading dose of 140 mg/kg po, followed by a total of 17 doses of 70 mg/kg acetylcysteine every 4 hours.

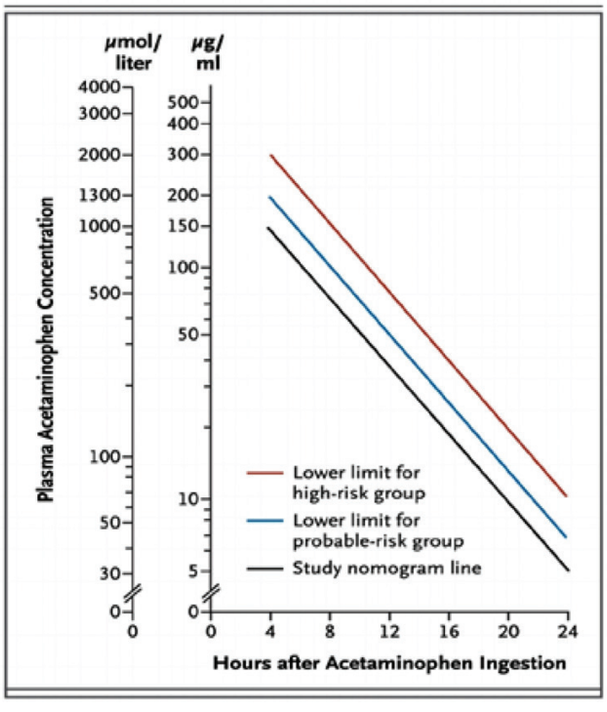

Figure 1: Rumack-Matthew nomogram

9. During the treatment, INR, plasma creatinine and ALT levels should be monitored. If there is any test abnormality at the end of the treatment or if the patient is symptomatic, further monitoring is required and additional treatment methods are investigated. Acetylcysteine treatment is continued.

References

1. Oliver LH, Lewis SN. Acetaminophen. In Judith E. Tintinalli, Editor. Emergency Medicine. 9th ed. New York: McGraw-Hill; 2010. p.1246-52.
2. Hendrickson RG, Bizovi KE. Acetaminophene. In Flomenbaum NE, Goldfrank LR, Hoffman RS, Howland MA, Lewin NA, et al Editors. Goldfrank's Toxicologic Emergencies. 8th ed. New York: McGraw-Hill; 2006. p.333-43. 3.
3. Rumack BH, Matthew H. Acetaminophen poisoning and toxicity. Pediatrics 1975; 55: 871-6.
4. Prior MJ, Cooper K, Cummins P, Bowen D: Acetaminophen availability increases in Canada with no increase in the incidence of reports of inpatient hospitalizations with acetaminophen overdose and acute liver toxicity. Am J Ther 2004, 11:443-45.
5. Satar S. Clinical toxicology in the emergency service. 2009.
6. Gülen B, Taşlıdere B. Parasetamol (Asetaminofen) Zehirlenmesi. In: Kekeç Z, editor. Acil Tıp Pratiğinde Klinik Toksikoloji, 1. Baskı. Ankara: EMA Tıp kitapevi yayıncılık; 2020.p.248-249.
7. Hendrickson RG, McKeown NJ. In: Walls RM, Hockberger RS, Gausche-Hill M, editors. Rosen Acil Tıp Kavramlar ve Klinik Uygulama, 9.Baskı. İstanbul: Yeditepe Üniversitesi Yayınevi; 2019.p.1852-1857.
8. Fontana RJ. Acute liver failure including acetaminophen overdose. Med Clin North Am. 2008;92(4):761-94.

9. Chun LJ, Tong MJ, Busuttil RW, Hiatt JR. Acetaminophen hepatotoxicity and acute liver failure. J Clin Gastroenterol. 2009;43(4):342-9.

10. Ozkaya O, Genc G, Bek K, Sullu Y. A case of acetaminophen (paracetamol) causing renal failure without liver damage in a child and review of literature. Ren Fail. 2010;32(9):1125-7.

11. Igarashi H, Ito T, Yoshinaga M, Oono T, Sakai H, Takayanagi R. Acetaminophen-induced acute pancreatitis. A case report. JOP. 2009;10(5):550-3.

12. Wolf SJ, Heard K, Sloan EP, Jagoda AS. Clinical policy: critical issues in the management of patients presenting to the emergency department with acetaminophen overdose. Ann Emerg Med. 2007;50(3):292-313.

13. Daly FF, Fountain JS, Murray L, Graudins A, Buckley NA. Guidelines for the management of paracetamol poisoning in Australia and New Zealand—explanation and elaboration. A consensus statement from clinical toxicologists consulting to the Australasian poisons information centres. Med J Aust. 2008;188(5):296-301.

14. Bateman DN, Dear JW, Thomas SHL. New regimens for intravenous acetylcysteine: where are we now? Clin Toxicol (Phila). 2016;54(2):75-8.

15. Chiew AL, Isbister GK, Duffull SB, Buckley NA. Evidence for the changing regimens of acetylcysteine. Br J Clin Pharmacol. 2016;81(3):471-81.

16. Klein-Schwartz W, Doyon S. Intravenous acetylcysteine for the treatment of acetaminophen overdose. Expert Opin Pharmacother. 2011;12(1):119-30.

17. Wightman RS, Nelson LS. Asetaminofen. In Judith E. Tintinalli, Editor. Emergency Medicine. 9th ed. New York: McGraw-Hill; 2010. p.1252-1258.

18. Kennon Heard, Richard Dart. Acetaminofen (paracetamol) poisoning in adults: Treatment. Available from: https://www.uptodate.com/contents/acetaminophen-paracetamol-poisoning-in-adults-treatment (Acces date: 04.04.2022)

19. Speeg KV Jr, Mitchell MC, Maldonado AL. Additiveprotection of cimetidineand N- acetylcysteine treatment against acetaninophen-induced hepaticnecrosis in therat. J Pharmacol ExpTher. 1985;234:550.

20. Al-Mustafa ZH, Al- Ali AK, Qaw FS, Abdul- Cader Z. Cimetidine enhances the hepatoprotectiveaction of N-asetilcisteine in micetreated with toxicdoses of paracetamol. Toxicology.1997;121:223.

21. Küçükardalı Y, Cihan U, Acar HV, et al. Comparison of the therapeutic efficacy of 4- methylpyrazole and N-acetylcisteine on acetaminophen hepatotoxicity in rats. Curr Med Res Opin. 2002;18:78.

22. Hamlyn AN, Lesna M, Record CO, et al. Methionine and cysteamine in paracetamol overdose, prospective controlled trial of early therapy. J Int Med Res. 1981;9:226.

23. Marbury TC, Wang LH, Lee CS. Hemodialysis of acetaminophen in uremicpatients. Int J Artif Organs. 1980;3:263.