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The Comparison of Reported Ingested Paracetamol Dose with Serum Blood Concentrations and Their Relationship with N-Acetylcysteine Administration: A Retrospective Study of 117 Patients

Alındığı İddia Edilen Parasetamol Dozunun Kan Parasetamol Düzeyleri ile Karşılaştırılması ve N-Asetilsistein Kullanımı ile İlişkisi: 117 Hasta ile Geriye Dönük Bir Çalışma

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Abstract

Introduction: We aimed to compare the patient reported ingested and blood paracetamol concentrations (BPC) and to investigate the indications for N-acetylcysteine (NAC) administration in referred patients.

Methods: This is a retrospective study of acute paracetamol intoxications (API) at the tertiary paediatric emergency department (ED) between June 2015-June 2019. We evaluated the demographics, cause of intoxications, reported doses (mg/kg), BPCs (8/4/12/16 and/or 24th hours). Indications of antidote usage and referral to ED were accepted as BPC >150 mg/kg.

Results: Overall, we reviewed 117 cases of acute API. The mean age was 8.97 (±6.0) years, and 68.3% were female. The reported ingested of paracetamol (RIP) median dose was 2725 mg (mean 138±51.9 mg/kg). Adolescents had a significantly higher RIP than that of younger subjects (p<0.001). BPC was performed in 88.9% of the patients at the 4th, 8th, 12th, 16th and 24th hour in 11.1%, 9.4%, 3.5% and 3.5% of cases, respectively. Although, only 34/66 of the referred cases had a RIP dose >150 mg/kg, physicians at the first healthcare facility tended to administer activated charcoal (90.9%), gastric lavage (68%) and intravenous NAC (48%). The referring healthcare facility physicians-initiated NAC particularly for patients who reported ingesting >150 mg/kg (p=0.001).

Conclusion: RIP doses should not be used to determine the need for NAC. The antidote should be used in centres where BPCs are not available or in a group of patients who cannot be transferred to a referral centre within the first eight hours.

Keywords: Paracetamol, intoxication, N-acetylcysteine, acetaminophen, children

Öz

Giriş: Akut parasetamol zehirlenmesi (APİ) ile başvuran çocuklarda aldığı bildirilen parasetamol dozu (BPD) ile kan parasetamol düzeyini karşılaştırmak ve sevk edilen hastalarda N-asetilsistein (NAC) uygulama endikasyonlarını araştırmaktır.

Yöntemler: Çalışmamız üçüncü basamak bir hastanenin çocuk acil servisinde (AS) Haziran 2015-Haziran 2019 tarihleri arasında APİ olan çocuklarda geriye dönük olarak yapılmıştır. Demografik özellikler, zehirlenmelerin nedenleri, BPD (mg/kg) ve kan parasetamol düzeyleri (8-4-12-16. ve/veya 24. saatte) değerlendirildi. Antidot ve AS'ye sevk endikasyonu için BPD >150 mg/kg olarak kabul edildi.

Bulgular: Toplamda 117 akut APİ olgusu incelendi. Hastaların yaş ortalaması 8,97 (±6,0) yıl ve %68,3'ü kızdı. Ortanca BPD dozu 2725 mg (ortalama 138±51,9 mg/kg) idi. Ergenlerde BPD miktarlara daha küçük çocuklara göre anlamlı derecede daha yüksekti (p<0.001). Hastaların %88,9'una 4. saat KPD görülürken; 8., 12., 16. ve 24. saatte sırasıyla hastaların %11,1, %9,4, %3,5 ve %3,5'inde KPD bakılmıştı. Sevk edilenlerin sadece 34/66'sında BPD >150 mg/kg olmasına rağmen, ilk merkezdeki hekimler aktif kömür (%90,9), gastrik yıkama işlemi (%68) ve damar içi NAC (%48) uygulama eğilimindeydiler. Hekimlerin üçüncü basamağa sevk etmeden önce BPD >150 mg/kg olması durumunda NAC kullandığı görüldü (p=0,001).

Sonuç: NAC endikasyonunu belirlemek için BPD kullanılmamalıdır. Antidot kullanımı, kan parasetamol düzeyi bakılamayan merkezlerde veya ilk 8 saat içinde üst merkeze sevk edilemeyecek hastalarda kullanılmalıdır.

Anahtar Kelimeler: Parasetamol, zehirlenme, N-asetilsistein, asetaminofen, çocuklar

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Introduction

The most commonly used antipyretic analgesic drugs in children are those containing paracetamol.[1] Although it is known as a drug that can be used safely in all age groups, side effects can be seen rarely, even when it is used in the recommended dosage range.[1,2] Conversely, paracetamol toxicity is a common cause of acute liver failure in children and adolescents.[2,3] In the United States, paediatric paracetamol exposures account for approximately 30,000 reports to the National Poison Data System annually.[4] Even though the benefit of gastric decontamination is uncertain, administration of activated charcoal (if the patient presents within one hour of ingestion of more than 150 mg/kg paracetamol) should be considered.[5]

There is no recommendation to administer NAC without an obtained blood paracetamol concentration (BPC) within eight hours. If there is going to be delay beyond eight hours after the ingestion in obtaining the BPC, then treatment should be initiated (if >150 mg/kg has been ingested).[6,7] It is strongly recommended to obtain blood samples from all patients for immediate measurement of the BPC (based on Rumack-Matthew nomogram generally recommended at the fourth hour after ingestion).[5-10] The mortality rate is reported to be 5% in patients who did not receive any treatment despite a high BPC at the fourth hour after ingestion; however, it has been shown that it can be reduced to as low as 0.4% when NAC is administered.[11] Although NAC administration has many advantages in situations of paracetamol toxicity, adverse reactions to NAC are common such as refractory nausea, vomiting and anaphylactic reaction.[12] Thus, the antidote treatment should be preferred only if indicated.

This study aimed to primarily compare the estimated ingested paracetamol dose (mg/kg) with BPC. We also investigated the indications for cases who already received NAC at the referring facility.

Materials and Methods

Study Design

This study was performed in a tertiary paediatric emergency department (ED) between June 2016 and June 2020. The study adhered to the ethical principles of medical research involving human subjects of the World Medical Association Declaration of Helsinki. The medical faculty scientific research Ethics Committee of Ege University provided ethical approval prior to the study (no: 18-12/5).

Patient Selection and Data Collection

We included all patients younger than 18 years old presented directly or who were brought by ambulance to the ED due to paracetamol intoxication. Intoxication cases without paracetamol intake were excluded from the study. We evaluated the following parameters from the medical records: Demographic characteristics of the patients; the characteristics of the institution which referred the patients to the ED; the form of medication (suspension/tablet) and the amount of the alleged ingested dose; the cause of intoxication (unintentional/suicide); physical examination and laboratory findings upon arrival [aspartate aminotransferase (AST), alanine aminotransferase (ALT), prothrombin time (PT), international normalized ratio (INR)]; the duration between the drug ingestion and presentation to the ED; gastrointestinal decontamination or the status of antidote administration; BPC (4-8-12-16-24th hours); follow-up duration in the ED and the outcomes.

Definitions

The minimal toxic dose for acute ingestion is 150 mg/kg for children or 7.5 to 10 g for adolescents.[4,13] The results of samples taken from the patients to evaluate the concentration of the drug in the blood were assessed with Rumack-Matthew nomogram.[14] According to the United States Food and Drug Administration classification, among the liver function tests as an AST >3× the normal value (>35 IU/L) or a total bilirubin >2× the normal was accepted as hepatotoxicity.[15] Acute liver failure was defined as elevated transaminase (AST >35 IU/L, ALT >45 IU/L) accompanied by coagulation disorder (INR >1.5 or prothrombin activity <50%, prothrombin time >14.7 s) and/or the presence of encephalopathy.[16]

Statistical Analysis

Data were analysed using SPSS 25.0 (IBM, Armonk, NY: IBM Corp.) program. In the comparison of continuous variables, we expressed values as mean ± standard deviation (SD) for parametric tests, median (minimum, maximum, interquartile range) for non-parametric tests and number and percentage for categorical variables. When parametric test assumptions were provided, One-Way Variance Analysis was used to compare independent group differences. Kruskal-Wallis Variance Analysis (post-hoc: Bonferroni correction Mann-Whitney U test) was used as a non-parametric test. Chi-square analysis was used to examine the differences between categorical variables. A value of $p<0.05$ was accepted as statistically significant in all analyzes.

Results

During the study period, 117 patients presented to the ED with paracetamol intoxication. Most patients were female (68.3%, n=80), and female/male ratio was 2.2/1. Fifty-seven percent of the cases (67/117) applied to the ED in out of working hours and 56.4% of the patients (66/117) were

referred from another health institution and brought by an ambulance. The mean age of the patients was 8.97 (±6.0) years; 52.1% (61/117) were younger than 6 years, 38.4% (45/117) were older than 10 years. The mean time between drug ingestion and ED presentation was 2.6 h (range 0.3-20 h) (Table 1).

Unintentionally ingestion occurred in all patients younger than 10; suicide was more common (73.3%) in adolescents (p<0.001). Younger children (<6 years) were more likely (73.6%) to ingested suspension forms of the medication; however, older children ingested the tablet form [93.3% (42/45)] (Table 2). Adolescents were likely intoxicated by tablet form (p<0.001). Most children (72.7%) (85/117) had multiple drug ingestion. One five-year-old patient had iatrogenic intravenous paracetamol intoxication.

"Abnormal" vital signs were detected in a minority of patients (n=23, 19.6%). Most commonly tachycardia (9.4%) and hypertension (7.7%) were noticed upon arrival (Table 3).

The median reported ingested paracetamol dose was 2725 mg (min: 375-max: 19500 mg) and 138±51.9 mg/kg. Sixty patients (51.3%) said that they ingested >150 mg/kg, one-fifth of patients alleged that they ingested >7.5 gr (Table 4). The adolescent group reported that they ingested significantly higher doses compared with the younger age group (p<0.001) (Table 2 and Table 4).

BPC was performed in 88.9% of the patients at 4th, 8th, 12th, 16th and 24th hour in 11.1%, 9.4%, 3.5% and 3.5% of cases, respectively (Table 4). Table 4 shows the median BPCs based on the hours after drug ingestion. While BPCs were within normal limits at the 4th hour, toxic levels were detected in 1 patient at the 8th hour, in 3 patients at the 12th hour, in 3 patients at the 16th hour and in 1 patient at the 24th hour (Table 4). No significant relationship was found between the reported ingested paracetamol dose and BPC at the 4th hour (p>0.05). There was not any difference on BPCs at the 4th hour between the two age groups (<6 years vs. adolescents) (18.8 and 27.8, respectively) (p>0.05).

At the 4th hour after drug ingestion, the median AST, ALT and PT were 29.5 IU/L (range 15-56), 13.5 IU/L (range 7-64) and 15.2 s (range 9.9-123), respectively. The mean INR was 1.06 (SD ±0.09). Elevated AST was detected in 21.4%, ALT in 3.4%, AST and ALT combined in 3.4%, prolonged PT in 3.4% and raised INR in 1.7% of the patients. Although transaminase levels were normal in half of the patients with toxic BPC at the 4th hour of admission; AST and ALT values increased in the other half which were defines as hepatotoxicity. There was no significant relationship between elevated transaminase and the reported ingested dose (p>0.05).

Even though only 34/66 of referred cases reported ingesting doses >150 mg/kg, physicians at the first healthcare facility tended to administer activated charcoal (90.9%, n=60/66), gastric lavage (68%, 45/66) and intravenous NAC (48%, 32/66). Activated charcoal was more likely (42/60) administered to patients who allegedly ingested doses >150 mg/kg, whereas 76.1% (34/45) of the patients underwent gastric lavage (Table 5). The first healthcare facility physicians initiated NAC particularly for patients who allegedly ingested >150 mg/kg (26/32, 81.3%) (p=0.001) (Table 5).

Only one third of cases who presented directly to the ED were given activated charcoal and one-fifth underwent gastric lavage. When the reported toxic dose (>150 mg/kg) was seen, then NAC was administered to 56.3% and 43.7% underwent gastric lavage (Table 5). In this group NAC treatment ratio was

Table 1. Demographics and admission features to the ED of the patients

Male/female ratio	2.2/1
Age (years) [mean (± SD)]	8.97 (±6.0)
Age groups (years) (n, %) <6 ≥6 >10 (adolescent)	 61 (52.1) 56 (47.9) 45 (38.4)
Admission time (n, %) Working time Out of hours	 50 (42.8) 67 (57.2)
Admission type (n, %) by parents/friends by ambulance	 51 (43.6) 66 (56.4)
The mean duration time between drug ingestion and ED presentation (h) [median, (min-max)]	2.6 (0.3-20)
Follow-up time in the ED (h) [median, (min-max)]	5.5 (2-21)

ED: Emergency department, h: hours, SD: Standard deviation

Table 2. Causes of intoxication and paracetamol forms by age groups

	Age (years)		**Alleged ingested dose** (mg) [median, (min-max)]
	<6	**≥6**	
Causes (n, %) Unintentional Suicide	 *61 (100) 0	 23 (41.1) *33 (58.9)	 2180 (375-3600) *6900 (1500-12200)
Paracetamol forms (n, %) Liquid Tablet	 *51 (96.2) 2 (3.8)	 5 (8.9) *51 (91.1)	 2200 (375-3600) *6400 (1500-12200)

*p<0.001

4% (2/51). Although the anaphylaxis was not observed in any of the patients after NAC treatment was started; only pruritus and rash were seen in 6 patients.

Table 3. Complaints and clinical findings on the admission to the ED

	n	%
Complaints		
No	**96**	**82.1**
Nausea-vomiting	14	11.9
Right upper quadrant pain	5	4.3
Altered mental status	2	1.7
Clinical findings		
Normal	**94**	**80.4**
Abnormal	23	19.6
Tachycardia	11	9.4
Hypertension	9	7.7
Icter	1	0.8
Encephalopathy	2	1.7

ED: Emergency department

The rate of performed gastric lavage in patients who presented to the ED was significantly lower when compared to referred patients (p<0.005). A similar proportion was identified in NAC administration (4% vs. 48%) (Table 5). NAC treatment was discontinued in most referred patients (25/32) who had received NAC in the referring healthcare facility.

Median length of ED stay of the patients was 5.5 h (range 2-21). Whereas, most patients (96.6%) were discharged from the ED and 3 (2.6%) were discharged from the ward. Severe toxic hepatitis developed in one patient who admitted to the intensive care unit, received NAC treatment and underwent liver transplantation.

Discussion

Paracetamol is one of the most widely used analgesic and antipyretics worldwide. It remains a major cause of poisoning

Table 4. The comparison of age, paracetamol drug forms and the rate of toxic levels with RIP doses and BPCs

	Age (years)		**Paracetamol drug forms**		**Toxic level** (n, %)	
	<6	**≥10**	**Liquid**	**Tablet**	**+**	**-**
RIP doses (mg) [median, (min-max)]	2160 (375-7500)	*7500 (1500-19500)	2200 (375-3600)	*6400 (1500-12200)	24 (20.5)	93 (79.5)
The amount of RIP doses (mg/kg) [median, (min-max)]	150 (30-500)	165.9 (40-280)	150 (30-500)	165 (40-280)	60 (51.3)	57 (48.7)
BPC (mcg/mL) (median)						
4. hour	18.8 (5-127)	27.8 (5-119)	21.0 (1-82)	18.3 (5-127)	-	104 (88.9)
8. hour	5.0 (3.8-18)	49.6 (10-76)	5.0 (3.8-18)	49.6 (10-76)	1 (0.9)	12 (10.2)
12. hour	5.0 (5.0-5.0)	28.7 (14-57)	5.0 (5.0-5.0)	28.7 (14-57)	3 (2.6)	8 (6.8)
16. hour	-	35.3 (23-68)	35.3 (23-68)	-	3 (2.6)	1 (0.9)
24. hour	30 (30-30)	-	-	-	1 (0.9)	3 (2.6)

BPC: Blood paracetamol dose, RIP: Reported ingested dose, *p<0.001

Table 5. The relationship between the treatments-interventions and RIP doses in children who admitted or referred to the ED

Treatments-interventions	**RIP doses**		***p**
	<150 mg/kg	**≥150 mg/kg**	
Referred by another hospital/health care			
Gastric lavage (n, %)			
+	11 (24.4)	34 (75.6)	>0.05
-	8 (38.1)	13 (61.9)	
AC (n, %)			
+	18 (30)	42 (70)	>0.05
-	2 (33.3)	4 (66.7)	
NAC (n, %)			
+	6 (18.8)	*26 (71.2)	**<0.05**
-	18 (52.9)	16 (47.1)	
Admitted to the ED by parents/friends			
Gastric lavage (n, %)			
+	4 (36.4)	7 (63.6)	**<0.05**
-	*31 (77.5)	9 (22.5)	
AC (n, %)			
+	8 (47.1)	9 (52.9)	>0.05
-	27 (79.4)	7 (20.6)	
NAC (n, %)			
+	1 (50)	1 (50)	>0.05
-	34 (69.4)	15 (30.6)	

AC: Activated charcoal, ED: Emergency department, NAC: N-acetylcysteine, RIP: Reported ingested dose, ***p<0.05**

in children and is a major cause of acute liver failure. Although, poisonings are not the commonest reason for admission to the ED (0.13%), the most common drug-based intoxication is paracetamol intoxication.[17] Previously reported studies showed that unintentional (mostly exploratory) ingestions were more common among younger children; however, intentional ingestions were more prevalent among older children and adolescents.[18-20] We found that all children younger than 10 years presented with accidental ingestion; however, most of the ingestions in older children and adolescents were suicidal attempts. In our cohort, the adolescent ratio (38%) was lower than that of previous studies; however, this difference can be explained by the significant number of poisoned adolescents managed by our adult ED which is physically separated from our ED.

Kominek et al.[21] showed that adolescents who ingested the drug for suicidal purposes took higher amounts than younger children who took paracetamol unintentionally. Even though in our age groups similar data were found, no positive correlation was identified between the reported ingested dose of paracetamol and BPC at the 4th hour. Since suicide attempts are often impulsive among teenagers, the reason for the exaggerated higher drug consumption in the past medical history was a wish to attract attention to oneself.

Although non-toxic glucuronides and conjugated sulphates are effective in the metabolism of paracetamol to a large extent, cytochrome P 450 (CYP) enzymes play a role in nearly 5%. By activating CYP enzymes, the N-acetyl-p-benzoquinone imine (NAPQI) metabolite is formed. NAPQI binds to cellular proteins covalently, leading to necrosis in hepatocytes. NAPQI metabolites were found to be higher in patients with hepatic damage and they show individual variability based on the factors affecting CYP activity.[12,22]

The benefit of gastric decontamination is uncertain. Administration of activated charcoal (charcoal dose: 50 g for adults; 1 g/kg body weight for children) if the patient presents within one hour of ingestion of more than 150 mg/kg paracetamol should be considered. The administration of antidotes and usage of enhanced elimination techniques have specific implications in the paediatric population. Since NAC treatment was an effective choice to prevent hepatotoxicity, studies have showed that if the patient is at risk, intravenous acetylcysteine should be initiated.[8,23,24]

Chiew et al.[25] reported an adult study with massive paracetamol overdose and they found that BPCs were markedly reduced in those receiving activated charcoal within 4 h, and hepatotoxicity which had a lower rate was developed.[26] Buckley et al.[8] reported the similar data with 981 patients and they showed that activated charcoal reduces the need for NAC after acetaminophen (paracetamol) overdose if administered within 2 hours. The present results showed that gastrointestinal decontamination (gastric lavage, activated charcoal) was performed for most referred patients in the referring facility. However, the rate of administration of gastrointestinal decontamination in our ED rate was very low. This difference can be explained by the national poisoning centre recommendation, which states that if there is going to be delay beyond 8 h after the overdose in obtaining the BPC, NAC treatment should be started if more than 150 mg/kg paracetamol has been ingested. Most of the referring hospitals did not have an opportunity to obtain BPC, but we do. In the present study we have seen that even if non-toxic ingestion occurred, physicians from the referring center tended to perform GI decontamination as well as initiate NAC. They used NAC 12 times higher (48.5% vs. 4%) when compared to the patients who presented directly to our ED. Furthermore, the antidote was administered to one-fifth of the referred cases even when the amount of paracetamol allegedly taken was not toxic. These results may be explained by the fact that physicians do not want to take any risks, prefer defensive medical approaches and do not have appropriate knowledge on paracetamol intoxications.[27]

Waring et al.[26] examined the relationship between BPC and risk of anaphylactoid reactions and they found that low BPCs (non-toxic =0-100 mg/L) were associated with higher anaphylactoid reactions.[28] In the present cohort, a huge difference can be observed in the management of paracetamol poisoning between referring hospitals and a tertiary paediatric ED hospital. If the physicians working in these hospitals complete the knowledge, skills and toxicology courses, improper referrals, high costs and treatments can be avoided. They should keep in mind that if BPC can be obtained within 8 h of ingestion, there is normally no indication to start NAC.

In a study conducted in New Zealand, has been shown that reported dose was a good predictor of a toxic paracetamol concentration as well as NAC indication.[27] However, previous studies have shown that reported dose is an independent predictor of hepatotoxicity, this has not influenced risk assessment in paracetamol poisoning.[8,28] The findings of the present study differ from those of the New Zealand study. We believe that this difference can be explained by different age groups, study (retrospective) design and the single-centre, small sample size cohort of the present study.

Study Limitations

The limitations of the study include (1) missing patient data due to the retrospective nature of our study, (2) single-centre results with small sample size cohort and (3) well-designed, prospective with large sample size studies are required to explain the relationships in this study.

Conclusion

Our results showed that intravenous NAC was given to most patients with non-toxic paracetamol ingestion in hospitals where BPC cannot be provided even if they could refer these patients to a centre where BPC could be measured in the first 8 hours. If the patient is at risk, intravenous NAC should be given. There is normally no indication to start NAC without a BPC provided the result can be obtained and acted upon within 8 h of ingestion. If there is going to be delay beyond 8 h after the overdose in obtaining the BPC, treatment should be initiated if more than 150 mg/kg of paracetamol has been ingested.

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Ethics

Ethics Committee Approval: The study adhered to the ethical principles of medical research involving human subjects of the World Medical Association Declaration of Helsinki. The medical faculty scientific research Ethics Committee of Ege University provided ethical approval prior to the study (no: 18-12/5).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: C.T., A.Y., F.E., E.U.S., Concept: C.T., E.U.S., Design: C.T., F.E., E.U.S., Data Collection or Processing: C.T., A.Y., E.G.B., F.E., M.U., M.K., Analysis or Interpretation: C.T., E.G.B., E.U.S., Literature Search: C.T., M.U., Writing: C.T., E.U.S.

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References

1. Marzuillo P, Guarino S, Barbi E. Paracetamol: a focus for the general pediatrician. Eur J Pediatr. 2014;173:415-25.
2. Acheampong P, Thomas SH. Determinants of hepatotoxicity after repeated supratherapeutic paracetamol ingestion: systematic review of reported cases. Br J Clin Pharmacol. 2016;82:923-31.
3. Heard K, Anderson V, Dart RC, Kile D, Lavonas EJ, et al. Serum Acetaminophen Protein Adduct Concentrations in Pediatric Emergency Department Patients. J Pediatr Gastroenterol Nutr. 2017;64:533-5.
4. Gummin DD, Mowry JB, Spyker DA, Brooks DE, Beuhler MC, et al. 2018 Annual Report of the American Association of Poison Control Centers' National Poison Data System (NPDS): 36th Annual Report. Clin Toxicol (Phila). 2019;57:1220-413.
5. Yesil Y, Ozdemir AA. Evaluation of the children with acute acetaminophen overdose and intravenous N-acetylcysteine treatment. Pak J Med Sci. 2018;34:590-4.
6. Antoine DJ, Dear JW. How to treat paracetamol overdose and when to do it. Expert Rev Clin Pharmacol. 2016;9:633-5.
7. Chiew AL, Isbister GK, Duffull SB, Buckley NA. Evidence for the changing regimens of acetylcysteine. Br J Clin Pharmacol. 2016;81:471-81.
8. Buckley NA, Whyte IM, O'Connell DL, Dawson AH. Activated charcoal reduces the need for N-acetylcysteine treatment after acetaminophen (paracetamol) overdose. J Toxicol Clin Toxicol. 1999;37:753-7.
9. Yarema MC, Green JP, Sivilotti ML, Johnson DW, Nettel-Aguirre A, et al. Can a serum acetaminophen concentration obtained less than 4 hours post-ingestion determine which patients do not require treatment with acetylcysteine?. Clin Toxicol (Phila). 2017;55:102-8.
10. Fisher ES, Curry SC. Evaluation and treatment of acetaminophen toxicity. Adv Pharmacol. 2019;85:263-72.
11. Chiew AL, Gluud C, Brok J, Buckley NA. Interventions for paracetamol (acetaminophen) overdose. Cochrane Database Syst Rev. 2018;2:CD003328.
12. Marzullo L. An update of N-acetylcysteine treatment for acute acetaminophen toxicity in children. Curr Opin Pediatr. 2005;17:239-45.
13. Lewis RK, Paloucek FP. Assessment and treatment of acetaminophen overdose. Clin Pharm. 1991;10:765-74.
14. Rumack BH, Matthew H. Acetaminophen poisoning and toxicity. Pediatrics. 1975;55:871-6.
15. CDER-PHRMA-AASLD Conference, clinical white paper, preconference study document before conference. "Drug-Induced Liver Injury: A National and Global Problem." Available from: https://www.fda.gov/media/116737/download.
16. Jiménez-Gómez JPMB, Donat-Aliaga E. Acute hepatic failure. Spanish Society of Gastroenterology, Hepatology and Pediatric Nutrition, eds Diagnostic-therapeutic protocols of gastroenterology, hepatology and nutrition pediatric. 1st ed. ed. Madrid, Spain: ERGON; 2010:97-205.
17. Lin YR, Liu TH, Liu TA, Chang YJ, Chou CC, et al. Pharmaceutical poisoning exposure and outcome analysis in children admitted to the pediatric emergency department. Pediatr Neonatol. 2011;52:11-7.
18. Mintegi S, Fernández A, Alustiza J, Canduela V, Mongil I, et al. Emergency visits for childhood poisoning: a 2-year prospective multicenter survey in Spain. Pediatr Emerg Care. 2006;22:334-8.
19. Azkunaga B, Mintegi S, Salmón N, Acedo Y, Del Arco L, et al. Intoxicaciones en menores de 7 años en España. Aspectos de mejora en la prevención y tratamiento [Poisoning in children under age 7 in Spain. Areas of improvement in the prevention and treatment]. An Pediatr (Barc). 2013;78:355-60.
20. Seifert SA, Kirschner RI, Martin TG, Schrader RM, Karowski K, et al. Acetaminophen concentrations prior to 4 hours of ingestion: impact on diagnostic decision-making and treatment. Clin Toxicol (Phila). 2015;53:618-23.
21. Kominek K, Pawłowska-Kamieniak A, Mroczkowska-Juchkiewicz A, Krawiec P, Pac-Kożuchowska E. Intentional and accidental

paracetamol poisoning in childhood - a retrospective analysis. Postepy Hig Med Dosw (Online). 2015;69:452-6.

22. Chiew AL, Domingo G, Buckley NA, Stathakis P, Ress K, et al. Hepatotoxicity in a child following an accidental overdose of liquid paracetamol. Clin Toxicol (Phila). 2020;58:1063-6.
23. Rumack BH, Bateman DN. Acetaminophen and acetylcysteine dose and duration: past, present and future. Clin Toxicol (Phila). 2012;50:91-8.
24. Bateman DN, Carroll R, Pettie J, Yamamoto T, Elamin ME, et al. Effect of the UK's revised paracetamol poisoning management guidelines on admissions, adverse reactions and costs of treatment. Br J Clin Pharmacol. 2014;78:610-8.
25. Chiew AL, Isbister GK, Kirby KA, Page CB, Chan BSH, et al. Massive paracetamol overdose: an observational study of the effect of activated charcoal and increased acetylcysteine dose (ATOM-2). Clin Toxicol (Phila). 2017;55:1055-65.
26. Waring WS, Stephen AF, Robinson OD, Dow MA, Pettie JM. Lower incidence of anaphylactoid reactions to N-acetylcysteine in patients with high acetaminophen concentrations after overdose. Clin Toxicol (Phila). 2008;46:496-500.
27. Duffull SB, Isbister GK. Predicting the requirement for N-acetylcysteine in paracetamol poisoning from reported dose. Clin Toxicol (Phila). 2013;51:772-6.
28. Schmidt LE, Dalhoff K, Poulsen HE. Acute versus chronic alcohol consumption in acetaminophen-induced hepatotoxicity. Hepatology. 2002;35:876-82.