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THE RETROSPECTIVE EVALUATION OF CASES WITH HIGH BLOOD PARACETAMOL LEVELS

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ABSTRACT

Introduction*: The aim of the study is to compare laboratory parameters and clinical outcomes of the patients taking paracetamol only and those of the patients using other medications in addition to paracetamol.*

Material and method*: 471 cases whose ages were 15 or over, and who had a history of paracetamol intake as a single drug or in addition to other medications, and had high serum paracetamol levels, admitted to our emergency department (ED) in a 24-month period. Patients were divided into 3 groups according to Modified Rumack-Matthew nomogram and whether they took paracetamol only or together with other drugs: Paracetamol levels higher than toxic level (Group 1), lower than toxic level and using only paracetamol (Group 2), lower than toxic level and using other medications in addition to paracetamol (Group 3). In all cases, alanine aminotransferase, aspartate aminotransferase, platelet counts and INR values were retrospectively recorded. Cases were evaluated in terms of the rates of discharge from the ED, hospitalization and mortality.*

Results*: Eighty two of 471 patients were in the Group 1, 264 cases were in the Group 2, and 125 cases were in the Group 3. Forty nine of patients admitted to the ED within 2 hours after drug ingestion. Gastric lavage was performed and activated charcoal was administered in 94% (n=443) of patients presenting to ED in the following 4 hours after ingestion of paracetamol. Only the cases in the Group 1 had a statistically significant difference in ALT, AST, PLT and INR values measured on admission and at the 12th hour. 377 cases were discharged after ED observation, and 94 patients were hospitalized. All patients were discharged with full recovery.*

Conclusion*: Determining the treatment protocol by measuring serum paracetamol level shortens the duration of hospital stay, decreases treatment costs and helps avoid unnecessary N-acetylcysteine applications.*

Key words*: Acetaminophen, Poisoning, Overdose.*

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Introduction

Paracetamol (acetaminophen, N-acetyl-p-aminophenol; APAP) is one of the widely used drugs for its analgesic and antipyretic effects throughout the world. Although it is generally a safe medication when consumed with an optimal dosing and amount, an excessive utilization may lead to findings of toxicity[1,2].

Following oral administration, paracetamol is rapidly absorbed through gastrointestinal system (GIS), and in therapeutic dosages, it reaches its peak serum level in the first 2 hours. This period may be longer when sustained-release tablets are ingested. While paracetamol is mostly metabolized in liver by sulfation (20-46%) and glucoronidation (40-67%), only less than 5% is eliminated directly through the kidneys. A very little fraction of paracetamol is oxidized by cytochrome P-450, producing a reactive and toxic metabolite named N-acetyl-p-benzoquinone imine (NAPQI). This metabolite is detoxified by glutathione in the liver, and following transformation to paracetamol-mercaptate, it is eliminated from the body[1,3].

Toxic amounts of paracetamol may lead to hepatic necrosis and/or acute tubular necrosis[4,5].

Toxicologic screening tests performed in the case of the suspicion of a drug intoxicaiton have important roles in both confirming the diagnosis and evaluating the effects of and determining to terminate antidote and/or elimination therapies[6,7]. Serum paracetamol levels may also be tested during toxicologic screening tests.

In this study, patients admitted to our emergency department in a 24-month period, having a history of either paracetamol use as a single drug or in combination with other medications and high serum paracetamol levels were retrospectively evaluated to investigate the relationship between their laboratory parameters and clinical outcomes. We also think that our study will contribute to the data about paracetamol intoxication in Turkey.

Materials and methods

In this cross-sectional study, charts of 439.431 cases aged 15 or above, who were admitted to Haydarpaşa Numune Training and Research Hospital Emergency Department in the 24-month period, between January 1st, 2011 and December 31th, 2012 were reviewed. 4602 cases with suspicion of drug intoxication were retrospectively evaluated; values of blood drug levels for paracetamol, carbamazepine, valproic acid, phenytoin, tricyclic antidepressants, salicylate and phenobarbital were recorded. Among these patients, totally 471 cases including both the cases whose serum samples were positive for paracetamol and the cases who took other medications in addition to paracetamol were included in the study.

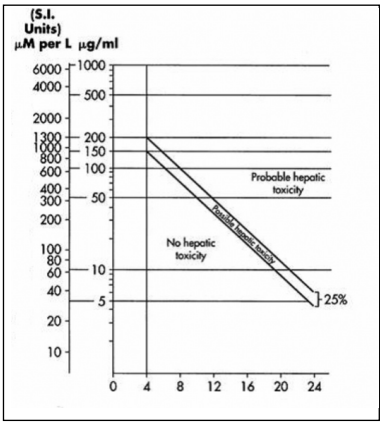

Figure 1: Modified Rumack-Matthew nomogram (adapted from reference 8).

These 471 cases admitted for drug intoxication and having a positive serum paracetamol level were divided into 3 groups according to Modified Rumack-Matthew nomogram[8] (Figure 1), and whether they had a history of single or multiple drug intake.

Group 1: Cases with serum paracetamol levels higher than the minimum level which may cause hepatic toxicity and the level which poses a risk for possible hepatic toxicity according to Modified Rumack- Matthew nomogram.

Group 2: Cases with a history of intake of paracetamol as a single drug and had serum paracetamol levels lower than the minimum level which poses a potential risk for possible hepatic toxicity according to Modified Rumack- Matthew nomogram,.

Group 3: Cases with a history of intake of other medications in addition to paracetamol and had serum paracetamol levels lower than the minimum level which poses a potential risk for possible hepatic toxicity according to Modified Rumack-Matthew nomogram,.

Cases admitted to the emergency department were evaluated for gender, age, monthly distribution, accidental or suicidal ingestion, single or multiple drug intake, time period between drug ingestion and admittance to the emergency department, Glasgow Coma Score, gastric lavage, activated charcoal and NAC application.

Blood levels of alanine aminotransferase (ALT), aspartate aminotransferase (AST), platelet counts and International normalized ratio (INR) values at the time of admission to the emergency department and 12 hours following admittance were recorded. Cases were evaluated in terms of the rates of discharge from the emergency department, hospitalization and mortality.

Biochemical and hematological analyses

Serum drug levels were measured with micro particular enzyme immune assay (MEIA) by Hitachi 902 analyzer (Roche Diagnostics, Tokyo, Japan) in the Emergency Laboratory. ALT and AST were measured with an Abbott plus Ci 4100 (Abbott Diagnostics, USA) clinical chemistry auto analyzer using a kinetic method. INR was assayed in a compact automatic coagulation analyzer, and complete blood count was performed with a CELL-DYN 3700 SL analyzer (Abbott Diagnostics, Chicago, Illinois, USA).

Statistical Analysis

Statistical analysis was performed using Statistical Package for the Social Science (SPSS) software (SPSS, Chicago, IL, USA, version 11.5). Student t test was used to evaluate the significance of differences between the averages, multiple groups were compared with One Way ANOVA (Bonferroni test) test, chi-square (Fisher's exact test) test was used for analysis of categorical variables. Paired samples t test was used for paired samples. The correlation between measurements was analyzed with Pearson correlation analysis. Spearman's rho correlation test was used for the parameters which did not have normal distribution. Results were given as mean ± standard deviation at the 95% confidence intervals. The P value of < 0.05 was considered to be statistically significant.

Results

Of these 4602 cases admitted to the emergency department with suspicion of drug intoxication within a period of two years, 471 cases (10.2%) were identified as positive for blood levels of paracetamol. Mean age was 29 ± 12 years in 471 patients. When groups were evaluated for age, Group 1 accounted for the lowest age group with 24.7 ± 8.5 years (Table 1 and Figure 1).

Parameters	Group I N=82	Group II N=264	Group III N=125	P
Age (yrs)	24.7 ± 8.5	28.0 ± 10.8	32.2 ± 14.5	< 0.0001
Day	1.98 ± 1.01	0.02 ± 0.22	0.26 ± 1.07	< 0.0001
Arrival Time (hr)	1.62 ± 0.89	1.66 ± 1.14	1.84 ± 1.18	0.246
Paracetamol level	167.3 ± 29.3	23.3 ± 32.3	10.3 ± 23.3	< 0.0001
AST-1 (IU/L)	22.0 ± 10.7	28.6 ± 45.7	23.4 ± 43.9	0.382
AST-2 (IU/L)	51.7 ± 68.2	25.5 ± 39.9	31.5 ± 51.4	0.118
ALT-1 (U/mL)	18.2 ± 9.2	28.3 ± 45.6	22.8 ± 43.8	0.152
ALT-2 (U/mL)	47.1 ± 65.8	26.8 ± 33.4	34.4 ± 90.8	0.15
PLT-1 (x1000/mm^3)	263 ± 55	266 ± 31	245 ± 63	0.392
PLT-2 (x1000/mm^3)	233 ± 52	264 ± 28	263 ± 129	0.106
INR-1	1.06 ± 0.10	1.09 ± 0.19	1.09 ± 0.13	0.659
INR-2	1.17 ± 0.13	1.08 ± 0.14	1.08 ± 0.11	0.006

Table 1: The comparison of mean age, arrival time, hospital stay (day) and laboratory values of groups 1, 2 and 3.

AST: Aspartate aminotransferase
ALT: Alanine aminotransferase
INR: International normalized ratio
PLT: Platelet counts

There was a statistically significant difference between the Group 1 and the other groups in terms of age (P < 0.0001). Two hundred and seventy three of the patients (57%) were female and 198 (43%) were male. When compared in terms of gender, the difference between the groups was statistically significant (P = 0.017). Eighty two patients had toxic levels of blood paracetamol level (Group 1). Two hundred and sixty four patients who took paracetamol as a single drug had blood paracetamol levels below the toxic level (Group 2). One hundred and twenty five patients who took paracetamol together with other drugs had serum paracetamol levels below the toxic level (Group 3).Forty nine % (n = 231) of the cases were admitted in the first two hours following ingestion, 45% (n = 212) in 2-4 hours and 6% (n = 28) after more than 4 hours passed (Table 2).

Parameters		Groups			n (%)	P
		Group I n = 82	Group II n = 264	Group III n = 125		
Gender	Female	59	147	67	273 (% 57)	0.017
	Male	23	117	58	198 (%43)	
Arrival time	0-1	2	38	16	56 (%11.9)	0.018
	1-2	44	94	37	175 (%37.1)	
	2-3	22	73	34	129 (%27.4)	
	3-4	12	42	29	83 (%17.6)	
	4-5	1	14	7	22 (%4.7)	
	≥5	1	3	2	6 (%1.3)	
Clinical Service (Hospitalized)	Emergency service	0	264	113	377 (%80.1)	< 0.0001
	Internal medicine	81	0	9	90 (%19.1)	
	Intensive care	1	0	3	4 (%0.8)	
Hospital Stay (Day)	0	0	264	113	377 (%80.1)	< 0.0001
	1	26	0	1	27 (%5.7)	
	2	41	0	3	44 (%9.3)	
	3	10	0	6	16 (%3.4)	
	4	3	0	1	4 (%0.8)	
	5	1	0	0	1 (%0.2)	
	7	1	0	0	1(%0.2)	
	9	0	0	1	1(%0.2)	
Total		**82**	**264**	**125**	**471**	

Table 2: Cross-tabulation of the demographic features of the groups.

Four hundred and sixty five cases were intoxicated as a result of a suicidal attempt and 6 cases were affected accidentally. None of the 6 patients

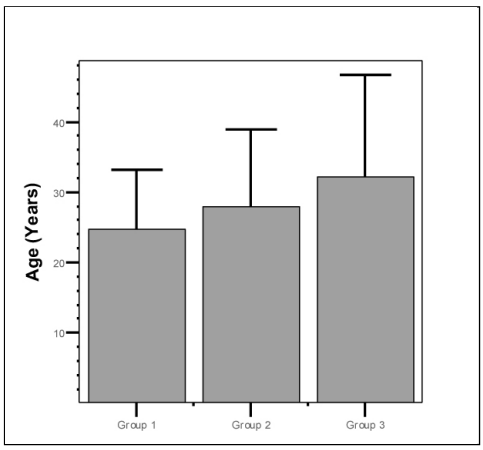

Figure 2: Age distribution of the groups.

who were accidentally intoxicated had toxic blood levels of paracetamol, and the lowest age was 72 among these patients.

Glasgow Coma Score (GCS) of 468 cases was 15 on admission to the emergency department. GCS of 2 cases was 13, and they had taken a tricyclic antidepressant in addition to paracetamol. GCS of one patient who had used benzodiazepine additionally was 12. Analysis of monthly distribution of the cases showed that the highest number of admission was in September and October (n = 101, 21.4%). However, the difference between monthly distribution of cases was not statistically significant (P = 0.307). While the number of females was higher than that of males for the first 11 months, the number of males exceeded that of females in the 12th month (Figure 3). Gastric lavage was performed and activated charcoal was administered in 94% of patients (n = 443) admitting in the first 4 hours after ingestion of paracetamol. Intravenous NAC treatment was given to all of 82 cases who ingested paracetamol in toxic dosages. Since 5 of these cases (6%) developed allergic reactions, intravenous NAC treatment was stopped, and NAC treatment was continued orally.

When all cases with positive blood paracetamol levels were assessed as a single group, mean blood level of AST was 24.3 ± 39.8 IU/L on admission and 34.9 ± 59.3 IU/L at the 12th hour of emergency department observation. Mean blood level of ALT was 24.2 ± 39.8 U/mL on admission and 32.2 ± 63.5 U/mL at the 12th hour. On the other hand, mean level of AST was 22.0 ± 10.7 IU/L on admission and 51.7 ± 68.2 IU/L at the 12th hour in the cases who ingested toxic amounts of paracetamol (Group 1). Their mean blood level of ALT was 18.2 ± 9.2 U/mL on admission and 47.1 ± 65.8 U/mL at the 12th hour. In cases who ingested toxic amounts of paracetamol, mean platelet count was 263 ± 55 x 103/uL on admission and 233 ± 52 x103/uL after 12 hours. Their mean INR value was 1.06 ± 0.10 on admission and 1.17 ± 0.13 after 12 hours (Table 1). When blood values on admission and at the 12th hour were compared, there was a statistically significant difference for the Group 1 (toxic amount of paracetamol ingestion) (Table 3).

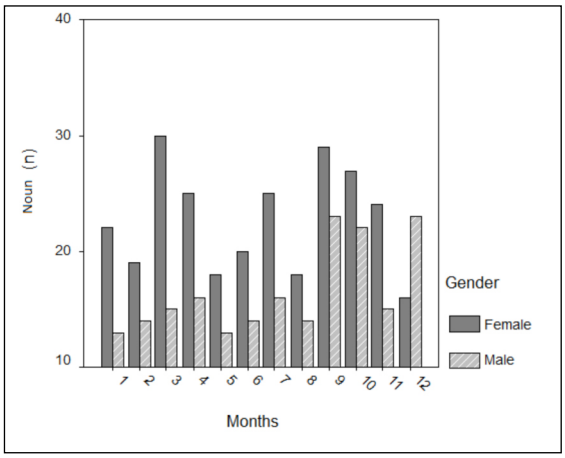

Figure 3: Monthly distribution of male and female cases.

Parameters	Group I N=82	P	Group II N=264	P	Group III N=125	P
AST-1 (IU/L)	22.0 ± 10.7	< 0.01	28.6 ± 45.7	0.6	23.4 ± 43.9	0.212
AST-2 (IU/L)	51.7 ± 68.2		25.5 ± 39.9		31.5 ± 51.4	
ALT-1 (U/mL)	18.2 ± 9.2	< 0.01	28.3 ± 45.6	0.757	22.8 ± 43.8	0.243
ALT-2 (U/mL)	47.1 ± 65.8		26.8 ± 33.4		34.4 ± 90.8	
PLT-1 (x1000/mm³)	263 ± 55	< 0.0001	266 ± 31	0.802	245 ± 63	0.233
PLT-2 (x1000/mm³)	233 ± 52		264 ± 28		263 ± 129	
INR-1	1.06 ± 0.10	0.003	1.09 ± 0.19	0.665	1.09 ± 0.13	0.983
INR-2	1.17 ± 0.13		1.08 ± 0.14		1.08 ± 0.11	

Table 3: The comparison of the laboratory values of groups 1, 2 and 3 on admission and at the 12th hour.
AST: Aspartate aminotransferase
ALT: Alanine aminotransferase
INR: International normalized ratio
PLT: Platelet counts

When other groups were analyzed, there were no statistically significant differences for ALT, AST, platelet counts and INR levels.

Following a 12-hour observation period, 377 cases were discharged from emergency department, 94 patients were hospitalized (90 patients in internal medicine ward, four patients in intensive care

unit). Sixty six of the hospitalized patients were females and 28 were males. Among hospitalized cases, Eighty two of the hospitalized patients had ingested toxic amounts of paracetamol. Twelve patients did not ingested toxic amounts of paracetamol but toxic levels of tricyclic antidepressants in 3, salicylate in 2 and valproic acid in 2 cases were detected in toxicologic screening. Five patients had a history of antibiotic, benzodiazepine or analgesic drug ingestion. Since we were unable to determine their blood levels, they were hospitalized due to a suspicion of toxic amount of intake. Seventy one (76%) of 94 cases were discharged in the first 2 days. Only one case was hospitalized for 9 days.

In the intensive care unit group, one patient had toxic amounts of paracetamol ingestion . In addition to paracetamol, toxic amounts of tricyclic antidepressants in two patients and a benzodiazepine in one patient were present. All patients admitted for paracetamol intoxication were discharged with complete recovery.

Discussion

Drug intoxication is an important public health problem that constitutes a significant fraction of emergency department workload, and requires a cautious management. When diagnosed and treated at an early stage, its management is generally quite easy. Intoxication cases form .7 to 5% of emergency department admissions in our country (9-13). In the current study, this rate was 1.05%. Paracetamol and nonsteroidal anti-inflammatory drugs are the ones most widely used in suicidal attempts following the psychotropic drugs[14, 15]. The rate of analgesic ingestion varies between 20.4 to 29.7% among drug intoxications[9,10]. In our study, this rate was 10.2%. We attribute the reason for this low rate to inclusion of only cases with paracetamol intoxication under analgesic drug category. In studies on excessive drug intake, the rate of female gender was found to be between 54-67%[16-19]. Females constituted the majority of the cases in the present study, too. Furthermore, studies have shown that intoxication was more common in young population[20,21]. Our study also revealed similar results; with the majority of our cases belonging to young population. Since the rate of female gender is higher than that of males, it may be suggested that female population has a greater tendency for intoxications. The reasons for intoxication being more common in women may be their sociocultural status in society, more repressive attitudes towards women than men and being more emotional. For suicidal tendency being more common in young population, the reasons may be lack of economic freedom, emotional trauma and excessive life expectations that fail to be fulfilled.

In this study, when the monthly distribution of paracetamol intoxication was investigated, it was found that it was more common in women than in men throughout all months except December. The reason for male predominance in December may be the economic problems of the year-end. It may be related to emotional stress caused by debts to be paid in this period, the difficulties in the payment of the year-end taxes or fear of unemployment and loss of economic freedom since companies go bankrupt often at the year-end.

Toxic amount of paracetamol in adults is > 7.5 g or > 150 mg / kg[1,22,23].Unless it is intentional, it is hard to get over such doses. Although overdosing is most frequently due to suicidal attempts in adults, children and elderly people are more frequently overdosed accidentally[3,24]. In our study, accidental ingestions took place in the elderly group.

Studies have shown that 34.2 - 55% of cases with drug intoxication were admitted to the emergency departments within 2 hours after ingestion[25,26]. Our results were consistent with the literature; 49% of our cases were admitted to the emergency department in the first 2 hours. Early admission may be suggested to be a sign of regret for ingestion in the early period. Orogastric or nasogastric decompression is an important issue in paracetamol intoxication as it is in all other drugs. Using activated charcoal is also helpful in preventing gastrointestinal absorption. It is well known that gastric lavage is more effective when performed within the first hour after ingestion[27]. In our study, since history was not always reliable for time of ingestion and using activated charcoal was an easy procedure, gastric lavage and activated charcoal administration were performed in all cases admitted within 4 hours after drug intake.

In emergency departments, toxicologic screening tests are used for confirmation of diagnosis and determination of management method. In some cases, test results for blood drug levels may alter the diagnosis and treatment method. Early diagnosis of drug ingestion is helpful for both rapid initiation of therapy and follow-up. Toxicologic analysis may be helpful in diagnosis of poisoning, monitoring antidote or elimination therapies, determining

blood values, initiation and cessation of treatment[6]. In this study, patients whose diagnoses were confirmed by determining the level of paracetamol in their blood were evaluated , and NAC treatment was started as needed.

It is advised to run test for blood paracetamol level 4 hours following ingestion. In our study, the results for blood paracetamol levels at the 4th hour and later on were evaluated in cases admitted for drug intoxication. Treatment methods, observation periods and hospitalization decisions were determined according to blood paracetamol levels. In drug ingestions, the patient history cannot always be reliable definitely.

If paracetamol levels could not be measured, it would have been necessary to initiate NAC therapy in most of the cases with history of paracetamol ingestion. Also, the lack of data for paracetamol in the patient history would have led to failure in starting NAC therapy when it was actually necessary. Thus, determining blood drug levels is an important issue. In this study, NAC was used in 82 patients whose the 4th hour blood paracetamol levels were 150 μg/ml or above. NAC can be used as an antidote in the treatment of paracetamol intoxication orally or intravenously. NAC, acting as a precursor of glutathione, fills glutathione reserves and it minimizes the liver damage by means of its antioxidant effects[1,3].

While oral treatment with NAC covers a 72 hours period divided into 4-hour fractions, IV NAC treatment is administered over a period of 20 hours. Twenty-hour IV regimen had been preferred due to patient compliance and ease of use in all cases whose intakes were within toxic dose range in the current study. However, in 6% of cases who developed allergic reaction, 72-hour oral NAC treatment was given following cessation of IV NAC treatment,.

In paracetamol-induced liver damage, the serum levels of liver enzymes AST and ALT start to increase. Elevations of bilirubin and INR, metabolic acidosis, coagulopathy, jaundice, renal failure, myocardial disorders, hepatic encephalopathy and coma may occur[1,3,28,29]. In this study, patients with toxic levels of paracetamol in Group I were found out to have statistically significant changes in ALT and AST levels, platelet counts and INR levels measured on admission and 12 hours following intake.

The hospitalization rate following drug poisoning was reported between 57.4 to 69.2%[9,17]. Our hospitalization rate was 20% in patients with paracetamol intoxication. We suggest that this low rate of hospitalization in patients with paracetamol intoxication may be due to being able to determine blood drug levels, guiding treatment according to determined blood values and also observation of the patients at the emergency department for a longer period of time. The mortality rates of patients admitted to emergency departments were reported to be between .03 to .05%[30-32]. However, even when paracetamol levels are within the toxic range, with early diagnosis and early initiation of NAC treatment when necessary, patients can be discharged uneventfully, without any mortal outcome. We think that, the uneventful discharge observed in all of our patients may be due to the fact that 72% of them had been admitted to our emergency department within the first 4 hours and NAC treatment was initiated early in all patients with unreliable ingestion history and in those with toxic blood paracetamol levels.

Limitations of our study were its retrospective nature and analysis of the data of a single-center. These limitations may be resolved by means of multicenter, nationwide, prospective studies in the future.

Conclusion

Among all drug poisonings, paracetamol intoxication is one of the serious challenges commonly encountered in emergency departments. In patients admitted for drug poisoning, an important issue is the unreliable history for the type and/or the amount of the ingested drug. In cases with suspected paracetamol intoxication, especially in young patients, determining blood paracetamol level is important for both confirmation of the diagnosis and determining the amount of ingested drug and guiding the management. Determining the treatment protocol by measuring serum paracetamol level shortens the duration of hospital stay, decreases treatment costs and helps avoid unnecessary N-acetylcysteine (NAC) applications.

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