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The importance of paracetamol blood levels on the cost and management of patients with paracetamol overdose

Fatih ÇALIŞKAN[1,*], Hızır Ufuk AKDEMİR[1], Ramazan AMANVERMEZ[2]

[1]Department of Emergency Medicine, Faculty of Medicine, Ondokuz Mayıs University, Samsun, Turkey
[2]Department of Biochemistry, Faculty of Medicine, Ondokuz Mayıs University Samsun, Turkey

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Abstract

We aimed to evaluate the effect of serum paracetamol level measurement on cost and patient management by evaluating the patients with a history of paracetamol overdose in the emergency department. This study was performed by investigating the data of 175 adult patients admitted to the emergency service after ingestion of the paracetamol-containing drug. Patients were divided into main three groups according to the narrative of ingested amount, and ten subgroups according to the serum paracetamol level, antidote treatment and hospitalization. According to the patients' narrative, the ingested paracetamol amount was toxic in 97 (55.4%) patients. Serum levels were non-toxic in 50 (28.6%), and toxic in only 4 (2.3%) patients. In intergroup cost analysis, the highest median cost per patient was in Group 4 ($ 332.9 [332.2 – 335.6]), and the lowest median cost per patient was in Group 3 ($ 98.0 [67.1 – 98.0]). When the patient groups in our study were evaluated in terms of cost per patient, there was a statistically significant difference between the groups ($p < 0.001$). Antidote administration, hospitalization and duration of treatment were independent variables affecting cost in our study. One unit increase in antidote administration, hospitalization, and the length of treatment caused to increase in cost about 67.3 units, 56.1 units, 2.2 units, respectively ($p<0.001$). The treatment cost can be reduced by measuring serum paracetamol levels. For avoiding a potential missed diagnosis of paracetamol overdose the routine measurement of paracetamol level warrants to reduce the cost of the patients who had an ingestion history of unknown paracetamol amount, especially in cases with altered mental status and psychiatric disorder who had suspected/elusive medical anamnesis about drug ingestion.

Keywords: paracetamol, ingestion, level, management, cost, emergency

1. Introduction

Paracetamol (acetaminophen) widely used for its anti-pyretic/analgesic effects is one of the most common medications ingested in overdose (1). It is cheap, easily accessible, and combined with many other drugs and accepted as a harmless medicinal agent by many users. Nevertheless, intentional and unintentional massive paracetamol ingestions are commonly seen in all around the world.

Paracetamol poisoning is a heavy burden on health systems. In a study conducted in the United Kingdom (UK) between 1992 and 1995, the average cost per patient was 181 Euro (€) due to paracetamol overdose. The total annual cost of paracetamol poisoning is approximately € 8 billion in the UK. Therefore, studies have focused on reducing the costs of diagnosis and treatment (2).

The measure of the paracetamol blood level can only reveal the actual risk of toxicity, especially in most of the patients who required the antidote therapy according to the narrative of the ingested amount. Choosing the right patients for hospitalization and antidote treatment may reduce the costs. The cost-effectiveness and correct antidote use can be achieved only by giving it to the patients who are above the treatment line using the Rumack-Matthew nomogram after the serum paracetamol measurement. Then, unnecessary antidote treatment is prevented by measuring serum paracetamol levels. With its serum level measurement, early diagnosis is made, and complications are prevented, particularly in the patients who do not need antidote according to the ingestion, but have a history of unreliable doses with high serum paracetamol levels (especially in suicidal and psychiatric patients). It provides convenience in the management of patients whose ingested amount is unknown, and unnecessary antidote administration can be prevented by measuring serum paracetamol level in patients who do not need antidote and when anamnesis cannot be taken in relation to paracetemol blood concentrations. For all these reasons, we aimed to examine the importance of serum paracetamol measuring on the patient management and cost in the patients with a history of excessive paracetamol ingestion in the emergency department.

2. Materials and Methods

2.1. Study design, setting, and population

This retrospective and descriptive study was conducted with the patients aged 18 years and above who admitted to the

* Correspondence: mdfcaliskan@gmail.com

emergency service after the ingestion of a paracetamol-containing drug. One hundred eighty-six patients met the inclusion criteria in this study. But due to lack of clinic findings, 11 patients were excluded from the study, and totally 175 patients were enrolled. This study was approved by The Clinical Research Ethics Committee of Ondokuz Mayıs University Medical Faculty (OMU CREC protocol no: 2012/172).

The sociodemographic characteristics, the presence of risk factors for liver damage (advanced age, malnutrition, chronic alcohol consumption, combined drug-using [cytochrome p450 inducers] and primary liver disease), vital signs, symptoms of patients on admission, the amount of paracetamol-containing medication (in grams), the other drugs and their amounts, the ingestion time and the medical history (the presence of psychiatric illness and/or suicidal attempt) were recorded. All the patients were evaluated according to a number of data with the results of liver function tests, serum paracetamol level, treatment (hydration, antidote therapy [intravenous and oral n-acetylcysteine], extracorporeal therapy), the requirement of critical care, the length of hospitalization duration, the hospitalized unite, total cost and prognosis (discharge, death).

The diagnosis for paracetamol poisoning was made by using the following definitions: 1) > 10 gr or 200 mg/kg over a 24 hour period, and 2) > 6 gr or 150 mg/kg per 24-hour period at least two consecutive days (3). The distribution of patients was determined with respect to Clinical staging (Stage 1-4) for paracetamol poisoning (3). Patients' prognosis evaluated according to discharge, liver damage, and death. The cut-off level of hepatocellular injury tests (AST, ALT) for hepatotoxicity was defined as 1000 IU / L and above (4,5). Patients were divided into main three groups (A: Ingestion of non-toxic amounts, B: Ingestion of toxic amounts, C: Ingestion of unknown amounts) and also ten subgroups according to the amount of paracetamol ingestion, serum paracetamol level, antidote treatment and hospitalization (Table 1). Due to the differences in fees of medical procedures, inpatient treatment applied to patients over the years, the total cost for each patient was calculated in the United States dollar ($) considering the current costs in 2020.

Table 1. The research groups according to the amount of paracetamol intake

Groups	Number of Patients(n=175)	The ingested amount*	Serum Parasetamol Level**	Antidote Treatment***	Hospitalization Status****
1	74	M_1	P_0	A_1	Y_1
2	18	M_2	P_0	A_2	Y_1
3	25	M_2	P_0	A_2	Y_2
4	4	M_3	P_0	A_1	Y_1
5	4	M_1	P_1	A_1	Y_1
6	7	M_1	P_2	A_2	Y_1
7	12	M_1	P_2	A_2	Y_2
8	10	M_2	P_2	A_2	Y_1
9	15	M_2	P_2	A_2	Y_2
10	6	M_3	P_2	A_2	Y_1

*The amount of paracetamol intake: M_1, Toxic; M_2, Non-toxic; M_3, Unknown. **Serum paracetamol level: P_0, Level cannot be measured; P_1, Toxic; P_2, Nontoxic. ***Antidote treatment: A_1, Antidote given; A_2, Antidote not given. ****The decision of hospitalization: Y_1, Hospitalized; Y_2, Not hospitalized

2.2. Data Analysis

IBM® SPSS® Statistics V21 software was used for statistical analysis of the data. Data were expressed as mean ± standard deviation (SD), median (minimum – maximum), and number (%) after it was determined if the data were parametric or non-parametric. The Kolmogorov-Smirnov/Shapiro-Wilk Test was used to evaluate the conformity of the quantitative data distribution to a normal distribution. It was determined that it would be appropriate to use non-parametric tests for data analysis in this study. Kruskal-Wallis Test was used for the statistical significance of inter-group costs, which were not found to fit the normal distribution. Regression analysis was performed to determine the independent variables affecting the cost. The statistical significance level was accepted as $p < 0.05$ for all tests.

3. Results

In perspective of the patients' narrative, the ingested paracetamol amount was toxic in 97 (55.4%), non-toxic in 68 (38.9%), and unknown in 10 (5.7%) of patients. Serum paracetamol level could not be measured in 121 (69.1%) of patients because of a lack of analysis kit in the emergency laboratory. Serum paracetamol levels in 54 (30.9%) of patients were measured. Serum paracetamol concentrations were non-toxic in 50 (28.6%), and toxic in only 4 (2.3%) of patients. A mild allergic reaction was seen in one patient (0.6%) during intravenous n-acetylcysteine (NAC) antidote therapy. No patient died and also underwent hemodialysis and liver transplantation in the study population. The characteristics of the patients are presented in Table 2. According to the laboratory parameters, hepatocellular damage markers (ALT, AST) in 8 (4.6%) of patients had increased, and also INR value in 3 (1.7%) of patients had elevated. In intergroup cost analysis, the highest median cost per patient was observed in Group 4 ($ 332.9 [332.2 – 335.6]), and the lowest median cost per patient was seen in Group 3 ($ 98.0 [67.1 – 98.0]). In the regression analysis, the independent variables affecting the cost were determined as antidote administration, hospitalization, and duration of treatment. 98.6% of the cost can be explained with these three independent variables. One unit increase in antidote administration, hospitalization, and the length of treatment caused to an increase in the cost about 67.3 units, 56.1 units, 2.2 units, respectively ($p<0.001$).

Table 2. The characteristics of the sample patients studied (n = 175)

Age	24 (18 -56)
Gender n (%)	
Female/Male	112 (64%) / 63 (36%)
Admission Time (hour)	4 (0.5 -12)
Medical History	
No previous history	130 (74.2%)
Depression disorder	32 (18.2%)
Drug intoxication	9 (5.1%)
Bipolar disorder	4 (2.2%)
Suicidal paracetamol intake	170 (97.1%)
Risk factors for Liver Failure	
No risk	78 (44.5%)
Additional drug ingestion	97 (55.4%)
Chronic alcohol user	5 (2.8%)
Primary liver disease	2 (1.1%)
Multidrug ingestion	
Present/Absent	106 (60.6%)/69 (39.4%)
Vital signs	
Systolic blood pressure	110 (70 -180)
Heart rate	80 (60 -116)
Ingested amount	
Toxic	97 (55.4%)
Non-toxic	68 (38.9%)
Unknown	10 (5.7%)
Serum paracetamol level	
Unmeasurable – no kit	121 (69.1%)
Toxic level	4 (2.3%)
Non-toxic level	50 (28.6%)
Clinical stage	
Stage 1/2	172 (98.3%) /3 (1.7%)
Lenght of treatment (hour)	24 (1 -96)
Treatment modalities	
Normal saline	175 (100%)
Normal saline+Decontamination [Gastric lavage, active charcoal]	175 (100%)
Normal saline + Oral NAC therapy	4 (2.2%)
Normal saline + IV NAC therapy	79 (45.1%)
Hospitalization	
Emercency observation room	120 (68.5%)
Intensive care unite	3 (1.7%)
Final status	
Full recovery	149 (85.1%)
Refuse to receive treatment	26 (14.9%)
Cost ($)	161.1(67.1387.9)

Data are presented as number (%) or median (min - max).

Fig. 1 presents the data of antidote therapy, hospitalization, duration of treatment, and cost values in study groups. When the patient groups were evaluated in terms of cost per patient, there was a statistically significant difference between the groups ($p < 0.001$). The cost per patient ($) was significantly lower in Group 6 (M1P2A2Y1) than in Group 1 (M1P0A1Y1) ($p=0.027$). In addition, the cost value was significantly higher in Group 1 compared to Group 7 ($p < 0.001$). However, there was no statistically significant difference between Group 4 (M3P0A1Y1) and Group 10 (M3P2A2Y1) in terms of the cost ($) per patient ($p > 0.05$).

4. Discussion

Paracetamol overdose is the most common etiological cause of acute liver failure (6). The patient management strategies for paracetamol overdoses include the rapid identification of high-risk patients and low-risk patients because of the need of antidote therapy. With accurate and current patient management strategies, avoiding unnecessary examinations and treatments can alleviate the financial burden on health systems.

Paracetamol-induced liver damage is related to the direct effect of paracetamol and its toxic product (NAPQI) produced excessively by the liver. In relation to drug metabolism, glutathione binds NAPQI and then it converts into non-toxic products (7). Thus, paracetamol intoxication lead to decrease in liver's glutathione stores (8). Moreover, it assumes that hepatic glutathione reserves may decrease in a number of conditions such as advanced age, malnutrition, fasting, and chronic liver disease are though to be risk factors for liver injury in paracetamol overdose. Isoniazid, rifampin, phenobarbital, chronic alcohol consumption may affect the cytochrome P-450 enzyme system, and could give rise to liver damage. Non-steroidal anti-inflammatory drugs, fibrates, and statins may cause paracetamol-induced liver damage as a result of unknown mechanisms. Obesity and non-alcoholic fatty liver disease are risk factors for paracetamol-induced liver injury (5,9).

Multidrug use (antiepileptic, antipsychotic, antidepressant drugs most commonly metabolized in the liver) was estimated as a risk factor for liver damage in our study group. However, there were also patients with chronic alcohol consumption, and chronic liver disease (HBV-induced liver disease) along with multiple drug intake. Actually, no significant differences were observed for the development of paracetamol overdose induced hepatotoxicity, the presence of multiple drug intake, chronic alcohol consumption, chronic liver disease, and the other risk factors for liver damage in this study. Hypoprotrombinemia, metabolic acidosis, and renal failure are associated with elevated aminotransferase levels in paracetamol-induced liver injury (10,11). In our study group, the increased levels in ALT, AST and INR were detected in a small number of laboratory parameters used as a marker of hepatotoxicity. Since hepatocellular damage markers were higher than 1000 IU / L, it was associated with toxicity (9); no patients with hepatotoxicity were detected in our study. This situation may be interested in the low number of patients and the absence of severe poisoning.

Litovitz et al. reported that the majority of patients with acute intoxication who applied to the emergency department were not in poor condition (12). In the study of Sorodoc et al., 51.9% of patients with acute intoxication had good general status (13). In our study, 98.3% of patients were asymptomatic (Stage 1 for paracetamol poisoning) when the complaints, symptoms, and physical examination findings of the patients were evaluated, considering that patients are asymptomatic in the early period of paracetamol-induced liver injury.

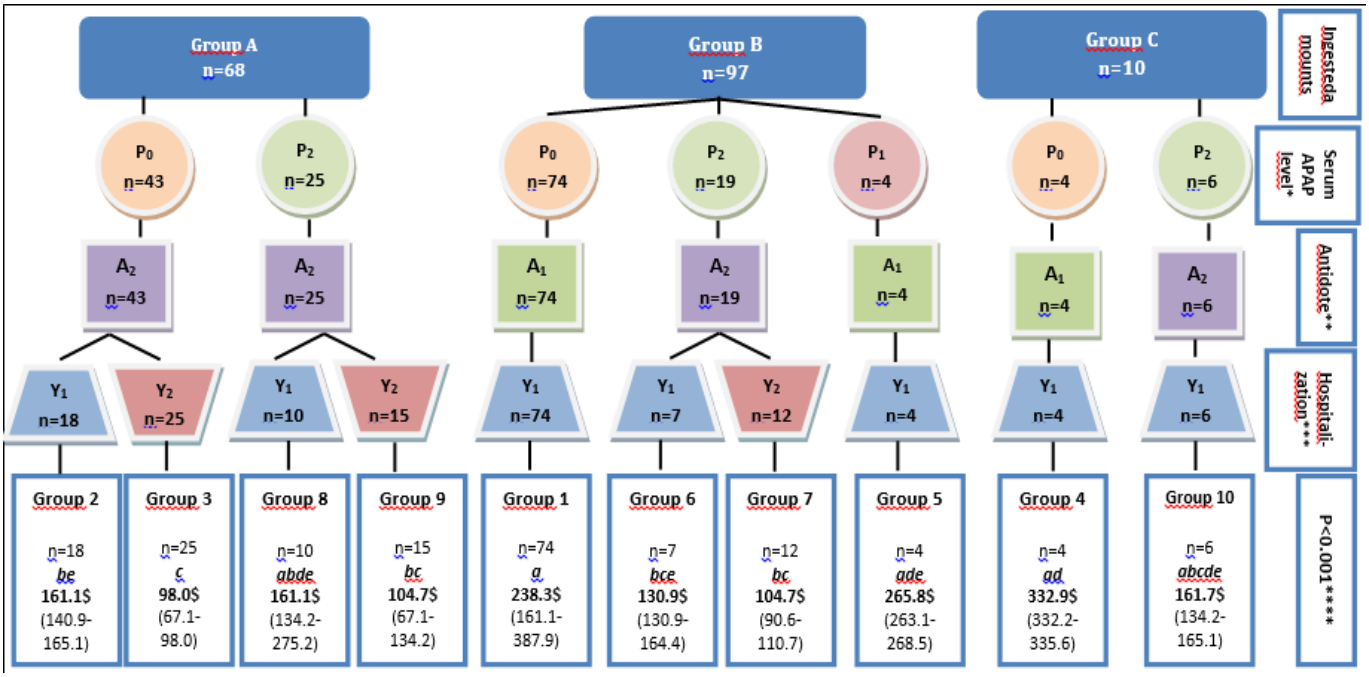

Fig. 1. Analysis of study groups according to ingested amounts, antidote therapy, hospitalization and costs using Kruskal-Wallis Test
Group A: Ingestion of non-toxic amounts, B: Ingestion of toxic amounts, C: Ingestion of unknown amounts.
* According to serum paracetamol level, "P0 = Level cannot be measured, P1 = Toxic, P2 = Nontoxic".
** According to antidote treatment, "A1 = Antidote given, A2 = Antidote not given".
*** According to the decision of hospitalization, "Y1 = Hospitalized, Y2 = Not hospitalized".
****Study groups were identified with the letters "abcde" using Kruskal-Wallis test according to cost differences. The presence of the same letter in the study groups indicates that there was no statistical difference between the groups.

The median value of hospital stay in patients with hepatotoxicity was 3 (1-192) days, and the median value of total hospital expenses was $ 2,123 (342–89,182) in a study (14). In our study, the median value of hospital stay was 24 hours. The patients with high ALT and AST values on admission were hospitalized for three days, and the median cost per patient was $ 94.0 (75.8-131.5). The fact that 14.9% of the patients left the emergency department before the completion of the treatment period could explain the total length of hospital stay and the lower total cost than other studies. The previous study included only patients who developed hepatotoxicity. Thus, the need for organ transplantation, hemodialysis, and the need for prolonged intensive care associated with these conditions increase both the total length of hospital stay and the cost. The absence of hepatotoxicity (ALT and AST ≥ 1000 IU / L) in our study may be another additional factor affecting length of hospital stay and cost. The independent variables affecting total cost and length of hospital stay were age, sex, comorbid diseases, paracetamol-related hepatotoxicity in the previous study (14). In our study, antidote administration, hospitalization, and duration of treatment were found to be independent variables affecting cost, considering that this condition is related to the absence of hepatotoxicity.

Antidote treatment is frequently arranged according to the patient's narrative of ingested amount in emergency departments where serum paracetamol level cannot be measured. Hesitative, low-reliability anamnesis, especially in psychiatric, or unconscious patients are challenging conditions for the emergency physician. However, there were no patients had a toxic serum level of paracetamol in the patient groups who had a non-toxic intake in the anamnesis.

In cases have no additional factor for the indication of hospitalization and follow-up, serum paracetamol measuring facilitates patient management (diagnosis, antidote treatment, hospitalization, and discharge) as long as the ingested amount is toxic according to the patient's anamnesis. When we compared the total costs of Group 1 and 6 in our study, serum paracetamol measuring was cost-effective, especially in patients who received excessive amounts of paracetamol in their medical history.

In cases with the ingestion of unknown amounts of paracetamol or suspected history of intoxication with altered mental status, the routine measurement of paracetamol level should be made to avoid a potential missed diagnosis of paracetamol overdose. Dargan et al. detected 4 (3.5%) patients poisoned with paracetamol among 115 patients presenting with collapse after routine measurement of serum paracetamol level. Based on their results, they suggested that the potential for missed paracetamol poisoning in such patients warrants the routine use of paracetamol screening in all patients presenting to the emergency department with a history of altered mental status (15).

Diagnosis for paracetamol poisoning can be made only by measuring serum paracetamol levels in patients who had no information about ingested amount such as group 10. If the serum paracetamol level could not be measured as in group 4, the patients should be closely monitored using the liver

function tests for paracetamol poisoning. In group 10, paracetamol over-intake was excluded using serum paracetamol level measurement, and antidote treatment was not applied. The fact that the cost per patient in Group 10 is less than Group 4 can be explained by the decrease in the length of hospital stay and laboratory examination costs. Measuring the serum paracetamol level seems to reduce the possible additional costs (hospital stay, follow-up of laboratory tests and antidote treatment). Similarly, serum paracetamol measuring appears to provide cost-effectiveness when the costs between groups 1 and 7 were evaluated. The measurement of serum paracetamol level decreases the cost by shortening the duration of hospital stay and clinical follow-up.

Serum paracetamol levels should be controlled in poisonings with unknown history of drug ingestion. As a result of this, the concomitant paracetamol overdose can be excluded or confirmed. If the determined level is non-toxic, unnecessary antidote treatment decreases, and it results in shortening the hospital stay and reducing the cost. In the view of our findings, we noticed that the routine measurement of serum paracetamol level in patients with paracetamol overdose of unknown ingestion and patients with multiple drug intake of unknown type contributed to patient management (diagnosis, antidote treatment, hospitalization and discharge).

In conclusion, our study aims to contribute to the development of correct diagnosis and treatment strategies in order to reduce the burden of massive paracetamol ingestion among the etiologic factors leading to acute hepatic failure by evaluating the effect of serum paracetamol level on the patient management and cost. Accordingly to our findings, it is suggested that the measuring of serum paracetamol level can permit to reduce patients' cost interested in an ingestion history of unknown paracetamol amount and the number of potential missed paracetamol poisoning in the presence of altered mental status and psychiatric disorder for patients in associated with suspected/elusive medical anamnesis about drug intake.

Although some countries have studies discussing the cumulative costs of paracetamol to their national economies (16,17), our study is the only study that evaluates the effects of paracetamol levels on cost and patient management in detail. The most important limiting factors of our study were retrospective study and absence of hepatotoxicity in the study group. Prospective studies involving more patients are needed to elucidate many factors affecting the cost and length of hospital stay and its relationship with serum paracetamol levels. In our country and other countries in the world, patients who applied to the emergency department due to excessive intake of paracetamol, the number of similar studies on patient management, and cost is not very high. Hence, our study is also essential in terms of shedding light on future studies.

Conflict of interest

None to declare.

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This study was approved by The Clinical Research Ethics Committee of Ondokuz Mayıs University Medical Faculty (OMU CREC protocol no: 2012/172).

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