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Evaluation and Comparison of Patients Poisoned with Acetaminophen and Nonsteroidal Anti-Inflammatory Drugs

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ABSTRACT

We aimed to determine and compare the clinical and demographical features, treatments, follow-up, poisoning scores and outcome of cases with the acetaminophen and NSAIDs intoxication.
Data of the patients who were at the age of 18 and older and applied to the Emergency Department with the acetaminophen or NSAIDs intoxication were retrospectively examined. The cases were divided into 2 groups as the acetaminophen and NSAIDs group. The cases' age, gender, drug dose, hospitalization status and periods, poisoning scores (PSS, APACHE-II) and last conditions in discharging from the hospital were compared.
The döşe was taken by 99 (55%) patients in the acetaminophen group was calculated as toxic, and intravenous acetylcysteine was administered to 70 (38.9%) patients as an antidote. When the APACHE-II scores of the patients hospitalized in the intensive care unit were examined, the mean APACHE-II score of 54 patients in the acetaminophen group was 3.15±3.70, the mean APACHE-II score of 34 patients in the NSAIDs group was 4.15±3.13 and it was statistically higher (p=0.031). All the patients followed-up in both groups were discharged with healing except only 1 (0.6%) patient who developed acute liver failure. Conclusion: The mean APACHE-II score was low in both groups. Therefore, following-up the patients in a unit such as a toxicology unit instead of the intensive care unit can be beneficial in terms of both reducing the place and labor force loads and cost. Moreover, the acetylcysteine treatments in the early period of the acetaminophen toxicity are very effective in decreasing the mortality and morbidity.

Key Words: Acetaminophen, nonsteroidal anti-inflammatory drugs, poisoning

Introduction

Both the acetaminophen (also known as paracetamol) and nonsteroidal anti-inflammatory drugs (NSAIDs) are safe, effective and widely available; therefore, they are the most commonly used agents worldwide (1, 2). The acetaminophen and NSAIDs are the most common overdoses drugs reported to the poison centers in the United States since they are frequently used and accessed easily over the counter (3).

NSAIDs show antiinflammatory, analgesic and antipyretic effects by inhibiting the cyclooxygenase (COX) enzyme in the prostaglandin synthesis and by reducing the superoxide radicals, nitric oxide synthase enzyme and proinflammatory cytokines (eg, TNF-α, interleukin-1). While the COX-1 enzyme inhibition creates the primary reason for the gastrointestinal side effects by preventing the gastric prostaglandin release, the COX-2 enzyme inhibition increases the rate of the cardiovascular side effects (4, 5).

The gastrointestinal effects such as abdominal pain, nausea-vomiting, upper gastrointestinal system bleeding or perforation, and cardiovascular effects are the primary side effects. Except this; it can cause to the acute kidney failure, metabolic acidosis and neurological effects such as headache, dizziness, tinnitus and even seizure in the overdoses. Although the fatal results are rare, they can be seen in the high dose intakes or repetitive intakes. There is no specific antidote in the NSAIDs poisoning, the treatment is completely symptomatic (5, 6).

Since the acetaminophen is a quite safety drug in the therapeutic doses, its gastrointestinal and cardiovascular side effects are at the minimum level. However, the high dose acetaminophen intake is the most frequent reason for the acute liver failure, especially in the developing countries (7).

While approximately 90-95% of the acetaminophen in the therapeutic doses is metabolized by the sulfation and glucuronidation in the liver, <5% part is transformed into the N-acetyl-p-benzoquinone imine (NAPQI) by the hepatic cytochrome p450 enzymes. The NAPQI is detoxified by rapidly transforming into the non-toxic metabolites by the hepatic

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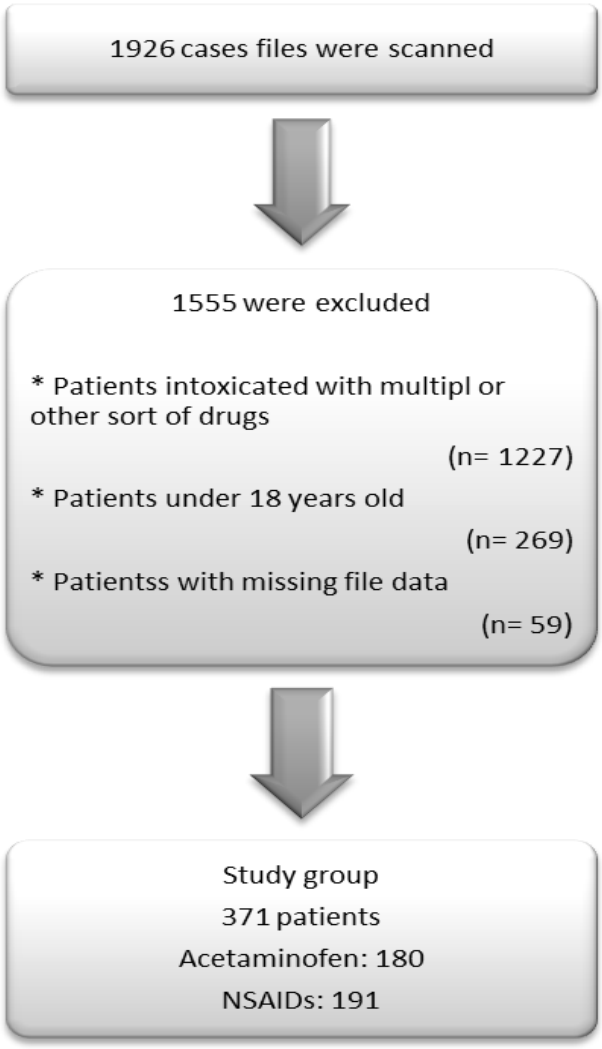

Fig. Subjects flow chart

glutathione and thrown out of the renal route. The large part of acetaminophen in the high dose intakes is metabolized by the cytochrome P-450 to the NAPQI. The hepatic glutathione sources gradually decrease and NAPQI bonds to the other hepatic macromolecules and acute liver failure profile develops as a result of the hepatocyte damage (8, 9). When it is taken as 200 mg/kg at once or more than 10 grams within 24 hours in the adults, it is accepted as the toxic dose. Again, the plasma acetaminophen concentration measured by the Rumack-Matthew nomogram at least 4 hours after the intake is used in determining the toxic dose. Acetylcysteine is an effective antidote for acetaminophen intoxication and is the main component of the treatment (10).

With this study, we aimed to determine and compare the clinical and demographical features, treatments, follow-up, poisoning severity scores and outcome of the acetaminophen and NSAIDs intoxication cases applied to the Emergency Department of a 3rd step hospital.

Material and Methods

Study Design: This study was performed by retrospectively examining the files of the patients at the age of 18 and older who applied to the third step hospital Emergency Department with the acetaminophen or NSAIDs intoxication between January 2013 and January 2017. The patient information is obtained by using the automation system and patient files. The cases' age, gender, symptom, application period, agent causing the intoxication, drug dose, whether they drink alcohol concomitantly, hospitalization status and periods, treatments administered, poisoning scores (Poisoning Severity Score (PSS), Acute Physiology and Chronic Health Evaluation (APACHE-II)) and last conditions in discharging from the hospital (well-being, death, healing with sequela, their discretionary discharges) were researched.

Study Group: The cases in the study were collected in 2 groups. While the patients intoxicated by the high doses of acetaminophen alone or in combination with the codeine or pseudoephedrine create the first group, patients intoxicated by the high doses of any kind of NSAIDs except salicylate create the second group. The criteria for including in the study are respectively as follows: patients who were at the age of 18 and older, whose patient information is avaible, who applied by the either acetaminophen or NSAIDs poisonings and have an intoxication history only with one agent. The criteria for excluding from the study are respectively as follows: patients whose patient information is missed and who have a poisoning history with more than one agent.

Statistical Analysis: The "SPSS for Windows 21.0" program was used and evaluated for the data's statistical analysis. While the numeric variables were specified as mean ± standard deviation (SD) in the descriptive statistics, the categorical variables were shown as number and percentage. The Student's t-test was performed for the comparisons of both groups in the numeric variables. The Mann-Whitney U-test was performed for the comparisons of both groups in the nonparametric variables. $p<0.05$ value was accepted as statistically significant.

Results

1227 of 1926 cases of which files were scanned for the study were excluded from the study by the reason of intoxication with the different agents or multi-agents, 269 of them were excluded from the study by the reason of being at the age of under 18, and 59 of them were excluded from the study by the reason of missing file information (Figure).

Table 1. Comparison of the groups in terms of age, amount of drug, duration of hospital stay

	Acetaminophen	NSAIDs	p value
Age	28.2±8.9	29.1±9.6	0.349
Amount of drug (number)	24.9± 16.1	24.8± 20.2	0.929
Drug intake time (hour ago)	2.48± 3.94	2.60± 4.38	0.800
Duration of stay in ICU	2.53± 3.55 (n:45)	1.97± 1.17 (n:25)	0.853
Duration of stay in Clinic	1.67± 0.96 (n:57)	1.70± 1.79 (n:42)	0.131

Table 2. Symptoms of the patients

	Acetaminophen n (%)	NSAIDs n (%)
None	77 (42.8)	106 (55.5)
Nausea - vomiting	59 (32.8)	36 (18.8)
Abdominal pain	26 (14.4)	21 (11.0)
Confusion	10 (5.6)	16 (8.4)
Headache	4 (2.2)	7 (3.6)
Weakness - exhaustion	3 (1.7)	3 (1.6)
Palpitation	1 (0.6)	2 (1.0)
Total	180 (100)	191 (100)

While 180 of 371 cases constituting the study group applied by the reason of acetaminophen intoxication, 190 of them applied by the reason of NSAIDs intoxication. The mean age was 28.2±8.9 in the acetaminophen group and 128 (71.1%) of them were female. The mean age was 29.1±9.6 in the NSAIDs group and 146 (76.4%) of them were female. There was no statistical difference with respect to the age and gender between the groups (p= 0.349 and 0.231 respectively). Again, there was no significant difference with respect to the drug amount taken (number), drug intake time, intensive care unit (ICU) hospitalization period and service hospitalization period between the groups (p>0.05), (Table 1).

Seven (3.9%) patients in the acetaminophen group and 11 (5.8%) patients in the NSAIDs group had a suicide history previously. Fifteen (8.3%) patients in the acetaminophen group and 26 (13.6%) patients in the NSAIDs group had a psychiatric diagnosis in the history, and 12 (6.7%) patients in the acetaminophen group and 14 (7.3%) patients in the NSAID group had alcohol intake simultaneously with drug intake.

When the cases' symptoms were examined during the application, while there was no symptom in the first rank, nausea and vomiting was the second and abdominal pain was the third rank in both groups (Table 2).

The dose taken by 99 (55%) patients among the patients poisoned by the acetaminophen was calculated as toxic, and intravenous acetylcysteine was administered to 70 (38.9%) patients as an antidote. Again, the gastric lavage was administered to 108 (60%) of the patients and activated charcoal was administered to 151 (83.8%) of patients in the acetaminophen group. The gastric lavage was administered to 81 (42.4%) patients and activated charcoal was administered to 158 (82.7%) patients in the NSAIDs group.

When the cases' PSS scores were examined, even there was statistically significant difference in terms of the PSS between the groups (p=0.017), the PSS score was '0' or '1' in a great majority of both groups. In other words, a significant difference was not clinically determined between the groups in terms of the PSS score.

When the APACHE-II scores of the patients hospitalized in the intensive care unit were examined, while the mean APACHE-II score of 54 patients in the acetaminophen group was 3.15±3.70, the mean APACHE-II score of 34 patients in the NSAIDs group was 4.15±3.13 and it was statistically higher (p=0.031) (Table 3).

While the exitus was not determined except for the patients who left hospital with their own decision in both groups, the moderate acute lung injury developed in 2 patients (one due to the ibuprofen, and the other due to the diclofenac) in the NSAIDs group. The full well-being was provided by the symptomatic treatment in these patients. The liver failure profile developed only in 1 (0.6%) patient in the acetaminophen group and was transferred to the transplantation center. The patients' hospitalization and discharge information and clinical outcomes were given in Table 4.

Table 3. PSS and APACHE-II scores of the groups

	Acetaminophen n (%)	NSAIDs n (%)	p value
PSS	None: 73 (40.6) Minor: 101 (56.1) Moderate: 3 (1.7) Severe: 3 (1.7)	None: 106 (55.5) Minor: 72 (37.7) Moderate: 11 (5.8) Severe: 2 (1.0)	0.017
APACHE-II	3.15±3.70	4.15±3.13	0.031

Table 4. Hospitalization and discharge results of the patients

	Acetaminophen n (%)	NSAIDs n (%)
Hospitalization in the clinic	57 (31.7)	42 (22.0)
Hospitalization in the intensive care unit	45 (25.0)	25 (13.1)
Transfer to other center	8 (4.4)	11 (5.8)
Leaving hospital with their own decision	40 (22.2)	70 (36.6)
Discharge from Emergency Department	30 (16.7)	43 (22.5)
Total	180 (100)	191 (100)
Clinical outcomes of the patients		
Full well-being	104 (57.8)	89 (46.6)
Healing with sequele	1 (0.6)	0 (0)
Leaving hospital with their own decision	75 (41.6)	102 (53.4)
Exitus	0 (0)	0 (0)
Total	180 (100)	191 (100)

Discussion

In our study, discharging with full well-being of all patients except for 1 patient in the acetaminophen group is an important and gladsome result in terms of following-up the patients applied with both acetaminophen and NSAIDs intoxication.

In a study performed in 2001 in which 529 patients were analyzed since they had a high dose acetaminophen poisoning and acetylcysteine was administered, the mean age of the patients was 31 and 68.2% of them were female. While the hepatic encephalopathy was determined in 82 (15.5%) patients during the application, coma was detected in 55 (10.4%) of them. While the liver transplantation was performed to 5 (1%) of the patients, 32 (6%) patients died (11). The high rate of adverse outcomes at the time of presentation and outcome may be due to the fact that the study was performed in previous years and most of the patients were critical and referred from other centers. In the study performed by Ronald et al. on 76 patients applied with the acetaminophen poisoning, 53 (70%) of the patients were female and the median age was 22. Twenty-nine (38%) of the patients received the acetylcysteine treatments, and only 1 patient died as a result of the acute liver failure (12). In addition, James et al. evaluated 53 patients with acute hepatic failure due to acetaminophen poisoning. The mean age of the patients was 33.6 and 66% of them were female. They determined in the study that the high dose acetaminophen was correlated by the high AST and ALT values and mortality. While 41 patients got spontaneously better in the study, 3 patients were administered the liver transplantation and 9 patients died (13). In our study, there was no statistical difference between the gender distribution and mean age in both groups. These results suggest that the suicidal purposeful drug intakes are more frequently seen in the young adults and females.

Acetylcysteine treatments play a key role and prevent negative results such as liver failure, transplantation or death in acetaminophen toxicity. The need for treatment is determined by the patient's blood paracetamol concentration and a line starting at 100 mg/L at 4 hours post overdose determines the need for acetylcysteine treatment. Also, in patients with a history of 200mg/kg or 10 gr intake over a single 24-hour period or 150mg/kg or 6 gr intake within a single 24-hour period the level is considered toxic and treatment is initiated without delay (14, 15). In our study, the intravenous acetylcysteine was administered to 38.9% of the patients and acute liver failure developed in only 1 (0.6%) patient. In our study, the mortality and morbidity rate was low since

most of the patients applied in the early period and the early treatment was started.

It is known that NSAIDs show the gastric side effects such as nausea, vomiting, and even gastrointestinal system bleeding by the reason of COX1 inhibition and the cardiovascular side effects by the reason of COX2 inhibition. However, it was shown by some studies and case reports that it also caused the acute liver injury even at the low therapeutic doses (16-19). Also, Donati et al. determined the acute liver injury depending on the NSAIDs use as 1.69% in the multicenter study they performed, and they also determined that this risk increased especially in the long-term and high dose intakes and moreover especially in the nimesulide and ibuprofen intakes (20).

Determining the toxic dose in the NSAIDs toxicity is difficult. Although there is a nomogram just for the ibuprofen toxicity, it is not clinically useful. Because of these reasons, the management of NSAIDs toxicity completely bases upon the symptomatic and supportive treatment (4). In our study, the acute lung injury developed in totally 2 (1%) patients in the NSAIDs group and full well-being was provided by the symptomatic treatment.

In our study, we aimed at evaluating and comparing the PSS scores of the patients in the acetaminophen and NSAIDs groups and APACHE-II scores for those hospitalized in the intensive care unit. The PSS is a scoring method used to grade the poisoning with the clinical findings and is classified as (0) none, (1) minor, (2) moderate, (3) severe, and (4) fatal poisoning (21). The PSS score in a great majority of the patients was 0 (none) and 1 (minor) in both groups.

In a multicenter study evaluating 119 patients who were admitted to the intensive care unit due to poisoning, APACHE-II and APACHE-III scores were higher in patients poisoned with caustic agents (n: 11) than those who were poisoned due to drug intake (n: 92), and high scores were associated with mortality. While the mortality was 54.5% in the patients poisoned by the caustic substance, it was 1.9% in the drug-induced poisonings (22). When we evaluated the APACHE-II scores that are predictive and frequently used in determining the mortality in the intensive care unit (23, 24), the mean APACHE-II score of 54 patients in the acetaminophen group was 3.15±3.70 and it was 4.15±3.13 for 34 patients in the NSAIDs group. Although it was significantly higher in the NSAIDs group, the mean APACHE-II scores of both groups were low and this result predicted that all of the patients followed-up were discharged with full well-being except one patient. An important problem determined here is that following-up these patients in the intensive care unit is not effective in terms of both the cost and place and labor force loads.

Limitations: There were a few limitations in our study. First of all, the drugs found in the NSAIDs group were collected in one group since they could not be identified according to their types due to the data limitation as our study was retrospective. The patient's history was based upon the toxic dose calculation since the nomogram value used in calculating the toxic dose in the acetaminophen group could not be measured and reached in most of the patients. Moreover, as our study was conducted in a single center, this was a limitation in terms of generalizing the results.

All the patients followed-up in the acetaminophen group were discharged with the full well-being except for one patient.

Although the mean APACHE-II score in the NSAIDs group was higher rather than the acetaminophen group, the mean APACHE-II score was low in both groups. Therefore, following-up the patients in a unit such as a toxicology unit instead of the intensive care unit can be beneficial in terms of both reducing the place and labor force loads and cost.

The treatment of acetylcysteine in the early period of the acetaminophen toxicity which is the most important reason for the liver failure especially in young patients is very effective in reducing the mortality and morbidity.

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