

Discrepancies between N-Acetyl Cysteine Prescription based on Patient's History and Plasma Acetaminophen Level

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ABSTRACT

Background: Fatalities from acetaminophen poisoning are common, but they are preventable by timely treatment with N-acetyl cysteine (NAC). In many medical centers, NAC is prescribed in keeping with the ingested dose of the drug as revealed through medical history. It seems to significantly differ from the real indications of NAC administration based on plasma level of acetaminophen. Overtreatment increases adverse drug reactions and it is time-consuming and costly.

Methods: Acetaminophen plasma level was checked by HPLC method in 170 admitted patients who had history of acute ingestion of more than 7.5 g acetaminophen within 4 to 24 hours prior to hospital admission. Indications for NAC prescription according to patient's history and adaptation from acetaminophen plasma level in Romack-Mathew nomogram were matched. Data were analyzed by SPSS software version 16.0.

Results: Mean age of the patients was 21.8 ± 6.05 years. In 75.8% of the patients, poisoning had occurred after suicidal attempts. Acetaminophen plasma level was between less than 2 and 265 $\mu\text{g/ml}$ (18.7 ± 28.88 , mean \pm SD). Only in 18 (10.6%) cases, overtreatment had been performed. Multiple logistic regression analysis showed that the number of suicidal attempts, number of ingested pills, and time of referral had positive relationships with acetaminophen plasma level.

Conclusion: If NAC is prescribed only based on patient's medical history, overtreatment may take place.

Keywords: Acetaminophen, Plasma level, Poisoning.

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INTRODUCTION

Acetaminophen (N-acetyl-p-aminophenol [APAP]) poisoning is quite common. It may lead to acute liver failure (ALF). Mitchell and his colleagues described metabolic changes of acetaminophen which would lead to liver damage for the first time (1). In England,

the ratio of poisoning with acetaminophen matched up to other drugs was approximately 14.3% in 1976, 42% in 1990, and 47.8% in 1993 (2,3). The trend has been the same in other countries such as Australia and Denmark (4,5). A multi-center study conducted in England between March 2000 and August 2001 showed that

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overdose of acetaminophen was the most frequent way for self-poisoning which was more common in the younger age group (6). According to the American Association of Poison Control Centers TESS, acetaminophen was responsible for more than 26,000 visits to health care facilities and approximately 74 deaths in the United States in 2008 alone (7). Currently, acetaminophen poisoning is the most common cause of ALF in both the United States and the United Kingdom (8).

N-acetyl-cysteine is an effective antidote for acetaminophen intoxication. One of the major dilemmas in treatment of acetaminophen intoxication is the right selection of patients who need antidote. The amount of drug ingestion and its plasma level using Rumack-Matthew nomogram are common approaches for determining necessity of administration of antidote. If treatment is started earlier than 8 hours after the overdose, the result will be satisfactory; however, delay in treatment reduces the efficiency of antidote. In some medical centers, such as the Poisoning Center of Loghman Hakim Hospital, a poisoning referral center in Iranian capital, Tehran, administration of antidote is based on the amount of drug ingested according to patient's history rather than Rumack-Matthew nomogram, because of the large number of the patients and inability to determine plasma acetaminophen concentration in a timely manner during the golden time of the treatment. In the Poisoning Center of Loghman Hakim Hospital, the toxic dose of acetaminophen is defined more than 7.5 g in adults or 150 mg/kg in children. There are some different definitions for toxic dose in other centers like 10 or 12 g in adults or 200mg/kg of acute acetaminophen ingestion (9,10). For evaluation of the defined toxic dose, it is necessary to measure serum acetaminophen level and compare it with the nomogram. Some reports have shown that the medical history of poisoned

patients may not be reliable and may be clinically misleading (11-14). In contrast, others have found that the reported doses of paracetamol have a close relationship with toxic plasma levels (15,16).

The present study was designed to prospectively examine connection of patients' history with plasma level of acetaminophen which was measured by HPLC to find whether the reported dose of ingested paracetamol has relationship with plasma acetaminophen. Moreover, the patient's gender, age, frequency of suicidal attempts, the dose of the drug or number of the tablets ingested and the time interval between ingestion and hospital admission were also determined to find the main risk factors for ingestion of more toxic levels of acetaminophen in history.

MATERIALS AND METHODS

This study was carried out prospectively on 170 patients admitted to Loghman Hospital between March 2007 and 2008. The inclusion criteria were consumption of more than 7.5 g acetaminophen during 3 to 24 hours before admission based on patient's history and antidote administration. Exclusion criteria were history of viral liver diseases, metabolic disorders, chronic liver diseases, storage diseases, chronic and acute alcohol consumption, use of any drug that could interact with acetaminophen metabolism, non-acute ingestion and uncertainty about the time of ingestion. Blood samples were taken from the patients and stored in tubes containing EDTA. The plasma was removed during two hours after sampling, and concentration of acetaminophen was determined using HPLC method. Water and methanol were used as variable phase and caffeine as the HPLC's internal standard. After admission and stabilizing patient's psychosomatic symptoms, more detailed and reliable history was taken in non-stressful condition without interrupting the course of the treatment, while assuring the patients about privacy

of the information. The information gained from the patients included their gender, age, number of suicidal attempts, amount of drug ingested, and time interval between intoxication and hospital admission. Data were matched against results of serum acetaminophen concentration. Then the acetaminophen concentrations were matched against Rumack-Matthew nomogram in relation to time interval between drug use and blood sampling.

Statistical analysis was performed using SPSS software V. 16.0. Quantitative variables were described by mean, standard deviation, and range while qualitative variables were reported with relative and absolute frequencies. Chi-square test was used to assess the relationship between qualitative variables and correlation coefficient was used to assess quantitative variables relationship. Moreover, linear regression test and generalized linear models were used to determine the effect of one variable after omitting the tampered effect of others. P-values less than 0.05 were considered statistically significant. Ethical concerns were taken into consideration in the study. The study was approved by the Local Ethical Committee of Forensic Medicine. The patients were informed about the reasons for blood samplings and there was no interference with their treatment course. Also, the patients were assured that their information will be kept confidential and the contents of their hospital record would not be disclosed.

RESULTS

The study population consisted of 170 patients including 76 males (44.7%, CI 95% 37.2-52.2%) and 94 females (55.3%, CI 95% 47.8-62.8%). The mean age of the patients was 21.8 ± 6.05 years.

Plasma levels of APAP were between <2 and 265 with mean of 18.7 ± 28.9 $\mu\text{g/ml}$. Overall, 18 patients

(10.6%, CI 95% 6.0-15.2%) had serum acetaminophen concentrations above treatment line in Rumack-Matthew nomogram, from whom 7 (4.1%, CI 95% 1.1-7.1%) were male and 11 (6.5%, CI 95% 2.8-10.2%) were female.

There was not a statistically significant relationship between sex and the drug toxic levels requiring antidote administration ($P=0.627$).

Based on arrival history, all patients had ingested more than 7.5 g acetaminophen and had been admitted for antidote therapy, but after early treatments and stabilizing patients' symptoms, more detailed history revealed that only 84 patients (49.4% CI 95% 41.9-56.9%) confirmed the arrival history, from whom 45 (53.5%) were male and 39 (46.5%) were female.

Moreover, 32 patients (18.8%, CI 95% 12.9-24.7%) who had consumed more than 7.5 g acetaminophen based on detailed history had toxic serum acetaminophen concentrations, whereas only 4 patients (2.4%, CI 95% 0.1-4.6%) with history of less than 7.5 g drug consumption had had toxic serum acetaminophen concentrations. There was a statistically significant relationship between the presence of toxic serum acetaminophen concentrations and history of ingestion of more than 7.5 g APAP based on detailed history ($P < 0.005$).

Absolute as well as relative distribution of the patients with toxic and non-toxic serum acetaminophen concentrations in proportion to age groups showed the higher prevalence of poisoning (97 patients [57%, CI 95% 49.6-64.5%]) in the third decades of life while 88 (90.7%) of them had serum acetaminophen concentrations less than treatment line. There was not a statistically significant relationship between age groups and toxic serum acetaminophen concentration ($P=0.406$).

Table1. Distribution of toxic plasma level of APAP and APAP ingestion dose through patients' detailed history in different age groups

Age groups	Plasma level= toxicN(%) in age group	Ingestion dose >7.5 g N(%) in age group	Total N(%) of all age groups
10-19	9(14.5%)	30(48.4%)	62(36.5%)
20-29	9(9.3%)	47(48.5%)	97(57.1%)
30-39	0(0%)	7(87.5%)	8(4.7%)
40-49	0(0%)	0(0%)	1(0.6%)
50-59	0(0%)	0(0%)	1(0.6%)
60-69	0(0%)	0(0%)	1(0.6%)

Overall, 128 patients (75.3%, CI95% 68.8-81.8%) had had suicidal attempts for the first time; amongst them 46 cases (35.9%) were in the second decade of their life and 74 (57.8%) were in the third decade of their life. No more than four suicidal attempts had been reported.

On the other hand, 160 patients (94.1%, CI95% 90.6-97.7%) with serum acetaminophen concentrations higher than treatment line had positive history of previous suicidal attempts. There was a statistically significant relationship between the number of suicidal attempts and serum acetaminophen concentration (P-value=0.001).

To reveal any association between different variables and serum acetaminophen concentrations, logistic regression analysis was performed. Only the number of suicidal attempts (OR 69.9, CI 95% 7.55-647.7), number of ingested pills (OR 1.06, 95%CI, 1-1.13), and each 3 hours of latency between drug consumption and sampling (OR, 2.74, 95%CI, 1.35-5.56) presented significant relationships with serum acetaminophen concentrations.

DISCUSSION

A total of 170 patients had been admitted for NAC therapy due to acute ingestion of more than 7.5 g acetaminophen in their arrival history; however, after determination of serum acetaminophen concentration and comparing it with Rumack-Matthew

nomogram, only 18 (10.6%) cases actually had needed treatment.

However, 16 (19%) cases had serum acetaminophen concentration higher than treatment line based on detailed history. Despite the presence of a significant relationship between serum acetaminophen concentration and history of ingestion of more than 7.5 g APAP, there were many patients who had been given NAC despite serum acetaminophen concentrations lower than treatment line in Rumack-Matthew nomogram.

There might be many reasons that contribute to the discrepancy, such as inability of the patients to remember exact time and amount of drug consumption. This happens since the patients are under stress and psychological crisis and might possibly try to attract more attention by expanding the problem. It may be possible too that they are unable to remember what had happened quite involuntarily. Consumption of other drugs which can change the rate of acetaminophen absorption may produce discrepancy between expected serum acetaminophen concentration and actual level as well. Concurrent use of narcotics may postpone the drug absorption, while anti-diarrheal drugs do not noticeably affect the rate of acetaminophen absorption (17). When there is latency in esophageal transit, peak plasma acetaminophen concentration is lower and it occurs 70 minutes later than the expected time on average (18). Consumption of different forms of acetaminophen, such as tablets or elixirs,

creates different plasma levels according to different conditions of consumption, like after or before meal. These differences are due to diverse bioavailability of various forms of the drug. In older people, the drugs systemic bioavailability is less than young people; however, it does not considerably change the therapeutic dose of the drug (19). Different diets may also change the amount of drug absorption. The absorption is delayed considerably with hydrocarbon-rich diets, and the drug urinary excretion is less during the initial hours. In protein- and fat-rich diets, no significant disparity is observed (20). A study over different races revealed some differences in acetaminophen's pharmacokinetics after single-dose APAP ingestion. For instance, absorption takes place faster in Chinese. Glucuronidation is less than sulfation in Chinese, too. In Chinese, the peak plasma concentration is more than Caucasians and they reach the peak faster (21).

In a Norwegian study performed on 158 poisoning cases, NAC was initiated for 68% of them after they had claimed to have consumed more than 10g acetaminophen. The treatment had been discontinued in 79% of them after it was clear that their plasma acetaminophen level was lower than the treatment line (17). Therefore, it seems that if treatment is initiated solely based on the patient's history, the antidote will be prescribed more than required.

In general, acetaminophen poisoning happens among young adults (22-23-24) while a greater portion of the lethal poisonings is seen among older age groups (23). Between 1995 and 2003, a study in Denmark performed on 1019 patients explained that paracetamol poisoned patients generally aged between 15 and 24; however, hepatotoxicity mostly took place in cases older than 40 years (24).

In the present study, the mean age of the patients was 21.8 years, but patients with suicidal attempts were only 3 of the 170 cases were older than 40. All of them

had high, but not over the treatment line, serum acetaminophen concentrations. Similar to other studies (25-27), young girls, especially those that aged 17-20 years, are the group with highest prevalence of acetaminophen poisoning. Although older age and male sex are the two known risk factors in committing suicide, the concept of safety of acetaminophen and its wide availability have possibly led to the frequent use of it by females. However, in spite of the relative prevalence of acetaminophen poisoning among females, the current study did not find a significant relationship between gender and severity of poisoning as measured by serum acetaminophen concentration more than treatment line and therapeutic range (more than 20 microgram in deciliter). Also, there were no significant relationships among various age groups with severity of poisoning and the need for treatment with antidote.

The present study assessed the validity of medical history for management of acetaminophen-intoxicated patients whose risk for hepatotoxicity cannot be measured by Rumack-Matthew nomogram within the first 8 hours of poisoning. Patients who consumed more than 7.5 g acetaminophen according to their history had more serum acetaminophen concentrations and their chance for finding over treatment line serum acetaminophen concentration was 1.06 (1-1.13) times more for every additional ingested tablet. Waring *et al.* showed that positive history of acute ingestion of more than 12 g acetaminophen increased the risk of hepatotoxicity (10). In situations that the patient is conscious and denies ingestion of acetaminophen, toxic and even positive serum acetaminophen concentration is unlikely; however, it is better to check serum acetaminophen concentrations in patients who have low levels of consciousness and in countries where poisoning with acetaminophen is frequent (28).

The number of previous suicidal attempts and time interval between drug ingestion and hospital admission positively affect serum acetaminophen concentration. More frequent suicidal attempt by a patient shows that the patient is highly motivated to succeed in his/her decision. Moreover, it shows inappropriate psychological status which might lead to the use of acetaminophen at toxic levels. Circumstances in which the patient refers to medical center with delay probably demonstrate patient's determination in committing suicide. Also, since symptoms of acetaminophen poisoning appear with delay, the patient may seek medical help only when the symptoms have appeared.

CONCLUSION

The findings of the present study suggest that patients tend to overestimate quantity of drug ingestion; however, there is some information in patient's history which has a close connection with the higher risk of poisoning. In conditions with high-dose drug consumption, positive history of committing suicide with drugs, and long time interval between drug ingestion and hospital admission, the risk of toxicity is higher and patients need more attention. In these situations antidote must be prescribed earlier rather than waiting for measurement of drugs plasma level.

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