Iranian Journal of Toxicology
ARAK UNIVERSITY OF MEDICAL SCIENCES
October 2021, Volume 15, Number 4

Research Paper:

A Basis for the Decision to Rule in or out Acetaminophen Toxicity: Assessment of the Serum Level Within 4 Hours Post Overdose

Nima Nabavi[1], Mohammad Moshiri[2], Shahrad Tajoddini[3], Bita Dadpour[2*]

1. Student Research Committee, School of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran.
2. Medical Toxicology Research Center, School of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran.
3. Department of Emergency Medicine, Neuroscience Research Center, Institute of Neuropharmacology, Kerman University of Medical Sciences, Kerman, Iran.

Use your device to scan and read the article online

How to cite this paper Nabavi N, Moshiri M, Tajoddini S, Dadpour B. A Basis for the Decision to Rule in or out Acetaminophen Toxicity: Assessment of the Serum Level Within 4 Hours Post Overdose. Iranian Journal of Toxicology. 2021; 15(4):265-270. http://dx.doi.org/10.32598/ijt.15.4.820.1

http://dx.doi.org/10.32598/ijt.15.4.820.1

Article info:
Received: 24 Apr 2021
Accepted: 03 Jul 2021
Online Published: 01 Oct 2021

***Corresponding author:**
Bita Dadpour, MD.
Address: *Medical Toxicology Research Center, School of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran.*
E-mail: *dadpourb@mums.ac.ir*

ABSTRACT

Background: Acetaminophen is a popular antipyretic and analgesic medication worldwide; however, its therapeutic window is narrow, which may lead to overdose or toxicity. This study was conducted to assess the correlation between the serum acetaminophen levels before and 4 hours after the acute toxicity with this drug. The objective of this study was to test the validity of the serum level to arrive at a clinical decision on the toxicity with acetaminophen.

Methods: This cross-sectional study was performed on patients hospitalized and treated with a diagnosis of acute acetaminophen overdose during one year (Sept. 2018 to Sept. 2019) at the Toxicology Department of Imam Reza Hospital, Mashhad, Iran. Patients were analyzed for demographics, time of ingestion, their first and second serum acetaminophen concentrations.

Results: A total of 204 patients (106 male & 98 female) were included in this study. The average dose of acetaminophen ingestion by these patients was 14.5±3.50 g and all patients were treated successfully with N-Acetyl-Cysteine (NAC). The variables of age (P=0.293), serum acetaminophen levels at 1-2 h (P=0.679), and at 2-3 h (P=0.126) did not have significant relationships with the serum acetaminophen level on the fourth hour. However, the serum acetaminophen levels tested between 3-4 h and acetaminophen intoxication dosage had significant relationships with the acetaminophen level on the fourth hour.

Conclusion: In patients with acute acetaminophen toxicity, the data on the serum levels obtained before a 4-hour timepoint from the ingestion were not useful to decide on the need for the rescue treatment with N-acetyl-cysteine.

Keywords: Acetaminophen, Acetylcysteine, Drug-related side effects, Adverse Reactions, Rumack-Matthew nomogram, Drug toxicity

Introduction

Acetaminophen or paracetamol (N-acetyl-para-aminophenol) is one of the most common and available antipyretic and analgesic medications worldwide [1]. Despite the fact that acetaminophen is an effective and safe drug at normal dosage, its therapeutic window is narrow, such that it is often overused intentionally or accidentally. The most common complication of acetaminophen toxicity is severe liver injury, which may progress to acute liver failure [2]. The acetaminophen toxicity is responsible for approximately 56,000 emergency room visits per year and is also the most common cause of liver transplantation in the United States

[DOR: 20.1001.1.20082967.2021.15.4.7.2]
[DOI: 10.32598/IJT.15.4.820.1]

and the second most common worldwide. Therefore, this toxicity is a significant clinical problem [3, 4].

To prevent the acetaminophen hepatotoxicity, treatment with N-Acetyl-Cysteine (NAC) should be initiated as soon as possible within first 6 h post ingestion, and based on its serum concentration as determined by the Rumack-Matthew nomogram [5]. To use this nomogram reliably, the serum levels from 4-24 h post-ingestion should be used. This starting point was chosen because of the initial data available at the time of nomogram production and the possibility of delayed drug absorption [5, 6]. On the other hand, acetaminophen is absorbed rapidly and reaches the serum peak level within one hour of the ingestion, suggesting that early serum levels can be predictive of the toxicity [5]. Moreover, the acetaminophen serum level before 4 h from the ingestion can help accelerate the patient care decisions in the emergency rooms [7, 8].

A study by Douglas et al. [8] concluded that the serum concentrations between one and 4 h after acetaminophen ingestion can accurately predict the treatment requirements. Several case reports have indicated that the acetaminophen serum level continue to rise 4 h post-ingestion, especially due to multi-drug uses or massive overdose with acetaminophen [9-11]. However, few studies that have been conducted on this subject, have yielded conflicting results. To resolve this issue, we conducted this study and evaluated the correlation between the acetaminophen serum levels before and after the 4-hour timepoint from the acetaminophen ingestion in patients who presented to the emergency room at a general hospital with symptoms of acute intoxication with this drug.

Manterials and Methods

Study design and subjects: This cross-sectional study was conducted on patients hospitalized and treated with acute acetaminophen overdose diagnosis from September 2018 to September 2019 in the Toxicology Department of Imam Reza Hospital, in Mashhad, Iran.

Inclusion and exclusion criteria: All patients presented to the emergency department at Imam Reza Hospital between 1 and 4 h of acute acetaminophen ingestions were included voluntarily in this study. Patients who had a past medical conditions, co-ingestion of drugs, unknown ingestion time, undetectable acetaminophen serum levels, and those with chronic acetaminophen usage were excluded from the study.

Methods: Serum acetaminophen concentration tests were performed twice for all patients who met the inclusion criteria. The first test was conducted at admission, i.e., <4-hr post-ingestion, and the second one was repeated at ≥4-hour post-ingestion. All serum acetaminophen concentration test samples were read on a spectrophotometer (Pharmacia LKB Novaspec II, Cambridge, UK) in the central laboratory of the Hospital. For each patient, the age, sex, exact time of ingestion, the time and data for the first and second acetaminophen serum concentration tests were recorded.

Data analyses: After collecting the data, they were analyzed on SPSS software, version 22. Pearson's correlation coefficient test was used to evaluate the relationship between the serum acetaminophen levels, obtained regularly, starting shortly after admission and then hourly thereafter, up to 4 h post-ingestion. Using Pearson's multiple correlation analysis, all variables, such as age, acetaminophen dosage, and the serum concentrations representing before and after 4 h were entered into the statistical model. The variables that had the least statistical correlation with the dependent variable, i.e., the serum concentration for the fourth hour, were excluded from the model. A P-value less than 0.05 was set as the statistical significance for all variables.

Ethical consideration: A written study protocol and informed consent letter were available for review and signing by the patients prior to inclusion in the study. Moreover, the study protocol was fully approved by the Ethics Committee of Mashhad University of Medical Sciences (Registered #: IR.MUMS.fm.REC.1396.516) prior to the implementation.

Results

Study population: A total of 204 patients, consisting of 98 females (48%) and 106 males (52%) were enrolled in the study voluntarily. The mean patients' age was 40.85±2.25 years old with the minimum and maximum being 18 and 56 years old, respectively. The average dose of acetaminophen ingested by the patients was 14.5±3.50 g, all of whom were treated successfully with NAC prior to discharge from the hospital.

Upon Pearson's multiple correlation analyses of all variables, i.e., age, acetaminophen intoxication dosage, the serum concentrations for the first, second and third hours post ingestion, only two variables correlated well with the serum acetaminophen levels at 4-hour post ingestion. These were the serum acetaminophen levels representing the 3-4 h post ingestion and the acetaminophen dosage that caused the toxicity (Table 1).

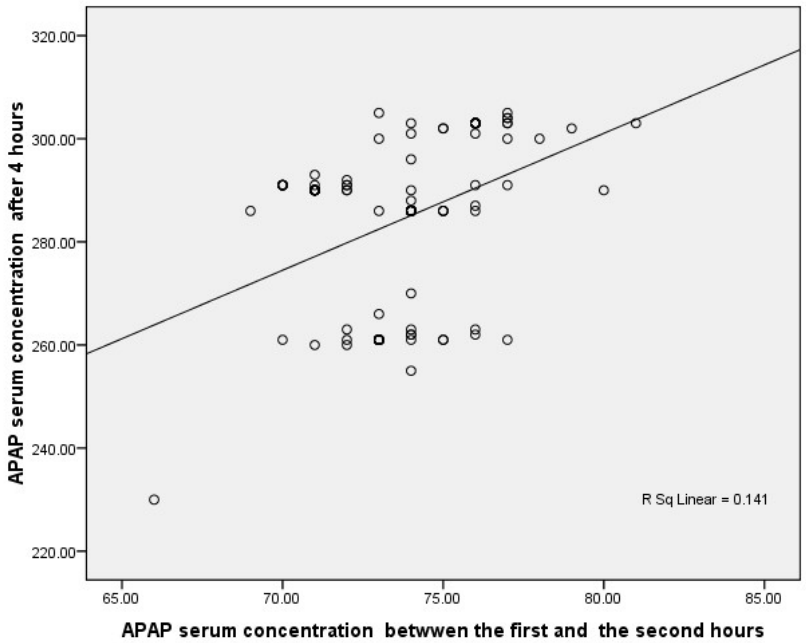

Figure 1. Correlation of serum acetaminophen levels between the first and second hours with that of post four hours

APAP: Acetaminophen.

The acetaminophen level versus gender: In men, if the serum acetaminophen level was greater than 66 µg/mL on the first hour, the acetaminophen serum level on the fourth hour could be estimated reliably (r=0.141, P<0.001), which would approximately be 2.655±0.553 (CI= 1.65-3.55; P<0.001) multiplied by the acetaminophen concentration on the first hour (Figure 1).

The serum acetaminophen levels for women measured between the 3rd and 4th h could only estimate 19% (P=0.040) of the level on the fourth hour (β=1.307±0.52, CI= 0.8-2.06, P=0.044).

Discussion

Upon admission, for most patients with acute acetaminophen exposure who presented to the Emergency Department within 4 h post-ingestion, their serum samples were sent to the laboratory for chemistry analyses. However, the serum acetaminophen concentrations during this time could not be used to determine the need for NAC therapy, because they could not be plotted on the Rumack-Matthew nomogram. The best time for starting the NAC therapy was between 6 to 8 h post-ingestion. During this period, the risk of possible hepatotoxicity from acetaminophen was minimal compared to starting the NAC therapy earlier [12, 13]. Our results demonstrated that the acetaminophen concentration within less than 3 h post-ingestion could not be useful for making clinical decisions at all. Conversely, the serum acetaminophen concentrations obtained within 3-4 h post-ingestion significantly correlated with the concentrations obtained after 4 h from the ingestion.

In a study conducted by Froberg et al. [6] between 2009 and 2011, 83 patients with acute acetaminophen exposure were evaluated for the Negative Predictive Value (NPV) of serum acetaminophen concentrations within 4 h post-ingestion. They reported that a serum acetaminophen concentration of less than 100 µg/mL obtained prior to 4 h post-ingestion, had 98.8% NPV for excluding the toxicity threshold (95%CI). However, due to the potential false-negative rate of 6.5%, they did not recommend the use of serum concentrations prior to four hour from the acetaminophen ingestion to reliably rule out the toxicity [6]. Similarly, Douglas et al. [8] demonstrated that a serum acetaminophen concentration of <100 µg/mL obtained between one and 4 h post-ingestion, had 94.6% NPV. They concluded that the serum level could be used to exclude the need for the rescue treatment [8]. Although the findings of Froberg et al. [6] were similar to those of Douglas et al. [8], they offered different and unclear conclusions.

In another study on 2454 patients conducted by Yarema et al. [7], the serum acetaminophen levels obtained within 2-4 h post-ingestion had a sensitivity of 96% and an NPV of 70%. Also, the co-ingestion of anti-muscarinic

Table 1. Correlation of either age, acetaminophen intoxication dosage, or serum

Variables	Correlation		Regression
	R^2	P	Unstandardized Coefficients β (95%CI)
Serum acetaminophen levels at 1-2 h	0.0001	0.679	0.059 (-0.222 - 0.314)
Serum acetaminophen levels at 2-3 h	0.04	0.126	0.222 (-0.603 - 0.506)
Serum acetaminophen levels at 3-4 h	0.54	<0.001	0.596 (+0.336 - 0.855)
Age (y)	0.03	0.293	0.006 (-0.05 - 0.17)
Acetaminophen intoxication dosage	0.190	<0.001	2.943 (+2.314 - 3.578)

Acetaminophen levels <4 h with serum acetaminophen levels ≥4 h.

drugs reduced the sensitivity to 86%, and with opioids to 91%. They stated that the ruling decisions based on acetaminophen concentrations in the first 4 h after an acute overdose were not yet established at that time. A cut-off limit of 100µg/mL may sometimes lead to miss the dangerous acetaminophen exposures [7]. Another retrospective, observational study demonstrated that pre-4-hour acetaminophen levels could not be used to decide for NAC therapy [14]. They also reported that co-ingestions of anti-cholinergic or opioid drugs with long-term absorption rates, can delay the NAC rescue therapy [14].

Conclusions

In conclusion, in patients with acute acetaminophen intoxication who present to emergency rooms within the first 4 h after exposure, laboratory data obtained before the 4-hour landmark for the serum acetaminophen levels are not useful to decide the need for NAC therapy. Conversely, the serum acetaminophen data obtained after the 4-hour timepoint are reliable to rule in or out the need for NAC therapy. It is also recommended to use the Rumack-Matthew nomogram to determine the need for the rescue therapy.

Ethical Considerations

Compliance with ethical guidelines

The ethical aspects, including plagiarism, data fabrication, double publication, have been completely observed by the authors. Moreover, the study protocol was fully approved by the Ethics Committee of Mashhad University of Medical Sciences (Registered#: IR.MUMS.FM.REC.1396.516).

Funding

This study was supported by Mashhad University of Medical Sciences (Grant No:# 960722).

Author's contributions

Conceptualization, funding acquisition and resources and supervision: Bita Dadpour, Mohammad Moshiri, Shahrad Tajoddini; Methodology: Bita Dadpour, Shahrad Tajoddini; Investigation, writing – original draft, and writing – review & editing: Nima Nabavi, Bita Dadpour, Mohammad Moshiri; Data collection: Bita Dadpour, Mohammad Moshiri, Shahrad Tajoddini; Data analysis: Bita Dadpour, Mohammad Moshiri.: Bita Dadpour.

Conflict of interest

The authors declared no conflict of interest.

References

[1] Ramachandran A, Jaeschke H. Acetaminophen Hepatotoxicity. Semin Liver Dis. 2019; 39(2):221-34. [DOI:10.1055/s-0039-1679919] [PMID] [PMCID]

[2] Ramachandran A, Jaeschke H. Acetaminophen toxicity: Novel insights into mechanisms and future perspectives. Gene Expr. 2018; 18(1):19-30. [DOI:10.3727/105221617X15084371374138] [PMID] [PMCID]

[3] Agrawal S, Khazaeni B. Acetaminophen toxicity. Statpearls [Internet]. [Last Update: July 18, 2021]. [PMID]

[4] Caparrotta TM, Antoine DJ, Dear JW. Are some people at increased risk of paracetamol-induced liver injury? A critical review of the literature. Eur J Clin Pharmacol. 2018; 74(2):147-60. [DOI:10.1007/s00228-017-2356-6] [PMID] [PMCID]

[5] Rumack BH. Acetaminophen hepatotoxicity: The first 35 years. J Toxicol Clin Toxicol. 2002; 40(1):3-20. [DOI:10.1081/CLT-120002882] [PMID]

[6] Froberg BA, King KJ, Kurera TD, Monte AA, Prosser JM, Walsh SJ, et al. Negative predictive value of acetaminophen concentrations within four hours of ingestion. Acad Emerg Med. 2013; 20(10):1072-5. [DOI:10.1111/acem.12222] [PMID]

[7] Yarema MC, Green JP, Sivilotti ML, Johnson DW, Nettel-Aguirre A, Victorino C, 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. 2017; 55(2):102-8. [DOI:10.1080/15563650.2016.1247959] [PMID]

[8] Douglas D, Smilkstein M, Rumack B. APAP levels within 4 hours: Are they useful? Vet Hum Toxicol. 1994; 36(4):356. https://eurekamag.com/research/029/832/029832309.php

[9] Doyon S, Klein-Schwartz W. Hepatotoxicity despite early administration of intravenous N-acetylcysteine for acute acetaminophen overdose. Acad Emerg Med. 2009; 16(1):34-9. [DOI:10.1111/j.1553-2712.2008.00296.x] [PMID]

[10] Smith SW, Howland MA, Hoffman RS, Nelson LS. Acetaminophen overdose with altered acetaminophen pharmacokinetics and hepatotoxicity associated with premature cessation of intravenous N-acetylcysteine therapy. Ann Pharmacother. 2008; 42(9):1333-9. [DOI:10.1345/aph.1K680] [PMID]

[11] Spyres MB, O'Connor AD, Gerkin RD. Limitations of the evidence supporting use of undetectable acetaminophen levels obtained< 4 hours post-ingestion to rule out toxicity. Clin Toxicol (Phila). 2017; 55(5):366. [DOI:10.1080/15563650.2017.1284335] [PMID]

[12] Sivilotti ML, Yarema MC, Juurlink DN, Good AM, Johnson DW. A risk quantification instrument for acute acetaminophen overdose patients treated with N-acetylcysteine. Ann Emerg Med. 2005; 46(3):263-71. [DOI:10.1016/j.annemergmed.2005.04.004] [PMID]

[13] Yarema MC, Johnson DW, Berlin RJ, Sivilotti ML, Nettel-Aguirre A, Brant RF, et al. Comparison of the 20-hour intravenous and 72-hour oral acetylcysteine protocols for the treatment of acute acetaminophen poisoning. Ann Emerg Med. 2009; 54(4):606-14. [DOI:10.1016/j.annemergmed.2009.05.010] [PMID]

[14] Seifert SA, Kirschner RI, Martin TG, Schrader RM, Karowski K, Anaradian PC. Acetaminophen concentrations prior to 4 hours of ingestion: Impact on diagnostic decision-making and treatment. Clin Toxicol (Phila). 2015; 53(7):618-23. [DOI:10.3109/15563650.2015.1059942] [PMID]

[DOR: 20.1001.1.20082967.2021.15.4.7.2]

[DOI: 10.32598/IJT.15.4.820.1]

This Page Intentionally Left Blank