



Supratherapeutic Dosing of Acetaminophen in Iranian Hospitalized Adult Patients

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Abstract

Acetaminophen is the most commonly used analgesic and fever-lowering agent that is prescribed in a high percentage of patients. Due to the high prevalence of the administration of this drug, even a small percentage of errors in prescription can be significant and have important implications. The aim of the present study was to determine the frequency of supratherapeutic dosing of acetaminophen among hospitalized adult patients and its association with clinical outcomes. We conducted a retrospective, cross sectional study of all hospitalized adult patients in a teaching hospital affiliated to Mashhad University of Medical Sciences, Mashhad, Iran. During the three-month study period, 4,781 (24.83%) out of 19,252 hospitalized cases received acetaminophen. Of those who received acetaminophen, 264 (5.5%) cases received a supratherapeutic dose at least once. Of 611 incidences of *supratherapeutic dosing*, 99.1% occurred in surgical wards and surgical intensive care units (ICUs), and 98.8% was associated with receiving parenteral formulations of acetaminophen. Multivariate analysis indicated supratherapeutic dosing of acetaminophen was significantly associated with multiple factors including female gender, older age, and longer length of hospital stays. All things considered, the percentage of hospitalized adult patients who received any dose of acetaminophen at our center was considerably less than other countries. Despite this, the frequency of instances of supratherapeutic dosing of this medication was significant (i.e. 17.6 days per 1,000 patient-days). Considering recent reports concerning the risk of hepatotoxicity associated with the repeated use of supratherapeutic doses of acetaminophen, continuous monitoring of acetaminophen utilization in order to prevent these instances is needed. Furthermore, based on the low percentage of patients who receive acetaminophen at our center, conducting research to study the pattern of prescription of analgesics and antipyretics in our center and its association with clinical outcome is logical.

Keywords: Acetaminophen, Supratherapeutic, Hepatotoxicity, Parenteral formulation, Analgesic, Antipyretic

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1. Introduction

Acetaminophen is the most commonly used analgesic and fever-lowering agent that is prescribed for a great majority patients in outpatient and inpatient settings. [1] The administration of this drug with doses less than 4 g is considered to be low-risk and safe. However, acute overdosing, repetitive doses greater than 4 g to 6 g per day, and lower doses in certain groups may be associated with liver toxicity [2-4]. Due to the high prevalence of the administration of this drug, even a small percentage of errors in prescription can be significant and have grave ramifications. [5]

The cases of acetaminophen-related liver toxicity can be divided into two groups: intentional (suicidal) and unintentional or accidental (due to high and multiple doses in the therapeutic range, usually for longer than three days). Many cases of overdoses of acetaminophen (up to 50% of cases) occur unintentionally and among acetaminophen-related deaths, about 20% of the cases were due to unintentional overdoses. [1, 2, 6] Unintentional overdoses of acetaminophen occur for a variety of reasons including unintentional overdoses of acetaminophen occurring in children below six years of age,

therapeutic misadventures (defined as taking supratherapeutic acetaminophen doses in order to achieve further effects), the intentional use of drugs prescribed for another person to relieve symptoms, and medication errors (for example, in taking, prescribing, or distributing drugs).

In recent years, despite the fact that much attention has been paid to the unintentional consumption of acetaminophen doses in the supratherapeutic range and the associated damage, little attention has been given to the pattern of use for this drug in hospitalized patients as well as to its unintentional overdoses in hospitalized patients. [3, 7, 8] In this respect, a handful of studies have shown that about 1% to 7% of hospitalized patients were exposed to supratherapeutic doses of acetaminophen, which has been associated with a significant increase in liver enzymes in patients. [3, 7] This frequency is estimated significantly higher for elderly patients and people with underlying liver disease. [7] Given the high frequency of acetaminophen prescription in hospitals, even a small percentage of costs and adverse effects can be significant. The aim of the present study was to examine the pattern of acetaminophen administration and the frequency of overdoses in hospitalized adult patients in a large teaching hospital in Iran, as a developing country. To the best of our knowledge, this is the first study to investigate the supratherapeutic prescription of acetaminophen in hospitalized adult patients in Iran and in other developing countries.

2. Material and Methods

Location and Date of Study: This study was conducted at Imam Reza Hospital, a 1000-bed general teaching hospital located in Mashhad. The study period lasted from April 2014 to May 2014.

Study Design: The study adhered to a retrospective cross-sectional design. The inclusion criteria for the study encompassed all the adult patients (15 years old and above) admitted to Imam Reza Hospital for any reason and had received at least one dose of acetaminophen in any form during the study period.

The data was collected through retrospective reviews of electronic and non-electronic health records. In this study, cumulative daily dose of at least 4 g or more in the people aged under 65 years and without underlying liver disease as well as a cumulative daily dose of 3 g or more in elderly people (65 years or older) or those with underlying liver disease were considered as supratherapeutic doses. [9-11]

For the patients who had received at least one dose of supratherapeutic acetaminophen, the following parameters were calculated and reported:

- The number of cases with at least one incidence of supratherapeutic dosing of acetaminophen.
- The number of days of supratherapeutic dosing of acetaminophen per 1,000 patient-days.

- Dosage form(s) of acetaminophen administered in the patients who received supratherapeutic dose(s).

- Hospital wards where the supratherapeutic dosing of acetaminophen occurred.

Age and sex distribution, length of hospital stay, (LOS) and clinical outcome (mortality) were also compared in case of the patients receiving supratherapeutic doses of acetaminophen and those receiving acetaminophen in the therapeutic range.

Statistical Methods and Sample Size: Patient data management was performed in the first phase using the Microsoft SQL Server database and data analysis was conducted in the final stage using SPSS software. The data concerning demographic and clinical observations of patients were analyzed using Chi square and Mann Whitney tests. Uni and multivariable logistic regression models (backward method) were used to find the association between independent variables and the accuracy of receiving supratherapeutic doses of acetaminophen. A P-value <0.05 was considered as the significance level.

Ethical Considerations: This research was approved by the Committee on Ethics of Mashhad University of Medical Sciences with the IR.MUMS.fm.REC.1394.579 code.

3. Results and Discussion

3.1. Results

A total of 19,252 adult cases were hospitalized in a three-month study period. Among these participants, 4,781 (24.83%) cases received acetaminophen. The median

age (25th percentile–75th percentile) was 43 (29–61) years. Here, 20.6% (986 out of 4,781 cases) of patients receiving acetaminophen were 65 years old or older. The female-to-male ratio of acetaminophen recipients was 1.23. Among those receiving acetaminophen, 264 (5.5%) cases took suprathreshold doses 117 (44.3%) of whom aged more than or equal to 65 years. There were only two (0.75%) cases with pre-existing liver disease. In total, 264 of 19,252 admitted patients, equivalent to 1.37% of all hospitalized adult patients, received acetaminophen at least for one day at a dose higher than therapeutic range (Figure 1).

A total of 34,715 patient-days were recorded in the hospital during the study period. Based on the results of, 611 suprathreshold acetaminophen-days were prescribed, which was equivalent to 17.6 suprathreshold acetaminophen-days per 1000 patient-days. Among these, 55 (9%) cases received greater than or equal to 5 g acetaminophen per day.

The average number of times each patient in the suprathreshold dosing group received acetaminophen at a suprathreshold level was 2.35 ± 2.2 (range, 1-15). In this respect, in 56.69% of the cases, the daily dose exceeded the maximum recommended dose for two days or longer. Besides, in 23.62% of the cases, it exceeded the maximum recommended daily dose for three days or longer.

356 (58.8%) suprathreshold acetaminophen-days were prescribed in surgical wards, eight (1.3%) days in the internal and burn wards, 246 (40.3%) days in surgical ICUs, and one (0.2%) day in the internal and burn ICUs. The dosage form(s) of acetaminophen prescribed in the suprathreshold dosing group was as follows: parenteral dosage form (Acetaminophen ampoule 1 g) in 604 (98.8%) cases, oral tablet (Acetaminophen tab 325 mg, 500 mg) in five (1%) cases, suppositories (Acetaminophen supp. 325 mg) (0%) in none of the cases, and acetaminophen combination products in three

Table 1. Results of univariate analysis of the association of patient-related factors with suprathreshold dosing of acetaminophen.

Variables	Suprathreshold Dosing of Acetaminophen			P value*
	Acetaminophen users, no (%) (n= 4781)	Yes (n= 264)	No (n= 4517)	
Sex				
Male	2143(44.8)	152 (57.6)	1992 (44.1)	<0.001*
Female	2637 (55.1)	112 (42.4)	2525 (55.9)	
Age, years				
15-29	1224(25.6)	24 (9.1)	1200 (26.6)	
30-49	1525(31.9)	50 (18.9)	1475 (32.7)	
50-64	1046(21.9)	73(27.7)	973 (21.5)	
≥ 65	986(20.6)	117 (44.3)	869 (19.2)	<0.001*
Length of Hospital Stay, median (interquartile), day	3 (7)	9 (8)	3 (7)	<0.001**
Crude in Hospital Mortality	254 (5.3)	15 (5.7)	239 (5.3)	0.4*

Table 2. Multivariate analysis of factors associated with supratherapeutic dosing of acetaminophen.

Factors	Univariable OR (95% CI)	P-value	Multivariable adjusted OR (95% CI)	P-value
Gender (Female)	1.72 (1.33-2.21)	<0.001	1.334 (1.030-1.728)	0.029
Age (Years)	1.031(1.024-1.037)	<0.001	1.028 (1.022-1.035)	<0.001
Length of hospital stay (days)	1.02 (1.01-1.03)	<0.001	1.022 (1.015-1.030)	<0.001

OR: odds ratio; 95% CI: 95% confidence interval

(0.5%) cases (adult cold tab and acetaminophen codeine tab).

The results of the univariate analysis of patient-related factors in supratherapeutic dosing of acetaminophen showed that, in females, participants of older ages and higher LOS were significantly associated with supratherapeutic dosing (Table 1).

In addition, the results of multivariate analysis of the above-mentioned factors showed a statistically significant association between the three variables of age, gender, and duration of hospitalization with supratherapeutic dosing of acetaminophen (Table 2).

The hospital mortality rate in the patients was 5.3% (254 out of 4,781 cases). In terms of the mortality rate in the two groups, there was no significant difference between the supratherapeutic dosing group and the one received acetaminophen at the therapeutic range (P-value: 0.8) (Table 1).

3.2. Discussion

In the present study, less than a quarter of hospitalized patients received acetaminophen 5.5% of which received

supratherapeutic doses. In this study, it was estimated that for every 1,000 patient-days of hospitalization, the risk of receiving acetaminophen in supratherapeutic doses was about 18 events. We found that almost all the patients that received acetaminophen with supratherapeutic doses were surgical patients who received parenteral dosage forms of acetaminophen. In addition, the findings demonstrated that the chance of supratherapeutic doses of acetaminophen was significantly higher among women in older ages, who were hospitalized for longer periods of time.

In recent years, several studies have been conducted on the issue of unintentional consumption of acetaminophen in supratherapeutic doses, especially in outpatient settings. However, little attention has been paid to the pattern of use of this drug in hospitalized patients and the intake of supratherapeutic doses in those settings. A review of the literature has shown only two studies addressing this issue. [7, 3]. The first multicenter study conducted in Boston, Massachusetts between June 2010 and August 2010 showed that, among 14,411 admitted

patients, 60.7% received acetaminophen among which in 6.6% of the cases, the daily dose exceeded the maximum recommended dose. In addition, their study showed that 22.3% of the patients above 65 years and 17.6% with chronic liver disease received acetaminophen at doses higher than the therapeutic range. [7] The other study was conducted in France between 2006 and 2011 the results of which showed that out of 44,404 prescriptions of acetaminophen in hospitalized patients, 404 (1%) cases received suprathereapeutic dosing. [3]

The results of the present study showed that, in contrast to the studies performed in other parts of the world [12], a much lower percentage of hospitalized patients received acetaminophen. In explaining these findings, there are several hypotheses which need to be addressed and verified in future studies. First, physicians in Iranian healthcare centers might be overly concerned about the administration of acetaminophen and prescribe it in the case of a small percentage of patients (as compared to other healthcare centers). Second, a majority of the physicians in Iranian healthcare centers might be excessively concerned about the administration of *higher doses* (within the therapeutic range) of acetaminophen and consequently prescribe it at lower doses. Last but not least, other sedatives and fever-lowering agents including narcotics and non-steroidal anti-inflammatory drugs (NSAIDs) might be administrated more frequently with the purpose of relieving symptoms and replaced acetaminophen (while acetaminophen is safer in lower doses of the drug). [6] The

latter assumption could be attributed to the willingness of doctors to prescribe the drugs, the insistence and interest of the patients, or the drug's ease of use compared to acetaminophen dosage forms.

Another important point in the present study was a very low percentage of patients with underlying liver disease who were exposed to suprathereapeutic doses of acetaminophen. It might be due to the low rate of overall prescription of high doses of acetaminophen in medical center. Another possible reason might be the fact that the physicians in healthcare centers are overly concerned about the safety of acetaminophen prescription in those with underlying liver disease. Although the present study did not compare liver enzymes and renal function in the two groups, previous studies showed that patients who received suprathereapeutic dosing of acetaminophen experienced a significant increase in alkaline phosphatase levels. [3] Moreover, in terms of the repeated suprathereapeutic ingestion of acetaminophen, it seems probable that not only the daily dose but also the number of consecutive days of acetaminophen ingestion is an important factor in acetaminophen-induced liver and kidney injury. [13] Kozer et al. also reviewed the reported cases of repeated suprathereapeutic doses of acetaminophen in children and concluded that those treated with higher doses for more than two days needed to be evaluated for possible liver injury. [8]

Given the importance of the unintentional toxicity of acetaminophen, especially in developed countries, the US Food and Drug

Administration recently convened a meeting with the participation of three advisory committees in order to consider the issue and explore several strategies to reduce the mortality and morbidity associated with this problem including the decrease in the maximum dose of acetaminophen from 4,000 mg to 3,250 mg [11]. Other strategies such as decreasing the maximum dose of acetaminophen existing in various dosage forms, and removing acetaminophen combination products, especially in combination with narcotics, have also been addressed elsewhere [2].

All things considered, it seems that the presence of clinical pharmacists specialist in pharmacotherapy (to monitor drug doses and related interactions) alongside physicians may help reduce errors in prescribing. In addition, due to the low percentage of acetaminophen prescription (regardless of dose) in this study, compared to other studies in the world, researchers suggest future studies to be conducted in order to examine the pattern of use of analgesics and fever-lowering agents in healthcare centers in the country. This is due to the fact that the use of other types of analgesics that can be potentially more harmful than acetaminophen may be an important issue to be considered.

This study had several limitations which need be pointed out. First, the results of a single-centered study in a teaching hospital cannot be guaranteed to be generalized to other medical centers in the country. However, our medical center is one of the largest

hospitals in the country and therefore encompasses a large volume of patients in the city and province. Second, drug dosage and therapeutic range based on the weight of the patients were not calculated due to the lack of an accurate measurement of weight in all cases. As noted in Zhou's study [7], the rate of supratherapeutic dosing of acetaminophen is probably underestimated, specially due to the lack of consideration of patients' weight (in order to adjust the dose with the weight); however, the patients in the present study were adults (and not children) so that this factor was less problematic. Third, the data lacked reliability since the researchers could not consider alcohol consumption due to cultural constraints in the community. This is despite the fact that alcohol consumption is one of the most important and risky factors in hepatotoxicity at higher doses of acetaminophen. The other limitation of the present study was the lack of the investigation of the use of other drugs at the same time, which could be a significant cause of liver toxicity in case of higher doses of acetaminophen in the therapeutic range.

4. Conclusion

The percentage of acetaminophen prescription in patients admitted to the medical center was significantly lower than that of previous studies conducted elsewhere in the world. However, the risk of receiving supratherapeutic dosing of acetaminophen was about 18 days per 1,000 patient-days, which was a significant amount. This was

significantly higher in women in older ages, who were hospitalized for longer periods of time. This was especially high in those hospitalized in surgical wards and received the parenteral dosage form. According to numerous reports on the likelihood of liver toxicity development and complications due to the use of multiple doses of acetaminophen at a high therapeutic or above therapeutic level, it seems that a careful monitoring of the prescription pattern for this drug is required to reduce the mistakes in its administration. In addition, due to the low percentage of acetaminophen administration in hospitalized patients in this study, it is suggested that studies be designed to determine the pattern of use of analgesics and fever-lowering agents in medical centers in the country as well as to examine the effects of specific prescription behaviors on the clinical outcome of patients' treatment.

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