



## A Drug Utilization Evaluation Study of Intravenous Acetaminophen in a Large Teaching Hospital

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### ABSTRACT

**Background:** Intravenous (IV) acetaminophen has become the most commonly chosen analgesic medication in critical care settings. Overall, the cost of the drug is higher than oral and rectal acetaminophen. As a result, numerous studies have been performed to evaluate the appropriateness of IV acetaminophen use based on guidelines. A lot of studies have shown that there is poor quality in compliance with guideline in developing countries. Current study aims to evaluate prescribing behavior of IV acetaminophen regimens in hospitalized adults in Tehran, Iran.

**Methods:** We enrolled 277 patients (including 137 men and 140 women) with age ranged between 18-65 years. Demographic data and clinical and preclinical parameters such as blood urea nitrogen (BUN) and creatinine levels, name of ward, prescribing reason, doses, dose intervals, number of doses, type of vehicle used and durations of infusion were collected and recorded for analysis.

**Results:** Our results have shown that guideline adherence was seen only in 20 (7.22%) out of 277 patients. IV acetaminophen is prescribed mostly by emergency medicine specialists, and it is more inappropriately prescribed by these specialists in comparison to other specialists. It was also found that non-compliance of IV acetaminophen prescribing with guideline imposes additional 1038 USD for 3 months of the study.

**Conclusion:** The evaluation of prescribing indicators showed low quality prescription by medical specialists. The pattern of prescribing depending on the medical specialties was also different. In addition, overuse and misuse of IV acetaminophen imposes substantial cost and the economic burden on healthcare system.

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### Introduction

In the today's health care system, where resources are limited and demand is rising rapidly, it is crucial that hospitals and healthcare institutions execute evidence-based strategy to utilize medicines use (1). The consideration of the dosage form and proper route of administration is an essential step in the prescribing of drugs to achieve optimum clinical outcome from the limited financial resources (2, 3).

Inappropriate prescribing and frequent adverse drug reaction (ADR) are linked with pain management regimens and analgesic strategy. Numerous studies have demonstrated that these adverse events are costly and

they are associated with increased morbidity and longer hospital length of stay (4,5). These adverse events are main concerns among clinicians and administrators within hospitals and have induced most healthcare institutions to carry out a range of strategies. These strategies include supervision of prescribing by clinical pharmacists,(6,7) continuous education concerning proper prescribing,(8) and drug utilization evaluation (DUE)(9-12). DUE is a policy by which clinical pharmacists can determine the frequency of improper prescribing and make provision of drug therapy. DUE uses precise criterion to determine both the process and clinical outcomes of prescribing. At

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present, DUE is considered a principal mean for assessing the quality of prescribing (13-15).

Intravenous (IV) acetaminophen, also known as paracetamol and APAP, has become an established part of a multimodal analgesic strategy and pain management regimens (16). It exerts its analgesic mechanism through a variety of central and peripheral activities, including cholinergic, noradrenergic, nitric acid synthase, cannabinoid, serotonergic, and N-methyl-D-aspartate receptor activation (17). It is produced in an extensive range of doses and dosage forms and it is a relatively safe, low cost and generally available medicine (18). Due to its effectiveness and acceptable safety profile, IV acetaminophen has become the most commonly chosen analgesic medication in critical care settings, particularly as part of a multimodal analgesia strategy engaged to reduce opioid consumption (19, 20). Despite its safety when prescribed appropriately, acetaminophen is one of the most frequent overdoses reported to poison centers because of hepatotoxicity, which may progress to serious outcome (21).

In organized health care systems, IV acetaminophen utilization evaluation must be carried out as organizationally authorized guidelines which are practically designed, criterion based, and managed according to a clinical care path by an interdisciplinary team, and systematically conducted. These clinical guidelines could be considered as program to improve healthcare practice and can lead to an overall decrease in IV acetaminophen misuse/overuse and ultimately in reducing financial costs. According to the food and drug administration (IFDA) in Iran, the rate of acetaminophen consumption more than tripled between 2015 and 2016 (22). Given the importance of DUE and the limited information on IV acetaminophen-use evaluation in Iran hospitals, the goal of the current study was to evaluate prescribing behavior of

IV acetaminophen regimens in hospitalized adults in Ziaieian hospital, Tehran, Iran.

### Methods

This retrospective study was done on 277 patient records (with age ranged between 18-65 years) in a 155-bed university affiliated general hospital. A drug utilization evaluation (DUE) program was carried out from December 2015 to February 2016. The study was conducted in Ziaieian Hospital, Tehran, Iran. The hospital had two surgical wards, ICU/CCU, hemodialysis, pediatrics and neonatology, geriatrics, internal medicine, gynecology and postpartum wards. Any patient who received IV acetaminophen and aged between 18 and 65 years old was included in the study.

The primary outcome of this study is utilization evaluation of intravenous acetaminophen use in patients aged 18 to 65 who received this medication in all wards. The secondary outcome includes determining the reasons for the prescriptions and the amount of the usage of the IV acetaminophen in different wards of the hospital.

Institutional Research Committee approved this study prior to the initiation of data collection. A predefined guideline based on the Prescribing Guidelines of Tehran University of Medical Sciences' criteria was utilized to evaluate the appropriateness of IV acetaminophen prescribing (Table 1). Demographic, laboratory and clinical data were retrieved from the patient's files. Data gathered included: blood urea nitrogen (BUN) and creatinine levels, name of ward, prescribing reason, doses, dose intervals, number of doses, type of reconstitution solvent used and durations of infusion. In addition, primary and final diagnoses were noted. All data extraction was performed by clinical pharmacist supervision. Participants were followed up until the end of treatment course.

**Table 1.** Guideline for drug utilization evaluation of Tehran University of Medical Sciences.

Indication of acetaminophen	Fever
	Short-term treatment of mild to moderate acute pain
	Short-term treatment of moderate to severe acute pain with opioid analgesics
	Prohibit or limit non-steroidal analgesic use
Indication of intravenous acetaminophen	
Inability to take oral acetaminophen	NPO due to oral intolerance
	Nausea and vomiting
	Aspiration risk
	Lack of absorption by oral route
	Ileus
	Short bowel syndrome
Inability to use rectal acetaminophen	Rectal tube
	Rectal surgery
	Diarrhea
In the following cases, injectable acetaminophen does not have indication	Administration of different forms of acetaminophen simultaneously
	Ability to take oral form or use rectal acetaminophen
	Chronic pain management

Data were analyzed by SPSS software. Independent sample T-test and Chi square test were used to compare quantitative and qualitative variables, respectively. Data were expressed as mean  $\pm$  SD or percentage. P-values less than 0.05 were considered statistically significant.

## Results

During the 3-month study period, a total of 277 patients were enrolled in the study. The population of the study consisted of 137 men (49.5%) and 140 (50.5%) women. The mean age of the population was 46.7 years, ranging between 18 and 65 years. Based on the Glomerular Filtration Rate (GFR), 31.05% of patients had GFR >90, 30.69% had GFR 60-90 and data was not available for others (n=106, 38.27%).

Patients' demographics are shown in Table 2. Women and age group 25-35 had received a greater rate of IV

acetaminophen. Most of patients (43%) receiving IV acetaminophen were without any underlying chronic disease (Table 2).

In Table 3, the number of patients who could not take oral or rectal acetaminophen due to different reasons is listed. From 227 patients, 187 (67.5%), 66 (23.8%) and 3 (1.1%) could receive acetaminophen as oral formulation, rectal formulation and both oral/ rectal formulation, respectively.

Among the surveyed specialties the most incompatibility with the guideline was related to the emergency medicine specialists (78.5%).

Furthermore, our results showed that the most reason for acetaminophen administration was short-term treatment of mild to moderate acute pain or fever and incompatible with guideline (Table 4).

**Table 2.** Patients' demographics.

Parameters		Rate (%)
Gender	Male	49.46%
	Female	50.54%
Age group	18-25	12.27%
	25-35	25.27%
	35-45	18.77%
	45-55	20.58%
	55-65	23.10%
Underlying diseases	Liver failure	9 (3.25%)
	Chronic alcoholism	1 (0.36%)
	Renal failure	10 (3.61%)
	Liver failure and Renal failure	1 (0.36%)
	Other	137 (49.46%)
	Without underlying diseases	119 (42.96%)
Ward	Intensive care unit	2.53%
	Cardiac care unit	1.08%
	women surgery	5.42%
	Men surgery	7.22%
	Gynecology and postpartum	0.36%
	Internal medicine	5.78%
	Emergency medicine	77.62%
Prescribers' medical specialty	Anesthesiologist, Critical care	6 (2.17%)
	Internal medicine	10 (3.25%)
	Emergency medicine	214 (77.26%)
	Infectious diseases	15 (5.42%)
	General surgeon	15 (5.42%)
	Neurologists	4 (1.55%)
	Reconstructive surgeon	5 (1.81%)
	Gynecologist	1 (0.36%)
	Cardiologist	4 (1.44%)
Orthopedic surgeon	1 (0.36%)	

**Table 3.** Reasons of patients' inability to take oral or rectal acetaminophen

Inability to take oral or rectal form	Rate (%)
NPO due to oral intolerance	20 (7.2%)
Nausea and vomiting	61 (22%)
Aspiration risk	1 (0.4%)
Lack of absorption by oral route	0 (0.0%)
Ileus	0 (0.0%)
Short bowel syndrome	0 (0.0%)
Rectal tube	0 (0.0%)
Rectal surgery	1 (0.4%)
Diarrhea	4 (1.4%)
NPO, Diarrhea	2 (0.7%)
NPO, Inability to change status	7 (2.5%)
Total	181 (65.3%)

Only in 20 (7.2%) out of 277 patients adherence to guideline was seen. IV acetaminophen is prescribed mostly by emergency medicine specialists, and it is more inappropriately prescribed by these specialists in comparison to other specialists (Table 4).

**Table 4.** Indications for prescribing Intravenous (IV) acetaminophen and its compliance with guideline.

Clinical Reason for Prescribing IV acetaminophen	Compliance with guideline	Rate%	Total
Headache	Yes	1 (3.23%)	31 (100%)
	No	30 (96.77%)	
Trauma and fracture	Yes	5 (62.5%)	8 (100%)
	No	3 (37.5%)	
Abdominal pain	Yes	5 (8.47%)	59 (100%)
	No	54 (91.53%)	
Fever	Yes	3 (4.41%)	68 (100%)
	No	65 (95.59%)	
Chest pain	Yes	2 (5.41%)	37 (100%)
	No	35 (94.59%)	
Generalized pain	Yes	0 (0%)	9 (100%)
	No	9 (100%)	
Headache and fever	Yes	0 (0%)	7 (100%)
	No	7 (100%)	
Fever and abdominal pain	Yes	4 (16.67%)	24 (100%)
	No	20 (83.33%)	
Chest pain and fever	Yes	0 (0%)	13 (100%)
	No	13 (100%)	
Fever and generalized pain	Yes	0 (0%)	9 (100%)
	No	9 (100%)	
Other	Yes	1 (8.33%)	12 (100%)
	No	11 (91.67%)	
Total	Yes	21 (7.58%)	277 (100%)
	No	256 (92.42%)	

**Table 5.** Prescribing quality based on TUMS guideline.

Indication of acetaminophen	Compliance with the guideline	Rate%	Total
Fever	Yes	4 (5%)	80 (100%)
	No	76 (95%)	
Short-term treatment of mild to moderate acute pain	Yes	9 (7.26%)	124 (100%)
	No	115 (92.74%)	
Short-term treatment of moderate to severe acute pain with opioid analgesics	Yes	6 (17.14%)	35 (100%)
	No	29 (82.86%)	
Prohibit or limit non-steroidal analgesic use	Yes	0	0
	No	0	
Fever and Short-term treatment of mild to moderate acute pain	Yes	2 (6.67%)	30 (100%)
	No	28 (93.33%)	
Fever and Short-term treatment of moderate to severe acute pain with opioid analgesics	Yes	0 (0%)	7 (100%)
	No	7 (100%)	
Short-term treatment of mild to moderate acute pain and Short-term treatment of moderate to severe acute pain with opioid analgesics	Yes	0 (0%)	1 (100%)
	No	1 (100%)	
Total	Yes	21 (7.58%)	277 (100%)
	No	256 (92.42%)	

In Table 5, we evaluate the prescribing indication in accordance to Tehran University of Medical sciences guideline.

Direct costs including cost of IV catheter, reconstitution solvent, infusion sets and medication were calculated. It was found that non-compliance of IV acetaminophen prescribing with guideline imposes 1038 USD additional expenditure in a 3 months period.

### Discussion

The main purpose of this study was to evaluate the administration of IV acetaminophen in different wards of a teaching hospital in Tehran with the prescribing protocol that proposed by Tehran University of Medical Science. In this study, 277 patients in 7 wards of this hospital were qualified to enter our study. In our findings 92.42% of prescriptions were not in accordance with the guideline, and the main reason was prescribing IV acetaminophen while other routes have been possible.

In a similar study in Australia for IV acetaminophen, prescriptions were not adhered with the protocol in 25% and the main reason for the disagreement observed in 90% of this group, as in our study, was the administration of IV acetaminophen while an alternative route was available, the most common reason of prescribing intravenous

acetaminophen has been reported for pain due to visceral surgery. No allergic reaction has been reported (23).

In one study which was performed to evaluate albumin utilization in two groups of 50 patients in Mashhad, the first group was evaluated before guideline application and the second group was assessed after guideline application. Their results have shown significant decreases in inappropriate dose and duration of treatment with albumin from 55.5% to 16.7%, significant reduction in albumin vials and average cost of patients ( $317.78 \pm 3.15$ - $149.81 \pm 1.91$  USD) and non-significant reduction in inappropriate utilization of albumin from 62% to 57.5% (24). Some studies have noticed the benefits of early change of an injectable form to oral routes could be lower costs, lower adverse reactions, and better time saving (25).

In clinical trials, use of IV acetaminophen has been associated with better clinical outcomes in terms of fewer overall complications, shortened hospitalization period, and reduced total resources (26, 27). Irrational use of medications have been reported in several studies conducted in Iran and other countries with different rates of irrational use even up to 76.2% (28). Considering the fact that IV acetaminophen cost in Australian hospitals is about one hundred fold the expenditure of the oral formulation

and twofold the expenditure of the rectal formulation but in our study it was found that non-compliance of IV acetaminophen prescribing with guideline imposes 1038 USD additional expenditure on health care system of the hospital. (29). Our study has also shown that application of IV acetaminophen in emergency department is higher than other departments of our hospital. Obviously, given the high number of patients referred to emergency department, it is expected that application of IV acetaminophen to be higher than other departments.

In conclusion, the evaluation of prescribing indicators showed low quality prescription by medical specialists. The pattern of prescribing depending on the medical specialties was also different. In addition, overuse and misuse of IV acetaminophen imposes economic burden on healthcare system. In recent years, different educational strategies have been improved and developed to promote the prescribing quality in Iran (30). However, most of these programs have been conducted concerning general practitioners and thereby more effective managerial approaches is required to educate all medical specialties for the improvement of prescribing in Iran. In addition, it has been widely accepted that the clinical pharmacist plays a vital role in various aspects of healthcare, including quality use of drugs (31). Clinical pharmacist interventions are associated with improved clinical outcomes, improved prescribing pattern and increased efficiency of drug use (32). Thus, clinical pharmacist services, and guideline implementation is recommended.

Although the authors consider the findings of the current study to be valid, certain limitations should be acknowledged. This study was carried out in a single setting in a large city and consequently the results may not be extrapolated to other hospitals.

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