



Parenteral Opioid Analgesics Utilization Pattern in Amir-al-Momenin Hospital, Zabol-IRAN

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ABSTRACT

Opioids are the most available medicines to get rid of any general severe pain and avoiding of any deleterious sequential that can worsen patient outcomes. Rational prescription of opioid analgesics with respect to the possibility of abuse is a big concern in the medical care costs. Zabol, where is located in eastern part of Iran and has common border with Afghanistan has the most opioid traffic in the region. In this study the rational prescription of parenteral opioid in Amir-al-Momenin general hospital was investigated. A retrospective drug utilization review was performed on 509 in-patients who received parenteral opioids including Morphine, Pethidin, Pentazocin, Fentanyl, Alfentanil, Sufentanil and Methadone from March 21st to September 23rd, 2011. Multivariate conditional regression modeling was used to determine independent predictors for daily parenteral opioid consumption. Total daily parenteral opioid consumption was 38.63 DDDs/100bed-days for Morphine, Pethidine and Pentazocin and 84564.78 PFEQs/100bed-days for Fentanyl, Alfentanil and Sufentanil and 766 mg for Methadone. Pethidine was the most frequently prescribed parenteral opioid. Most patients who were prescribed by the intramuscular routes, ordered PRN. Daily parenteral opioid consumption was the highest in the emergency ward whereas it was considered as the lowest in the intensive care unit [ICU]. According to our findings, total daily parenteral opioid consumption was almost high in Amir-al-Momenin Hospital. Unlike to some relevant factors that can effect on the consumption of analgesic opioids like gender, age, drug-drug interaction and etc, we found no rational prescription and consumption in the mentioned hospital.

Keywords: Drug; Utilization; Opioid; ATC/DDD; Hospital; Zabol

INTRODUCTION

Pain is the main reason for over 50% of cases referring to the emergency departments [1] and infact the first reason for visiting the physicians [2, 3]. Pain is defined as an unpleasant sensory and emotional experience that can cause or potentiate tissue damage [4]. Responses to pain among human are affected by psychological and pathophysiological factors. Considering the fact that pain has an abstract nature, the physicians are used to evaluate it according to the patient statements [2]. Appropriate treatment begins with accurate evaluation of the patient's pain. Analgesic is selected individually depending on the cause of continuing pain, age and clinical conditions. Moreover, dose adjustment, route of drug administration, the desired intervals are determined according to clinical responses [5]. A part from the fact that pain and its treatment have great economic consequences in the communities [2], opioid analgesics are the most widely used class of medications [6] especially in high risk patients [7] which are quite costly for health care systems. Although there are particular subjects in Drug Utilization Researches [DUR] however little knowledge is available on their usage patterns. Affecting important factors [8] as well as numerous reports of extensive failures in appropriate pain treatment, especially in the application of these drugs [9-12], highlights the

necessity of more studies on DUR for opioid analgesics. From the various reasons which cause the pain management failure, it could be pointed out: lack of knowledge in the principles of treatment and pharmacological properties of drugs; fear of addicting to opioid analgesics; patient noncompliance with the medical staff; inappropriate diagnosis of pain cause and unsuitable estimates of patient's pain intensity [5, 13, 14].

There are not lots of DURs studies about opioid analgesics using Anatomical Therapeutic Chemical classification/defined daily dose system [ATC/DDD]. Most of their results have been reported in terms of DDD/1000 inhabitants per day or DDD/million inhabitants per day, while less of DURs studies have been reported in terms of DDD/100 bed-days. For example, it could be pointed to studies at the teaching hospital Ciudad Sanitaria [15], the general hospital Nuestra Senora de Covadonga [16] and the general university hospital La-Paz [17] in Spain, the teaching hospital Uppsala in Sweden [15] and the teaching hospital Taleghani in Tehran-Iran [18].

Zabol as a city located at the Eastern part of Iran and next to Afghanistan with its strategic location near to greatest narcotic traffic had never DURs studied on parenteral opioid analgesics consumption [19]. So this study has been carried out to investigate parenteral opioid analgesics consumption in the Amir-al-Momenin general hospital of Zabol in IRAN.

MATERIALS AND METHODS

A retrospective drug utilization review using ATC/DDD system suggested by the DUR group of the World Health Organisation [WHO] was carried out in this study. Investigation was performed on 509 inpatients during 6 months who received injectable opioids from March 21st to September 23rd, 2011, at Amir-al-Momenin Hospital wards. The hospital is a teaching medical center, affiliated to Zabol University of Medical Sciences with 367 inpatient beds. Opioid analgesics included were Morphine, Pethidin, Pentazocin, Fentanyl, Alfentanil, Sufentanil, and Methadone. Patients information was consist of gender, age, kind of hospital ward, cause of hospitalization, inpatient bed-days, opioid analgesics intake [the type, dose, routes of drug administration and frequency of consumption], other medications during hospitalization, the underlying diseases, addiction to drugs or tobacco, usage of the antagonist and nursing report in accordance with the prescription [the type, dosage, method and frequency of consumption].

Statistical results of Morphine, Pethidin and Pentazocine are considered in DDD and DDD/100 bed-days [Table1]. Based on the latest version of the ATC / DDD provided by WHO in 2012 [20], the DDD is undefined for the other investigated drugs. Therefore, the dose of Methadone is limited to unit of "mg" while complementary therapeutic equivalent dose were used for Alfentanil, Fentanyl and Sufentanil [21-24]. Since the effectiveness potency of Alfentanil, Fentanyl and Sufentanil is on average 17.5, 100 and 750 times respectively greater than Morphine [25], Fentanyl was placed as a drug with intermediate effectiveness potency between these three drugs. Thus, the results were expressed in terms of PEFQ and PEFQ/100 bed-days while equivalent coefficient of these drugs in grams was obtained 0.175, 1 and 7.5 respectively, based on the Parenteral Fentanyl Equivalent [PFEQ].

Table1: ATC classification codes and DDD valid opioid analgesics according to ATC / DDD system

Parenternalnarcotic analgesics	ATC code	DDD valid
Morphine	N02AA01	30 mg
Pethidin	N02AB02	400mg
Pentazocine	N02AD01	200 mg

For statistical analysis of data, SPSS 17.0 software was used. At the first step, in order to investigate the effects of dependent variables on daily opioid analgesics consumption, initial analyses were performed using statistical tests based on the data types of variables and statistical significance less than 0.1 [$P \leq 0.1$]. These non-parametric tests include Spearman's rank correlation, Kendal's rank correlation, Mann-Whitney and Kruskal-Wallis. Due to the interaction between variables with $P \leq 0.1$, ridge regression analysis has been used to detect the final model which represents the relationship between independent and dependent variables to opiate drug consumption. These statistical analyses have been performed between two variables with a value of p less than 0.05. It should be noted that certain categories of studied qualitative and multiple nominal variables which were assigned to few patients, were merged into a bigger category in order to be able to make any comparison as well as statistical analysis.

RESULTS

Among 509 in patients with mean age 37 ± 20 whom used parenteral opioid analgesics, the male population [66%] was nearly twice greater than the female population [34%]. Most of consumers belonged to the age group between 20 to 49 years old. All surgical wards at the hospital having 55% of cases showed the highest number of drugs consumption and the emergency department took the second place with almost 12% of cases. External causes of morbidity and mortality [chapter 20, ICD-10] [26], injury, poisoning and other certain consequences of external

causes [chapter 19, ICD-10] [26] and diseases of the digestive system [chapter 11, ICD-10] [26] were the most common underlying reasons to use these medications including 56% of cases. Only 6% of these patients were substance abuser and smoker and 1% of patients were consumer of antagonist. Most drug interactions with parenteral opioid analgesics were assigned to the moderate interactions [54%]. Interaction between parenteral opioid analgesics and medication using for underlying diseases were not found in 76% of patients, while severe interactions in this group had greater percentage than moderate interactions table 2.

Table 2. Review of the percentage of interactions between parenteral opioid analgesic and Concomitant medications or underlying diseases

Type of interaction	Non-interaction	Moderate interaction	Severe interaction
Drug interaction with parenteral opioid analgesic	38%	54%	8%
Parenteral opioid analgesic interaction with underlying disease	76%	6%	18%

The consumption of Morphine, Pethidin, Pentazocine and their total consumption in different wards of hospital in terms of DDD and DDD/100 bed-days has been expressed in Table 3. Emergency department had the highest consumption for each of these medications and also total of them in term of DDD/100 bed-days.

Table 3. The consumption of Morphine, Pethidin, Pentazocine and their total consumption in Different wards of hospital

Ward	Morphine		Pethidin		Pentazocine		Total	
	DDD	DDD/100 bed-days	DDD	DDD/100 bed-days	DDD	DDD/100 bed-days	DDD	DDD/100 bed-days
Men surgery	138.90	12.34	372.00	58.31	0	0	510.90	39.33
Women surgery	19.33	11.65	82.85	67.30	0	0	102.18	41.76
ICU	10.20	4.30	13.18	2.464	0	0	23.38	11.19
Internal medicine	1.00	1.10	52.83	62.89	0	0	53.38	35.185
Emergency	2.32	36.87	81.07	147.66	2.00	200.00	85.39	149.81
Gastroenterology	1.50	5.55	15.83	58.64	0	0	17.33	32.98
Crusher	0	0	0	0	0	0	0	0
Pediatric	0.37	10.79	0.83	83.30	0	0	1.20	27.27
Infectious diseases	7.17	22.82	0	0	0	0	7.18	22.82
CCU	2.73	3.33	39.67	40.89	0	0	42.40	29.44
Gynecology and Obstetrics	0.50	12.82	8.33	119.04	0	0	8.83	81.03
Maternity	1.50	21.43	10.83	43.51	0	0	12.33	38.66
All Wards	185.52	10.80	677.43	61.30	2.00	200.00	864.96	38.63

The consumption of Alfentanil, Fentanyl, Sufentanil and their total in different wards of hospital in terms of PFEQ and PFEQ/100 bed-days has been expressed in Table 4. Maternity, crusher and emergency wards had the highest consumption for each of medications respectively while crusher ward had the highest total consumption.

Table 4. The consumption of Alfentanil, Fentanyl, Sufentanil and their total consumption in different wards of hospital

Ward	Alfentanil		Fentanyl		Sufentanil		Total	
	PFEQ	PFEQ/100 Bed-day	PFEQ	PFEQ/100 Bed-day	PFEQ	PFEQ/100 Bed-day	PFEQ	PFEQ/100 Bed-day
Men surgery	2502.50	1001.80	9710.00	1042.74	1518.75	429.39	13731.25	1278.87
Women surgery	875.00	2786.62	2805.00	1702.06	412.50	1630.43	4092.50	1864.87
ICU	0	0	1735.00	488.73	182.50	223.21	1922.50	541.55
Internal medicine	0	0	275	280.61	0	0	275.00	280.61
Emergency	0	0	250	657.89	150.00	1923.07	400.00	1030.93
Gastroenterology	0	0	50	2500.00	0	0	50.00	2500.00
Crusher	0	0	850	40467.19	0	0	850.00	40476.19
Pediatric	0	0	20	5000.00	0	0	20.00	5000.00
Infectious diseases	0	0	300	1200	0	0	300.00	1200.00
CCU	0	0	300	1764.70	0	0	300.00	176.47
Gynecology and Obstetrics	0	0	200	25000.00	0	0	200.00	25000.00
Maternity	350.00	15909.09	450.00	2393.61	0	0	800.00	3883.49
All Wards	3727.50	1317.13	16945.00	1025.04	2268.75	481.90	22941.25	1238.12

Methadone consumption [mg] in different wards of the hospital has been expressed in table 5.

Table5. Methadone consumption in different wards of the Zabol Amir-al momenin Hospital

Ward	Methadone [mg]
Men surgery	67.5
Women surgery	55
ICU	50
Internal medicine	157.5
Emergency	5
Gastroenterology	150
Crusher	0
Pediatric	0
Infectious diseases	209
CCU	77
Gynecology and Obstetrics	0
Maternity	5
All Wards	776

Routes of administration for Morphine, Pethidin, Methadone and Pentazocine have been compared in Figure 1. As it is shown, Pentazocine and Methadone had the highest number of intravenous administration [IV]. Routes of Morphine administration had the highest intention in the physician’s prescriptions especially at pediatric department. It should be noted that the intravenous administration has been preferred to intramuscular way [IM] in the emergency department, ICU and CCU whereas subcutaneous injection [SC] has been also observed in the ICU. Based on different subsequent types of drugs usage, the percentage of inpatients has been shown in Figure 2, separately. As it is obvious, particular consecutive reception for the medications has not been defined by the physicians especially for Pentazocine and Methadone. PRN is allocated to more percentage of consecutive reception methods than scheduled ones [including BID, TDS & QID] in emergency and obstetrics & gynecology departments. The Percentage of parenteral opioid analgesics receivers in this study has been indicated in Figure 3. According to this figure, Pethidin and Pentazocine have been prescribed to the highest and lowest Percentage of patients, respectively.

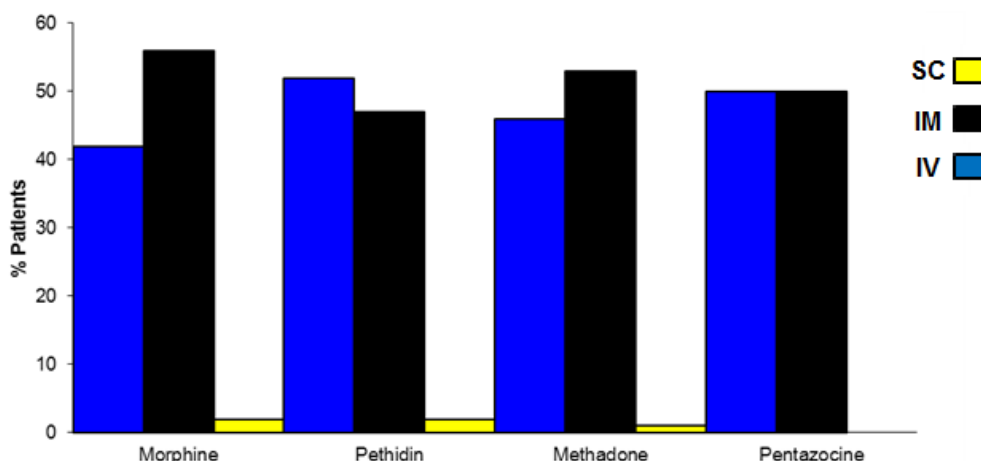


Fig.1:Routes using for Morphine, Pethidin, Methadone and Pentazocine administration in Inpatients of Zabol Amir-al Momenin Hospital

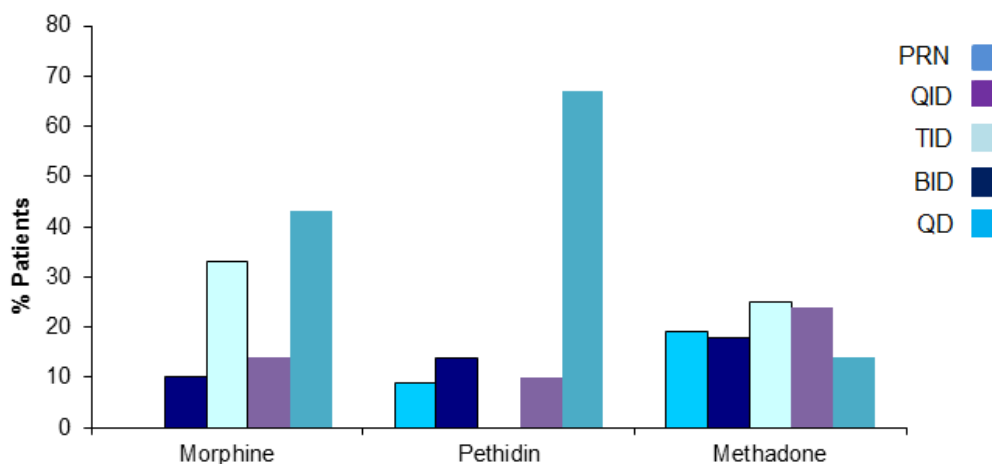


Fig.2:Percentage of inpatients with different sequence types of Morphine, Pethidin, Methadone and Pentazocine use

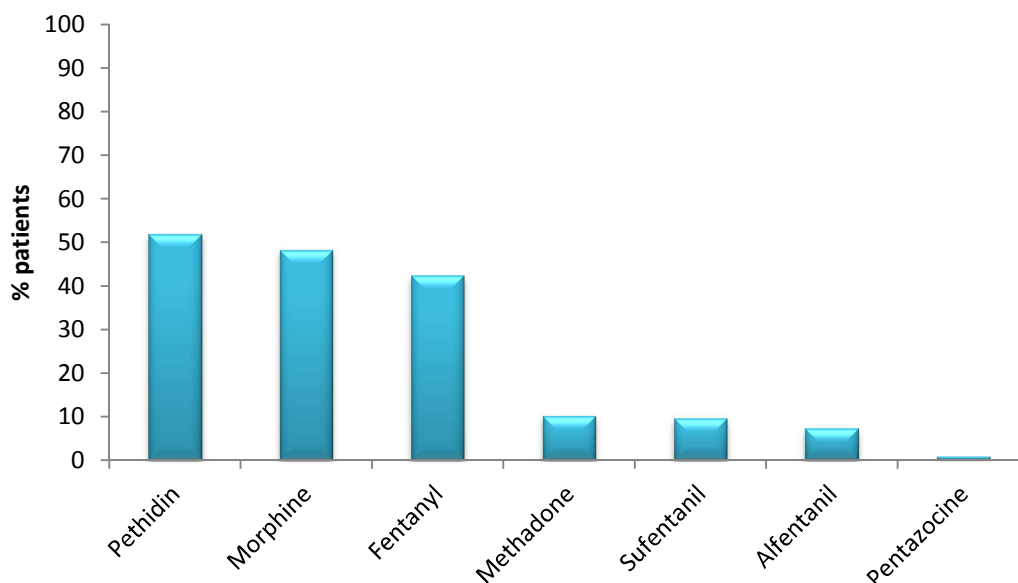


Fig.3:Percentage of inpatient in Zabol Amir-al Momenin Hospital whom received parenteral opioid analgesics

According to the nursing reports, a total compliance in type, dosage, route and frequency of consumption with physician’s prescriptions were seen in 61% of cases. Most of non-compliance cases were respectively included: non-prescribed drug infusion, no injection of prescribed drugs, non-compliance with physician’s desired dosage and the sequence of drug use, Morphine replacement with Pethidin or conversely done.

Study of independent variables associated with daily dose of drug consumption in terms of DDD / bed-day, after initial analysis with a value of $P \leq 0.1$, six independent variables have been chosen for final analysis, including: age, gender, drug interaction with parenteral Opioid analgesic, parenteral Opioid analgesic interaction with underlying disease, cause of hospitalization and ward in hospital. For investigating the interactions between these six variables, statistical analyzes have been done for each pair of variables with a value of $P \leq 0.05$. The results of initial analyses illustrated that there were extensive interactions between selected variables, so ridge regression analysis has been performed. However, no strong correlation was observed between the above variables and the consumption of parenteral opioid analgesics in terms of DDD/bed-day while there was only a weak and inverse correlation [$P < 0.05$, $r = 0.17$] between the consumption of parenteral opioid analgesics and their interaction with underlying disease. Therefore, with an increase in the interaction severity, a relative decrease in the consumption of drugs per bed-day was observed.

Another similar study was done for Alfentanil, Fentanyl and Sufentanil in terms of PFEQ/bed-day. Also in this study, after initial analysis the previous independent variables were selected except drug interaction with parenteral Opioid analgesic. Similar results were obtained from ridge regression analysis so that a weak and inverse correlation [$P < 0.05$, $r = 0.15$] was observed between the consumption of parenteral opioid analgesics and their interaction with underlying disease.

By using Kruskal-Wallis test with a value of $P < 0.1$ to investigate the amount of used opiate drug, it was observed that there were significant differences in DDD/ bed-day in different wards of the hospital. Comparing each of two wards by using Mann-Whitney test, a significant difference was observed between emergency departments [with average maximum consumption of medications] and ICU [with average minimum of medications] with other wards. Nevertheless, this difference was not observed between the other ones.

Different wards of the hospital based on the amount of parenteral opioid analgesics consumption in terms of DDD / bed-day were categorized in the table 6. No significant difference was found between different parts of each group while there was a meaningful difference between the different groups.

Table6: Categorizing different wards of the hospital based on the amount of parenteral opioid analgesics consumption in terms of DDD / bed-day

Group	Ward	Mean \pm SD	Median, inter-quartile range [25% -75%]
1	Emergency	5.072 \pm 5.825	4.167 [1.000 – 8.333]
2	Women surgery	1.506 \pm 3.262	0.333 [0.176 – 1.677]
	Men surgery	1.028 \pm 1.731	0.368 [0.167 – 1.139]
	Maternity	0.785 \pm 0.570	0.417 [0.117 – 0.833]
	CCU	0.482 \pm 0.671	0.278 [0.172 – 0.550]
	Other wards	0.799 \pm 1.018	0.462 [0.119 – 0.833]
3	ICU	0.155 \pm 0.190	0.111 [0.019 – 0.167]

DISCUSSION

Having a quite precise estimation of drugs consumption amount in terms of DDD/100 bed-days, it makes possibility to compare drugs used in various wards of hospitals and medical centers in worldwide [27]. In compare with other studies on parenteral opioid analgesics, it is shown that there are relatively high consumption of these drugs in Amir-al-Momenin hospital than to other hospitals in Tehran, Iran or even than other foreign countries. Consumption of these drugs was reported 4.67 DDD/100 bed-days in Taleghani hospital surgical ward in Tehran–Iran 2003 [18]. Meanwhile, the amount of the opioid drugs consumption in the surgical wards of Amir-al-Momenin hospital was almost 36.30 DDD/100 bed-days that the difference was mainly seen for Pethidin [about 69 times]. A possible reasoning for the study results could be the high prevalence rate of drug abuse in Zabol. Official statistics about abuse of this substance is limited in this region. However, interview with the members of the hospital show that real estimation of people addicted with narcotics and tobacco were more than what registered in the medical profile of patients. Extensive global pharmaco-epidemiological studies show the effect of demographic variables on the amount of opioids demand in order to pain relief. Although, initial statistical analysis showed the effectiveness of some demographic variables, but the final analysis results using ridge regression method did not show significantly a strong relation between them. In respect to interaction of parenteral opioid analgesics with medication used for underlying diseases, a weak and inverse correlation was observed in the daily dose of them. This problem could indicate the relative awareness of medical staffs to the underlying disease and its effects on the amount of opioid demand at the hospital. Nevertheless, the lack of considerations about the effect of other demographic variables on the daily dose of opioid analgesics could increase probability of hazards occurrence and multiple insufficiencies during the pain management. However drug interaction with parenteral opioid analgesic is relatively high that indicate some pharmacological interaction that can cause high consumption of opioids . So health authorities should notice to replace those medicine with the ones with no interactions.

Table 7. Consumption of parenteral opioid analgesics in surgical departments at Amir-al-Momenin hospital and Taleghani hospital

Hospital, year	Morphine [DDD/100bed-days]	Pethidin[DDD/100bed-days]	Pentazocine [DDD/100bed days]
Amir-al-Momenin, 2011	12.25	59.75	0
Taleghani, 2003	0.63	0.87	0.2

Further Pethidin injection had the highest number of received parenteral Opioid analgesic patients, even more than Morphine which was more effective and less toxic in compared with other drugs [28-34]. This study shows that the average daily consumption of Pethidin was greater for patients more than 60 years old [80.82 \pm 182.28 DDDs / day], rather than patients less than 60 years old [62.80 \pm 84.87 DDDs / day]. Considering all of these points, irrational use of Pethidine injection is one of the most challenging issues in terms of in-patient parenteral Opioid analgesic consumption.

In contrary, Pentazocine took the best position in irrational use of parenteral Opioid analgesics, that our data showed the importance of the risks for using this medication from the health authorities point of view.

There are different injectable routes of parenteral analgesics administration. According to the results of this study, intravenous administrations have priority over the intramuscular injections only in emergency, CCU and ICU departments. In addition, in the most of prescriptions, the specific route of drug administration had not been determined by physicians in the pediatrics, ICU, maternity, men surgery and internal medicine wards. In general, nurses preferred IM injection to IV route of administration.

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