



Drug Utilization Review of parenteral opioid analgesics in cardiovascular surgery department of Shahid Modarres Hospital, Tehran

Vatanpour H, Soltani M, and Sufi H

Toxicology & Pharmacology, Pharmacy School, Med. Sci. Uni. of Shahid Beheshti, Tehran Iran

ABSTRACT

Persistent pain continues to be a common problem among patients undergoing cardiac operations and the need for controlling such pain is believed to be as a prime necessity in terms of the patient's well being, health care costs and avoiding negative consequences provoked by the pain itself. Regarding to the newly established guidelines, opioid analgesic agents are considered as the mainstay of moderate to severe acute pain. Nonetheless, the underutilization of opioids for pain relief is still a persisting huge challenge. This survey, applying as a concurrent Drug Utilization Review using ATC/DDD system provided and recommended by the DUR group of the World Health Organization, conducted on 108 inpatients who received opioid drugs by parenteral route during 9 months from February to November 2013 at the post-ICU ward of Shahid Modarres Cardiovascular Hospital, affiliated to Shahid Beheshti University of Medical Science, in Tehran. Our findings revealed that morphine was the most commonly prescribed parenteral opioid in the hospitalized patients and pethidine usage was in the lowest level for the geriatric patients, resulting in satisfaction with the analgesic procedure among most of the cases in our study. Both of the mentioned drugs were prescribed by intramuscular route, regarding PRN way of injecting as well. Comparative results of our study with the literature revealed relatively moderate and roughly rational consumption of morphine (10.282 DDD/100bed-days) and pethidine (0.013 DDD/100bed-days). Applying multivariate conditional regression modeling on the question of determining independent predictors for opioid usage, disclosed a direct correlation between the patient's weight and daily dose of parenteral opioid consumption.

Keywords: Drug; Utilization; Opioid; ATC/DDD; Cardiac Surgery; Iran.

INTRODUCTION

Despite considerable advances achieved in the specific field of managing acute pain in recent decades all over the world [1], yet it is widely reported that adherence to the principles and recommendations of pain guidelines in hospital settings is unsatisfiable, so that pain is routinely common in patients treated with analgesics [2, 3], and that pain still persists as the leading cause of case referring to physicians [4]. In addition to the fact that pain and its treatment procedure have notable economic consequences in the communities [4, 5], sub optimally managing individual patients with acute pain can lead to a number of adverse sequelae such as myocardial ischemia, hypoventilation and atelectasis, thromboembolic complications and releasing indigenous corticosteroid leading to impaired immune system responses. A strong association between prolonged acute pain and subsequent development of chronic pain is also considered [6, 7].

Skin incision, intraoperative tissue retraction and dissection, sternotomy, pericardiotomy and intranasal cannulations and drainage all contribute to intense pain after cardiac surgery [8]. As expected, managing such pain remains challenging. It's worth mentioning that the prevention and treatment of the abovementioned pain would be widely considered necessary for humanitarian and physiological reasons [9].

Regarding to the latest WHO pain management guidelines, opioid analgesic agents are considered as the mainstay of moderate to severe acute pain [7]. Nevertheless, the underutilization of opioids for pain relief is still remained as a big challenge. Current literatures reported different usage patterns of these agents in some countries, primarily due to fear of opioid addiction, its respiratory depression, considering these medications inappropriate to treat pediatric patients and experiencing external pressure by relatives of patients against opioid prescription [10-13].

Although in recent years there has been an increasing interest in favor of the specific field of Drug Utilization Review (DUR) for evaluating usage pattern of parenteral opioids applying the ATC/DDD methodology provided by WHO Collaborating Centre for Drug Statistics Methodology to enable making comparisons of drug use between countries, regions, and other health care setting [14], however, far too little attention exclusively has been paid to in-hospital settings [15] and out of them, with specially regard to cardiovascular department, very few studies are available reporting their results in terms of DDD/100bed-days.

There have been also some important attempts to describe determinants of opioid prescribing in hospitalized patients. Performing multivariable analysis, it has been shown that opioid prescribing pattern is associated with some variables related to demographic characteristics of patients, nurse gender, concomitant medications, comorbidity and psychological and cultural factors affecting opioid usage among patients and medical staff [16-22].

MATERIALS AND METHODS

This study was performed at the post-ICU ward of Shahid Modarres Cardiovascular Hospital, with totally 31 beds, affiliated to Shahid Beheshti University of Medical Science, in Tehran. A concurrent Drug Utilization Review using ATC/DDD system provided and recommended by the DUR group of the World Health Organization [14] was conducted on 108 inpatients who received opioid drugs by parenteral route during 9 months from February to November 2013 in the mentioned ward. The number of inpatients for this study was chosen on the basis of adopted guidelines for concurrent drug utilization studies suggesting at least 30-100 cases to be entered [23]. Concerning the ATC classification system, out of all injectable opioid analgesic agents included in the ATC category N02A, we only recorded morphine (ATC code, N02AA01) and pethidine (ATC code, N02AB02) in the prescriptions allocated to our cases. The latest official DDD values provided by the WHO Collaborating Center for Drug Statistics Methodology assigned to the mentioned drugs were used as a unit of measurement in order to describe their usage. The adopted DDD values were 30 mg and 400 mg for parenteral morphine and pethidine, respectively [14].

Patient characteristics in this survey concerned age, gender, inpatient bed-days, possibly taking other medications during consumption of opioid agents (poly pharmacy) with regard to pharmacodynamic principles, possibly concomitant conditions (co-morbidity), analgesia satisfaction, drug addiction, height and weight. Supervising nurse's gender related to each individual patient took into account, as well. Additionally, we conduct an investigation aiming to evaluate method and frequency of consumption.

Using SPSS 17.0 software for statistical analysis of data, preliminary analysis, based on the types of variables and regarding statistical significance less than 0.1 (P value ≤ 0.1), was applied to investigate the influence of the mentioned variables on daily opioid consumption (expressing as DDD/bed-day). In order to detect the final model representing the real relationship between independent and dependent variables affecting opioid usage, non-parametric tests has been used in this step including Spearman's rank correlation and Mann-Whitney. No Ridge regression analysis needed subsequently, since we found no interaction between the final variables with regard to P value ≤ 0.05 .

It should be noted that out of all the variables, three of them (consisting supervising nurse's gender, route and frequency of parenteral opioid administration) were excluded from the analysis, due to being the same for all of the patients.

RESULTS

Among 108 parenteral opioid analgesics receivers entered into this survey, 56.5% were women and 43.5% were men, having a mean age of 51 ± 19.4 years. Most of the cases belonged to the age group between 50 to 70 years old. 94.5% and 10% of the cases have been offered morphine and pethidine, respectively, meaning only 4.5% of receivers have been concurrently treated with both of the medications.

According to the descriptive results of our study, most of the patients (77.8%) acclaimed to be satisfied with the analgesic procedure conducted on them, where no statically significant correlation found between the patient analgesia satisfaction and patient gender/type of opioid medication consumed. There was also no significant correlation between the patient gender and the type of opioid agents used for every individual patient.

Of the study population, 16.7% subjects were substance abuser. The rate of the existence of co-morbidity and poly pharmacy regimen among the patients were 89.9% and 84.3%, respectively. Our finding revealed that morphine was the most commonly prescribed parenteral opioid in the hospitalized patients. Additionally, we observed that pethidine usage was in the lowest level for the geriatric patients (aged 60 and over) in comparison with those of adult (18-59 years of age) and pediatric (2 to less than 18 years of age) patients. Figure 1 illustrates parenteral opioid consumption among our cases categorized by age.

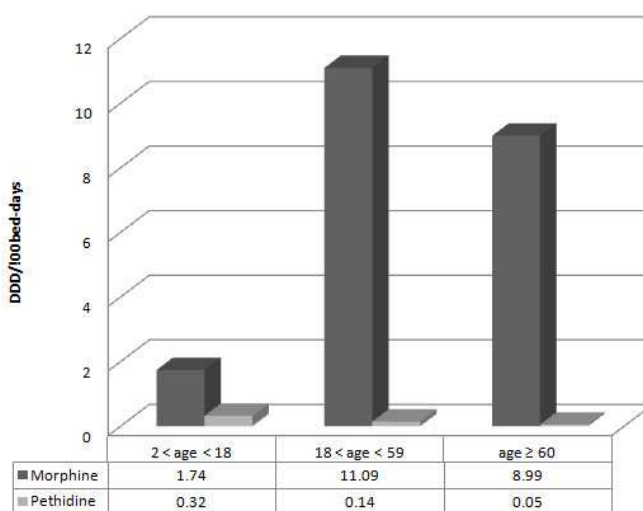


Figure 1. Usage pattern of parenteral opioids categorized by age

All the nurses in our study were female and almost all the opioid drugs used for our patients were prescribed by intramuscular route and regarding PRN way of injecting (without considering any scheduled intervals of administration), as well. Total consumption of parenteral opioids in our study was 9.543 DDD/100bed-days (Table 1).

Table 1. Consumption of perenteral opioid analgesics in cardiovascular surgery department of Shahid Modarres Hospital in the present study

Drug	Drug usage (DDD/100bed-days)
Morphine	10.282
Pethidine	0.013
Pentazocine	0
Overall	9.543

A preliminary multivariable analysis considering documented demographic patient datum including age, gender, opium addiction, weight, height, opioid analgesia satisfaction, concomitant multiple drug usage (poly pharmacy regimen) and underlying disease besides cardiovascular conditions (comorbidity) in association with daily dose of drug consumption expressing in terms of DDD/100bed-days conducted in the present survey (with a value of $P \leq 0.1$), indicating that out of all the above independent variables, only weight and polypharmacy have been shown a meaningful correlation. To clarify possible interaction between these two variables, another statistical analysis with a value of $p \leq 0.05$ has been performed. Since we found no meaningful correlation between the mentioned variables, there was no need for conducting complementary Ridge regression analysis.

Our findings illustrated that there were a direct correlation between the weight of the patient and daily dose of drug consumption, meaning the more weight of patient was, the more daily dose of opioid drugs has been consumed. We

also surprisingly found that the patients with poly pharmacy regimen have been prescribed more opioids in comparison with those who possess no documented polypharmacy regimen (regarding pharmacodynamics characteristics of the drugs).

DISCUSSION

Postoperative pain is common problem among patients undergoing cardiac operations, typically experienced as incisional pain associated with sternotomy, chest tube insertion, and eventual leg vein incision [8]. The need for controlling postoperative pain is considered as a prime necessity in cardiac surgery in terms of the patient's well being, health care costs and avoiding negative consequences provoked by the pain itself [24-26].

Implementation ATC/DDD methodology for evaluating drug usage amount in terms of DDD/100bed-days, have made it possible to compare drug consumption among various wards of hospitals and medical centers across the world. Although this procedure is uncommon, it is strongly recommended by WHO to make cross-national and international comparisons between different datasets [14].

Even so, the research in the specific field of evaluating parenteral opioid usage has been tended to focus on applying ATC/DDD system in terms of DDD/1000inhabitants/day, to date, and little attention has been paid to using the system in terms of DDD/100bed-days (the more appropriate index when in-hospital drug consumption is considered). Moreover, we found lack of enough studies using the mentioned methodology, exclusively conducting in the field of managing post-cardiovascular surgery pain.

Comparative results of our study with other ones (corresponding to all the surgical wards, not only concerning cardiovascular surgeries) revealed relatively moderate and roughly rational consumption of morphine and pethidine (tables 1 and 2).

Table 2. Consumption of parenteral opioid analgesics in surgical departments of some hospitals in Iran and Spain (15, 27).

Hospital, country, year	Drug	Drug usage (DDD/100bed-days)
Amir-al-Momenin, Iran, 2011	Morphine	12.25
	Pethidine	59.75
	Pentazocine	0
Taleghani, Iran, 2003	Morphine	0.63
	Pethidine	0.85
	Pentazocine	0.2
La Paz, Spain, 2008	Morphine	10.6
	Pethidine	-
	Pentazocine	-

Extensive pharmacoepidemiological studies worldwide confirmed the effect of demographic variables on the amount of opioids needed in order to pain relief [15, 16, 28-30]. On the question of the mentioned variables, this study found a direct correlation between the weight of patient and daily dose of parenteral opioid consumption. This finding is in agreement with Chang KY's (2006) findings which showed the positive effect of the patient's weight on opioid demand [30], while In another similar study conducted by Yen CR (2010), the patient's weight considered as the most important variable affecting opioid usage [16].

According to the result of this study, patients with polypharmacy regimen have been prescribed more daily doses of opioids (in comparison with patients who possess no documented polypharmacy regimen). This finding was unexpected and suggests the lack of awareness of medical staff to concomitant drug consumption issue and possibly occurring drug interactions. As a result, further studies on the current topic are strongly recommended.

Traditionally postoperative pain management with the regard to reactively approach is now considered insufficient, due to administration of the analgesic agents at the discretion of nurses and only on as-needed basis [31, 32]. According to the increasingly recommendations in the literature and the WHO analgesic ladder, a regular dose of analgesics would be preferably administered around the clock, meaning that Intermittent doses of intravenous opioids take priority over intramuscular route of administration [33-35]. Considering this fact, our results was in contrast to the new guidelines (all the cases in the present survey were taken parenteral opioids on PRN basis and

via IM route of administration). However, surprisingly, most of the patients were satisfied with the analgesic procedure implemented during this study.

A possible explanation for the abovementioned contradictory might be that pethidine, as a less effective and more toxic agent compared to morphine [4, 36-38], had the lowest number of receivers, particularly for those above 60 years old. Pentazocine, a more toxic agent even compared to pethidine [7, 37], was not prescribed at all. Another possible reasoning for the mentioned finding might be that healthcare providers have been regarded patient's demographic variables such as weight and Body Mass Index, subsequently. We should not also neglect the assumption that the uniformity of nurse's gender in our study, all being female, could bias in treating pain among the patients, especially among the male case [39].

We suggest further studies on the current topic aiming at applying interventions that match new guidelines, and involving more demographic variables, in cross-national and international scales, as well.

REFERENCES

- [1] Argoff CE. Recent Management Advances in Acute Postoperative Pain. *Pain Pract.* 2013 Aug 15.
- [2] Vallano A, Malouf J, Payrullet P, Banos JE. Analgesic use and pain in the hospital settings. *Eur J Clin Pharmacol.* 2007 Jun; 63(6): 619-26.
- [3] Maxam-Moore VA, Wilkie DJ, Woods SL. Analgesics for cardiac surgery patients in critical care: describing current practice. *Am J Crit Care.* 1994 Jan; 3(1): 31-9.
- [4] DiPiro JT. *Pharmacotherapy : a pathophysiologic approach.* 7th ed. New York: McGraw-Hill Medical; 2008. p. 989-1001.
- [5] Ebert MH, Kerns RD. *Behavioral and psychopharmacologic pain management.* New York: Cambridge University Press; 2011. p. 108,331,408,24.
- [6] Vadivelu N, Urman RD, Hines RL. *Essentials of pain management.* New York: Springer Verlag; 2011. p. 10,7,35,401,7,516.
- [7] Koda-Kimble MA. *Applied therapeutics : the clinical use of drugs.* 9th ed. Philadelphia: Wolters Kluwer Health/Lippincott Williams & Wilkins; 2009. p. 8-1 - 8-32.
- [8] Mueller XM, Tinguely F, Tevæarai HT, Revelly JP, Chiolero R, von Segesser LK. Pain location, distribution, and intensity after cardiac surgery. *Chest.* 2000 Aug; 118(2): 391-6.
- [9] Hammer GB, Golianu B. Opioid analgesia in neonates following cardiac surgery. *Semin Cardiothorac Vasc Anesth.* 2007 Mar; 11(1): 47-58.
- [10] Morgan JP. American opiophobia: customary underutilization of opioid analgesics. *Adv Alcohol Subst Abuse.* 1985 Fall-1986 Winter; 5(1-2): 163-73.
- [11] Davidson SN. Pain and opiophobia. *Healthc Forum J.* 1997 May-Jun; 40(3): 64-7.
- [12] Weinstein SM, Laux LF, Thornby JL, Lorimor RJ, Hill CS, Jr., Thorpe DM, et al. Physicians' attitudes toward pain and the use of opioid analgesics: results of a survey from the Texas Cancer Pain Initiative. *South Med J.* 2000 May; 93(5): 479-87.
- [13] Bennett DS, Carr DB. Opiophobia as a barrier to the treatment of pain. *J Pain Palliat Care Pharmacother.* 2002; 16(1): 105-9.
- [14] *Introduction to Drug Utilization Research.* Geneva: World Health Organization 2003.
- [15] H. Vatanpour. H. Sufi, J. Salamzadeh, G. Hajebi. Drug utilization review of parenteral analgesic opioids in Amir-al-momenin hospital at 1390 in Zabol–Iran. *Research in Pharmaceutical Sciences (RPS).* 2012;7(No 5, 13th Iranian Pharmaceutical Sciences Congress).
- [16] Yen CR, Tsou MY, Mandell MS, Chan CT, Chan KH, Chen TH, et al. An analysis of patient variables that influence intravenous patient-controlled analgesic use of morphine with quantile regression. *Anesthesiology.* 2010 Mar; 112(3): 688-95.
- [17] Burns JW, Hodsman NB, McLintock TT, Gillies GW, Kenny GN, McArdle CS. The influence of patient characteristics on the requirements for postoperative analgesia. A reassessment using patient-controlled analgesia. *Anaesthesia.* 1989 Jan; 44(1): 2-6.
- [18] Aubrun F, Salvi N, Coriat P, Riou B. Sex- and age-related differences in morphine requirements for postoperative pain relief. *Anesthesiology.* 2005 Jul; 103(1): 156-60.
- [19] Cepeda MS, Carr DB. Women experience more pain and require more morphine than men to achieve a similar degree of analgesia. *Anesth Analg.* 2003 Nov; 97(5): 1464-8.

- [20] Voulgari A, Lykouras L, Papanikolaou M, Tzonou A, Danou-Roussaki A, Christodoulou G. Influence of psychological and clinical factors on postoperative pain and narcotic consumption. *Psychother Psychosom.* 1991; 55(2-4): 191-6.
- [21] Heins A, Grammas M, Heins JK, Costello MW, Huang K, Mishra S. Determinants of variation in analgesic and opioid prescribing practice in an emergency department. *J Opioid Manag.* 2006 Nov-Dec; 2(6): 335-40.
- [22] Heins JK, Heins A, Grammas M, Costello M, Huang K, Mishra S. Disparities in analgesia and opioid prescribing practices for patients with musculoskeletal pain in the emergency department. *J Emerg Nurs.* 2006 Jun; 32(3): 219-24.
- [23] Green T. Drug and therapeutics committees : A practical guide. In: Holloway K, editor. *Introduction to Drug Utilization Research.* Geneva: World Health Organization 2003. p. 71-94.
- [24] Kehlet H. Acute pain control and accelerated postoperative surgical recovery. *Surg Clin North Am.* 1999 Apr; 79(2): 431-43.
- [25] Milgrom LB, Brooks JA, Qi R, Bunnell K, Wuestfeld S, Beckman D. Pain levels experienced with activities after cardiac surgery. *Am J Crit Care.* 2004 Mar; 13(2): 116-25.
- [26] Cogan J. Pain management after cardiac surgery. *Semin Cardiothorac Vasc Anesth.* 2010 Sep; 14 (3): 201-4.
- [27] Salcedo PG, Ambrosio AH, Ramon JMM. Estudio de utilización de analgésicos opiáceos en un hospital general Universitario. *REVISTA DE LA SOCIEDAD ESPAÑOLA DEL DOLOR.* 2009 ; 16 (7) : 373-80
- [28] Chia YY, Chow LH, Hung CC, Liu K, Ger LP, Wang PN. Gender and pain upon movement are associated with the requirements for postoperative patient-controlled iv analgesia: a prospective survey of 2,298 Chinese patients. *Can J Anaesth.* 2002 Mar; 49(3): 249-55.
- [29] Macintyre PE, Jarvis DA. Age is the best predictor of postoperative morphine requirements. *Pain.* 1996 Feb; 64(2): 357-64.
- [30] Chang KY, Tsou MY, Chan KH, Sung CS, Chang WK. Factors affecting patient-controlled analgesia requirements. *J Formos Med Assoc.* 2006 Nov; 105(11): 918-25.
- [31] Kruger M, McRae K. Pain management in cardiothoracic practice. *Surg Clin North Am.* 1999 Apr; 79(2): 387-400.
- [32] Carroll KC, Atkins PJ, Herold GR, Mlcek CA, Shively M, Clopton P, et al. Pain assessment and management in critically ill postoperative and trauma patients: a multisite study. *Am J Crit Care.* 1999 Mar; 8(2): 105-17.
- [33] Reimer-Kent J. From theory to practice: preventing pain after cardiac surgery. *Am J Crit Care.* 2003 Mar; 12(2): 136-43.
- [34] Pasero C, McCaffery M. Multimodal balanced analgesia in the critically ill. *Crit Care Nurs Clin North Am.* 2001 Jun; 13(2): 195-206.
- [35] Puntillo K. Stitch, stitch ... creating an effective pain management program for critically ill patients. *Am J Crit Care.* 1997 Jul; 6(4): 259-60.
- [36] Clark RF, Wei EM, Anderson PO. Meperidine: therapeutic use and toxicity. *J Emerg Med.* 1995 Nov-Dec; 13(6): 797-802.
- [37] Katzung BG. *Basic & clinical pharmacology.* 11th ed. New York: McGraw-Hill Medical; 2009. p. 628-55.
- [38] Goodman LS, Gilman A, Brunton LL, Lazo JS, Parker KL. *Goodman & Gilman's the pharmacological basis of therapeutics.* 11th ed. New York: McGraw-Hill; 2006.
- [39] Criste A. Do nurse anesthetists demonstrate gender bias in treating pain? A national survey using a standardized pain model. *AANA J.* 2003 Jun; 71(3): 206-9.