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Methadone Pharmacokinetics in Geriatric Critically Ill Patients Following Intramuscular and Intravenous Administration: A Pilot Study

Safoura Beik Rassouli[1], Mohammad Reza Rouini[2], Farhad Najmeddin[3], Azin Gheimati[3], Ali A Golabchifar[4], Kimia Tabib[5], Arezoo Ahmadi[6], Kourosh Sadeghi[3], Hooshyar Honarmand[3], Ali Mohammed Hadi[7], Mojtaba Mojtahedzadeh[3*]

[1]Sina Hospital, Tehran University of Medical Sciences, Tehran, Iran.
[2]Division of Biopharmaceutics and Pharmacokinetics, Department of Pharmaceutics, School of Pharmacy, Tehran University of Medical Sciences, Tehran, Iran.
[3]Department of Clinical Pharmacy, School of Pharmacy, Tehran University of Medical Sciences, Tehran, Iran.
[4]Department of Comparative Biosciences, Faculty of Veterinary Medicine, University of Tehran, Tehran, Iran.
[5]Department of Medicinal Chemistry, School of Pharmacy, Shahid Beheshti University of Medical Sciences, Tehran, Iran.
[6]Departments of Anesthesiology and Critical Care, School of Medicine, Tehran University of Medical Sciences, Tehran, Iran.
[7]Department of Clinical Pharmacy, College of Pharmacy, University of Basrah, Basrah, Iraq.

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A B S T R A C T

Background: Methadone is used for the pain management worldwide. Its special characteristics make it a potential alternative for pain management in critically ill and geriatric patients. Due to lack of studies in this population, we aimed to compare the pharmacokinetic behavior of Methadone following intramuscular and intravenous administration in geriatric Intensive Care Unit (ICU) patients and with previously reports in healthy volunteers.

Methods: According to the limitations in ICU setting, we could include 11 patients over 65 years old, who required opioid for pain relief in this study. Patients were randomized to receive 5 mg of Methadone IM or IV injection every 8 hours for 6 days. The Methadone plasma level detected with LC-mass tandem mass spectrometry, and pharmacokinetics parameters were evaluated for each subject in both 1st and 6th days of treatment.

Results: Based on our results, bioavailability of intramuscular Methadone in geriatric ICU patients was low and less than 40% of the dose was absorbed within first 12 hours. The volume of distribution of Methadone in the first day was significantly lower than the previously reported values in healthy subjects and significantly increased during these 6 days. The Methadone half-life in this population also significantly increased through this period.

Conclusion: Pharmacokinetic behavior of Methadone in geriatric ICU patients is unpredictable. Reduced volume of distribution and half-life may be observed initially, following with an increase to the normal range. It seems that IM administration of Methadone in geriatric critically ill patients may not provide target analgesic Methadone serum levels.

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Introduction

Pain control is one of the most important issues in Intensive Care Unit (ICU) patients and over 54% of post discharged ICU patients have recalled discomfort, However, their memory was often impaired (1).

*Corresponding Author: Dr Mojtaba Mojtahedzadeh
Address: Department of Clinical Pharmacy, School of Pharmacy, Tehran University of Medical Sciences, Enqelab Square, Tehran, Iran. Tel:+982166954709/ Fax:+982188322029..
Email: mojtahed@sina.tums.ac.ir

Methadone has been listed along with other opioids like Morphine and Fentanyl as primary medication for pain management (2) with a dose of 2.5 to 10 mg every 8 to 12 hours as described in the drug monograph. Although Methadone has unpredictable pharmacokinetic (PK) and pharmacodynamics (PD), especially in opioid naive patients (3). It has interindividual variability in pharmacokinetics parameters such as half-life, volume of distribution, time to steady state, bioavailability, unbounded fraction and clearance (4-6).

Methadone (6-dimethylamino-4,4-diphenyl-3-heptanone) is a synthetic long acting μ receptor agonist with pKa=9.2 which is 99% unionized in physiological pH that helps penetration to brain (4, 7). It has large volume of distribution and 98% of administrated Methadone will rabidly bound to tissues and 60-90% of central part drug will be carried by plasma proteins, especially Alfa-1 Acid Glycoprotein (AAG) (9). Lung tissue is the richest source of Methadone and brain is the poorest (10). Methadone distributes to the brain, gut, kidney, liver, muscle, and lung with tissue to plasma partition coefficients of 4.6, 37.2, 76.6, 44.2, 14.7, and 156.3, respectively, based on animal studies (11, 12). Methadone can be classified as a low hepatic extraction drug (9). Unchanged Methadone and its N-demetilated metabolite, mainly are excreted through the urine (13).

In spite of interindividual variability of methadone PK, this drug has some characteristics that make it suitable for critically ill patients. Long plasma elimination half-life of methadone can provide long analgesic duration (14). But we have to consider that Methadone PK parameters can change after repeated dosing regimen, increase in half-life and duration of action have been reported (15). Replacement of other opioids like Fentanyl with Methadone have shown to decrease the mechanical ventilation weaning time (16).

This long duration of action provides less frequent administration and facilitates the down-titration of opioids in ICU. So when patients experience tolerance with other opioids, Methadone can be used to treat chronic pain syndromes (17).

Hyperalgesia is a complex situation in some patients who get opioids. Hyperalgesia, as well as other adverse reactions like myoclonus, delirium and seizure has been explained by stimulation of N-methyl-D-aspartate (NMDA) receptor by 3-glucronidised metabolites of opioids like Morphine (18, 19). In contrast, Methadone is a NMDA receptor antagonist and has monoaminergic effect (20, 21), and retains no active metabolite (13). Hyperalgesic effect produced by this drug is less likely, and instead, it can be used for treatment of hyperalgesia and may be useful in the management of neuropathic pain (22). These unique features also make Methadone the least delirigenic opioid (23, 24). Furthermore it seems that Methadone is safe in renal failure and dialysis patients (25). These characteristics make methadone an attractive alternative for geriatric ICU patients who are vulnerable to delirium triggers.

Studies have discussed about Therapeutic Drug Monitoring (TDM) of Methadone in non-responder or poor responder patients (6). It has been proposed that analgesic minimum effective concentration (MEC) of Methadone is 58 ng/ml in the opioid naive adults (26). But for Methadone Maintenance Therapy in opioid users, keeping the plasma concentration of 250 ng/ml of (R)-Methadone or 400 ng/ml of (R,S)-Methadone has been recommended (6).

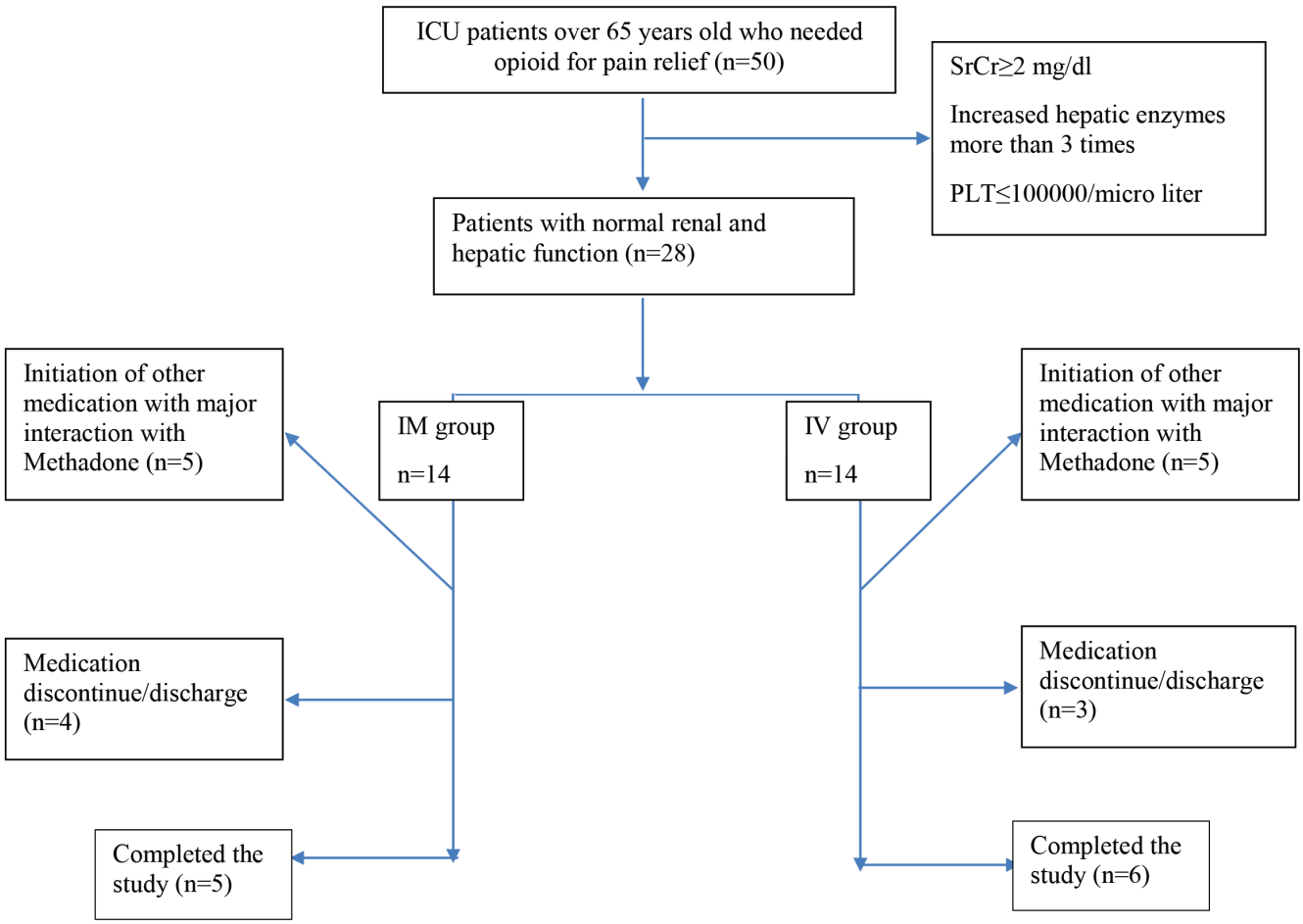
In addition to physiologic changes following critical illness (27, 28), geriatric patients have more complex condition because of age related changes such as decrease in lean body mass, total body water content and plasma proteins, Glomerulosclerosis, Neuroendocrine problems and polypharmacy (29).

Although almost all pharmacokinetic studies of parenteral methadone have been conducted on intravenous rout of administration, Methadone is labeled to be administered via intravenous (IV), intramuscular (IM) and sub-cutaneous injections in some countries. Besides, to the best of our knowledge, there are no studies on Methadone PK neither following IM administration in critically ill patients nor on ICU geriatric patients. This study aims to describe PK behavior of Methadone in older ICU patients following IM and IV administration as a pilot study.

Methods

This study was a prospective randomized clinical trial running at Sina hospital Intensive Care Unit (Tehran, Iran). Iranian Registry of Clinical Trials (IRCT) and Tehran University of Medical sciences Human Research Ethics Committee approved this study (IRCT2012091110817N1). Patients over 65 years old, who needed opioid for pain relief with normal renal and hepatic functions, were our target group. The exclusion criteria were serum creatinine over 2 mg/dl or urine output less than 0.5 ml/hour/kg, hepatic enzymes (SGOT and SGPT) increase more than 3 times, patients with platelets less than 100,000 per microliter, major drug interaction with Methadone in patent's drug list, Methadone discontinuation before the 6th day and experience of opioid usage in last 2 months.
Twenty geriatric patients included to the study. Patients randomly were divided in Intramuscular (IM) and intravenous (IV) groups with a simple randomization method based on predefined assignment sequences (Figure 1).

Figure 1. Flow chart of patient inclusion.



ICU: intensive care unit, IM:intramusclar, IV: intravenous, SrCr: serum creatinine, PLT: platelet.

Both groups were received 5 mg single dose of Methadone and blood samples were collected at 1, 2, 3, 4, 8 and 12 hours after administration in IV group and 1, 4, 8 and 12 hours in IM group to cover the distribution phase of IV administration and elimination phase in both IM and IV groups considering that the administration intervals cannot be more than 12 hours. Methadone administration was subsequently continued with 5 mg every 8 hours through the period from the second to the fifth days in both groups and at the 6th day, blood sampling was done exactly similar to the first day.

Collected blood samples were centrifuged for 15 minutes and separated plasma were stored in -70 °C until Methadone analysis.

Patients received Morphine or Fentanyl for breakthrough pain as PRN order. All other medications were under the supervision of ICU team as standard method.

Methadone assay

Plasma Methadone concentrations were determined by liquid chromatography tandem mass spectrometry, using a little modification of a previously described method (30). Plasma (200 µl) was pipetted into a 1.5 ml tubes and 100 µl of 500 mM sodium bicarbonate buffer (pH=11) was added. After two minutes' vortex mix, 400 µl of n-hexane was added, mixed for another 2 minutes and centrifuged for 15 minutes. A 250 µl portion of supernatant was transferred into a clean micro tube, dried under nitrogen and reconstituted with 200 µl of 12% isopropyl alcohol in 10mM ammonium acetate and acidified by 20 µl of pure Formic acid.

The final optimized LC separation was performed on a chromolith®performance RP-18e 100-4.6 mm HPLC column, with a mobile phase of water (pH=2.5): acetonitrile (70:30) at a flow rate of 1 ml/min. The Agilent technology 6410 Triple Quad mass spectrometer was operated in the

selected ion monitoring (SIM) mode at 310 m/z. The run time was 10minuets.

Standard curves were prepared including blank plasma and Methadone at a concentration range of 5-1000 ng/ml. Four different individual lots of blank plasma were extracted and analyzed as blanks and as QC0s. Quality control samples for the assessment of precision and accuracy of the assay were prepared by adding known quantities of Methadone powder to blank plasma samples in two concentrations (400 & 800 ng/ml) for 2 days.

Pharmacokinetic and statistical analysis

The PK parameters were determined by noncompartmental analysis model (31). These parameters included area under the plasma concentration versus times curve zero moment (AUClast (to 12 hours), AUCinf (to infinity) and % AUC extrapolated) and the first moment curve (AUMClast, AUMCinf). The AUMC is the area under the concentration times versus time curve. Both the AUC and AUMC were calculated using the trapezoidal method and the number of compartments were not concerned. Mean residence time (MRT, the average time that the drug stays in the body or plasma) was calculated as AUMC/AUC. To understand the Methadone disposition changes in geriatric ICU patients versus healthy subjects, Volume of distribution (Vd), Clearance (Cl) and half-life (T1/2) of Methadone also were calculated.

Analytical statistics were done using SPSS and Prism software and P value of <0.05 was considered as statistically significant. For the comparison of numeric data that didn't pass the normality test (Kolmogorov Smirnov test P value <0.05), we used nonparametric tests. Also we used Mc-nemar test for dependent data, Mann Whitney test for independent data and Wilcoxon Signed Rank test for comparison with healthy subjects. For normally distributed data, paired t-test for dependent data, unpaired t-test for independent data and one sample t-test for the comparison with healthy subjects were used.

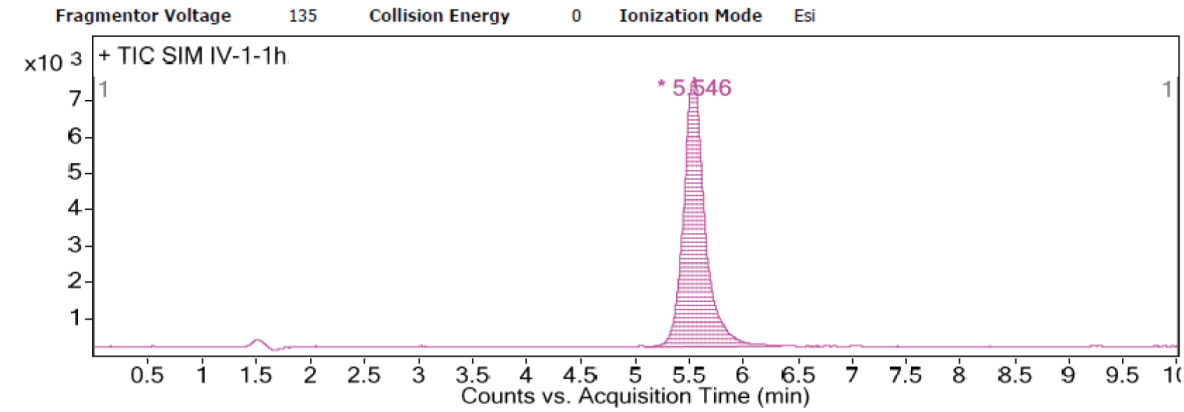
For descriptive statistics of not normally distributed numeric data, we have reported median with 25 and 75 percentiles and for normal distributed data, mean with standard error of mean (SEM) have been reported. Pharmacokinetic parameters of healthy subjects are based on previous studies (32).

Results

Analytical method validation

Retention time of Methadone peak was 5.5 minutes (Figure 2). The mean recovery of plasma extraction method was 70%. The within day-assay variability coefficients of variation were 3.2% and 3.0% for 400 and 800 ng/ml respectively and the between day-assay precision coefficients of variation were 6.0% and 2%, respectively (n=3). The limit of quantitation was 5 ng/ml of Methadone in plasma.

Figure 2. The chromatogram of Methadone on LC-MASS at 310 m/z.



Integration Peak List

Peak	Start	RT	End	Height	Area	Area %
1	5.094	5.546	6.350	7416	101938	100

Patients

Among twenty patients who meet our inclusion criteria, eleven patients completed the study (6 in IV group and 5 in IM group). Nine patients were excluded due to initiation of drugs with high interaction or early discharge/methadone discontinuation. The mean age of patients was 73.8 (range 72-81) and 75.2 (range 73-95) in IM and IV group respectively.

Patients were admitted to ICU because of central nervous system hemorrhages, multiple trauma or aneurysm. Nine patients were under the mechanical ventilation (Table 1). Up to 80% of the patients were received other opioids according to the ICU team decision.

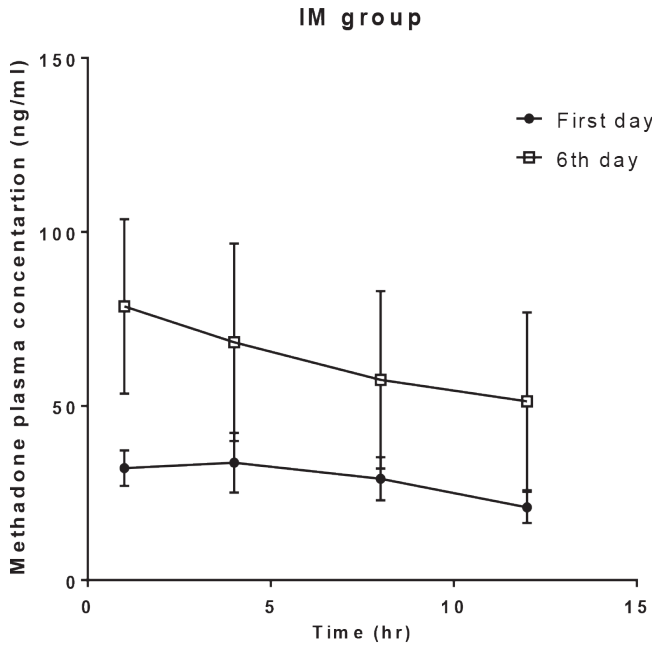
Table 1. Demographic characteristics of patients who have involved the study.

Patients Characteristics	IV group (6 patients)		IM group (5 patients)	
Age (years)	73-95		72-81	
Gender	Female	Male	Female	Male
	2	4	1	5
Causes of ICU admission	Multiple trauma, Subarachnoid hemorrhage, Bone fracture, Gastrointestinal bleeding, Intracerebral hemorrhage, Pneumonia		Subdural hemorrhage (2 patients), Intracerebral hemorrhage (2 patients), Abdominal aortic aneurysm	
Mechanical Ventilation	83% (5 patients)		80% (4 patients)	
Use of other opioids	83% (5 patients)		80% (4 patients)	

ICU: intensive care unit, IM:intramusclar, IV: intravenous.

Figure 3 shows Methadone plasma concentration-time curve (mean±SEM) of both group at the first and last days of study. In each group, the results of one patient were removed from the first day due to inappropriate sampling (more than 2 samples were hemolyzed). The mean plasma concentration of Methadone in the first hour of sampling in IV group was 600±300 ng/ml and 1200±600 ng/ml in first and 6th days respectively. For the best graphical illustration of Methadone concentration versus times curve, we exclude the first hour concentration in the second graph of IV group; although it was included in pharmacokinetic calculations.

Figure 3. Methadone plasma concentration-time curve (mean±sem) of both group.



Pharmacokinetics

Pharmacokinetics parameter of each day and the P value of differences between first and 6th day parameters and also healthy adult subjects PK parameters have been listed in Table 2 and 3 (32).

The volume of distribution was 77.8 (56.6, 165.1) and 107.8 (72.2, 216.4) liters in first and 6th day respectively and significantly increased during 6 days (P value=0.02). The Methadone half-life in this population were 7.8 (5.3, 25.6) and 18.55 (9.7, 23.3) hours in first and 6th day and also significantly increased through these 6 days. The Methadone clearance in this population has no significant difference between first and 6th day of sampling (7.1±1.4 and 7.3±1.6 (l/h) P=0.92) and also in comparison with healthy subjects (mean Cl of 6.9 l/h p=0.81) (Table 3).

Methadone Vd and T1/2 in geriatric ICU patients in the first day of sampling are significantly less in comparison with healthy subjects (212 l and 33 to 46 (39.5) hours respectively with P value=0.004 & 0.004), but this difference was not observed in the 6th day (Table 3).

Table 2. Methadone pharmacokinetics parameters of geriatric critically ill patients in two days of sampling and the difference.

Pharmacokinetics parameters	first day both groups n=9	6th day both groups n=11	P value of difference between 2days of sampling
Cl[g] (l/hr) mean±sem	7.1±1.4	7.3±1.6	0.92
Vd[h] (l) median (25%,75% percentile)	77.8 (56.6,165.1)	107.8 (72.2,216.4)	0.02
$T_{1/2}$[i] (hr) median (25%,75% percentile)	7.8 (5.3,25.6)	18.55 (9.7,23.3)	0.004

• The P value of<0.05 was considered as statistically significant. g: Cl: Clearance, h: Vd: Volume of distribution, i: T1/2: elimination half life

Table 3. the comparison of Methadone pharmacokinetics parameters in geriatric intensive care unit patients and healthy subjects.

Pharmacokinetics parameters	Healthy subject's parameters[32]	P value of difference between first day and healthy subjects	P value of difference between 6th day and healthy subjects
Cl (l/hr)	6.9±1.5	0.90	0.81
Vd (l)	212±27 l	0.004	0.37
$T_{1/2}$ (hr)	33-46	0.004	0.07

• The P value of<0.05 was considered as statistically significant. g: Cl: Clearance, h: Vd: Volume of distribution, i: T1/2: elimination half life

Table 4. Comparison between IV and IM group in AUC.

Parameters (mean±sem)	IV group			IM group			P value of difference between total data of IV and IM group
	First day n=5	6th day n=6	Total n=11	First day n=4	6th day n=5	Total n=9	
AUC last[a] (hr*ng/ml)	4708±2444	24811±15335	15673±8674	340.6±68	225.6±57	276.7±45.7	<0.0001
AUC inf[b] (hr*ng/ml)	5016±2393	10874±9362	8211±5079	1012±327	935.5±304.8	969.7±209.5	0.65
% AUC extra[c]	21.5±12.6	19.33±9.4	20.34±7.3	55.7±12.8	63.9±11.2	60.3±8.01	0.007

sem: standard error of mean

a: AUC last: Area Under the time-concentration Curve to t_{last} (12 hour)

b: AUC inf: Area Under the time-concentration Curve to infinity (extrapolated theoretically)

c: AUC Extrapolated: the percentage of AUC inf that exists after t_{last} (12hr)

$$\%AUCExtra = \frac{AUCinf-AUClast}{AUCinf} \times 100$$

note: the AUC last and AUC inf were calculated without the influence of accumulation in 6th day. (AUC 6th day in the table= actually AUC 6th day divided by R)

R= accumulation factor ($R = \frac{1-e^{-nk\tau}}{1-e^{-k\tau}}$)

The comparison of pharmacokinetic parameters between IV and IM groups are described in Table 4-5.

Table 5. Comparison between IV and IM group in MRT.

Parameters (mean±sem)	IV group		P value of difference between 2days of sampling in IV group (paired t-test)	IM group		P value of difference between 2days of sampling in IM group (paired t-test)	P value of difference between IV and IM group 1th and 6th day (unpaired t-test)
	First day n=5	6th day n=6		First day n=4	6th day n=5		
MRT last[d] (hr)	2.03±0.97	1.74±0.82	0.5	5.8±0.07	5.45±0.42	0.4	<0.001
MRT inf[e] (hr)	9.1±5.25	8.68±3.9	0.8	31.1±9.7	28.1±10.8	0.8	0.007
Time above MEC[f] (hr)	1.9±0.9	5.23±1.94	0.2	0	3.9±2.16	0.2	0.4

sem: standard error of mean

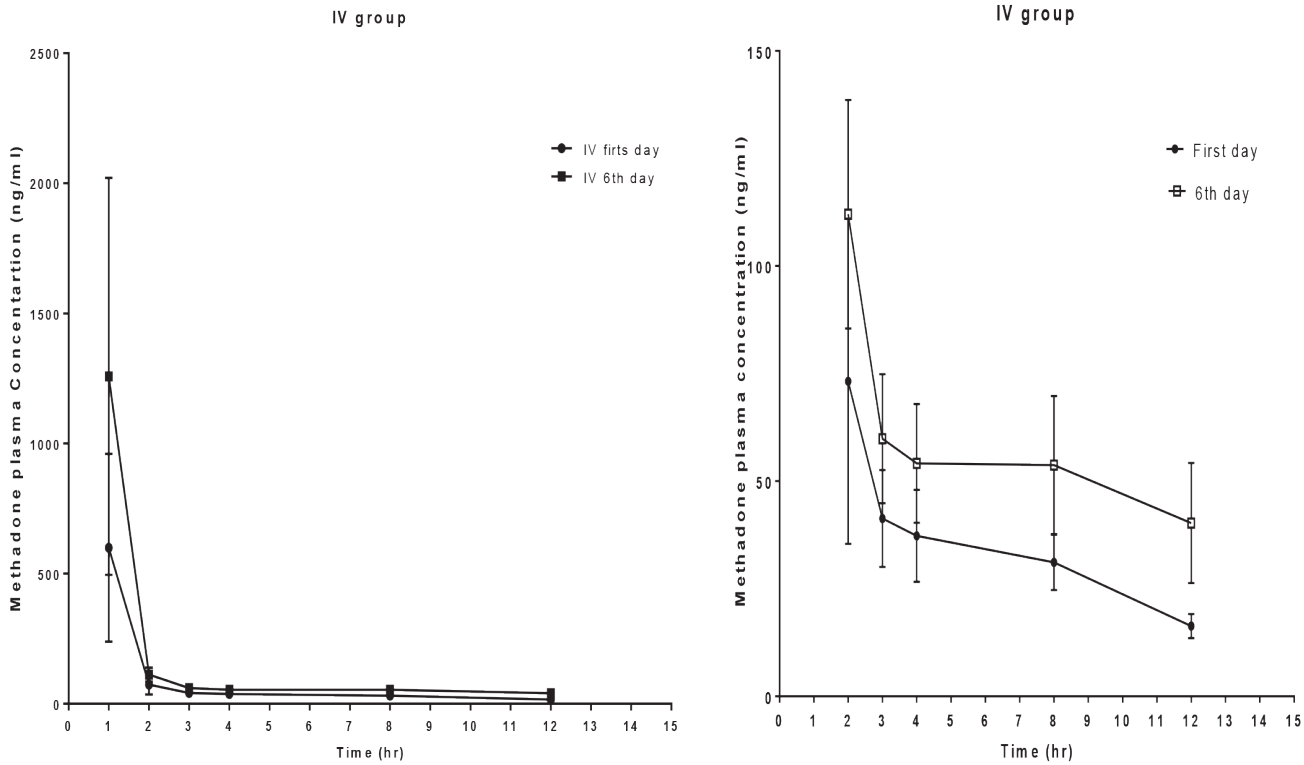
d: MRT last: Mean Resident Time to 12 hour, e: MRT inf: Mean Resident Time to infinity, f: Minimal Effective Concentration (58ng/ml)

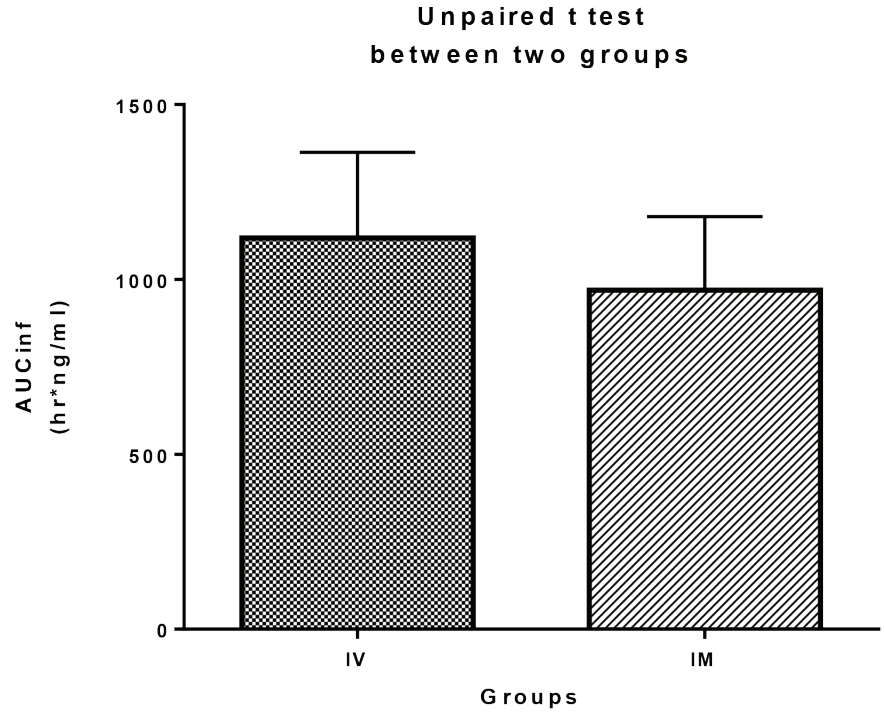
The total mean±SEM of AUCinf were 8211±5079 h*ng/ml and 969.7±209.5 h*ng/ml in IV and IM groups respectively, with no significant difference (unpaired t-test P value=0.65) (Figure 4).

The percentage of extrapolated AUC in IM group was significantly more than IV group (P value=0.007).

The MRT to infinity in IM group was significantly more than IV group (unpaired t-test P value=0.007). Time above MEC increased in both groups from first day to sixth day (1.9±0.9 hours in first day vs. 5.23±1.94 hours in sixth day in IV group and zero in first day vs. 3.9±2.16 hours in sixth day in IM group) but did not reach the statistical significance due to small sample size.

Figure 4. The difference between IM and IV group AUC to infinity.





Discussion

Known as a long acting opioid, studies show that the duration of Methadone analgesic effect is very shorter than its elimination half-life (33). This has been related to fast distribution and high tissue affinity of Methadone. After multiple doses and accumulation, the duration of Methadone analgesic effect will improve and could get up to 12 hours (15).

From our results (Figure 3) it is evident that administration of 5 mg of Methadone can provide analgesic plasma levels (higher than almost 60 ng/ml) approximately up to 4-6 hours. Although time above minimum effective concentration was more variable in IM rout and no patient experienced analgesic plasma level after first day IM administration.

There are limited data about analgesic effect of Methadone following IM administration. Beaver et al. has described Methadone effectiveness following single dose IM administration. More than half of the patients experience at least 50% pain relief with 8 mg single dose intramuscular Methadone at 1-2 hours with duration of action not more than 6 hours (34).

However there are recommendation against use of IM rout for geriatric and ICU patient due to unpredictable absorption and injection site pain and it is believed that the best rout of drug administration in ICU patients is intravenous (35, 36).

In agreement with these recommendations our results in the IM group reflect variable concentration-time curves and it seems that Methadone muscular absorption in geriatric population is not reliable for management of acute pain, especially with single dose administration and PRN use.

A comparison between AUCinf of IM and IV group shows that the bioavailability of Methadone after muscular injection was above 90% in geriatric ICU patients. But the large percentage of AUCextra (AUC from 12h to infinity) in IM group reflects that the absorption occurs so slowly and less than 40 percent of IM injected Methadone may be absorbed within 12 hours.

On the other hand, according to higher MRT of Methadone in IM group, it seems that IM administration make a stable level of Methadone in blood. So it may be useful for management of chronic pains with multiple injections.

Methadone distribution can best be described with 3 compartmental model and rapid distribution of drug have been reported (37).However, no pharmacokinetic study have been published in geriatric patients. As mentioned above, we used noncompartmental method for description of PK parameters in this study. In comparison our results show that distribution phase of methadone occurs slower in geriatric ICU patients which may lead to supratherapeutic level in first hour (up to 600 ng/ml following 5 mg single dose IV administration) and declines rapidly to therapeutic serum levels. Delayed distribution phase and decreased Vd results in a higher plasma concentration of Methadone with a same dose in comparison with other population.

This disturbance may be explained by hypo perfusion state of critically ill patients (35). In geriatric people, usually cardiac output and vascular flexibility diminish and make reduction in peripheral tissue perfusion (38). Additionally, Methadone is a p-glycoprotein substrate drug and some researchers have suggested that the activity of p-glycoprotein increases in people over 56 years old (39). This can lead to resistance against drug penetration into the cells.

Considering that about 80% of our patients were under the Mechanical Ventilation (MV), it has been suggested that the effect of MV on drugs PK is similar to the effect of heart failure and usually decrease the cardiac output (CO) and make reduction in volume of distribution and elimination of drugs (40).

As mentioned above, Methadone is mainly carried by AAG in blood. AAG is an acute phase protein that increases in first 48 hours of a stress situation (41) and also it has be described that it may increase in elderly (42). This increase can keep Methadone in the central compartment and decrease Vd.

Wolf et al., have calculated the Methadone pharmacokinetics parameter in healthy subjects and opioid users after a single oral dose. The elimination half-life, volume of distribution and clearance of Methadone in healthy subjects were 33-46 h, 212±27 l and 6.9±1.5 l h-1 respectively (32). Based on our results, elimination half-life and volume of distribution in geriatric critically ill patients were significantly decrease compared with healthy subjects (Table 3).

Considering that clearance of Methadone dose not differ significantly in comparison with healthy subjects, it seems that the reduction of Methadone half-life in this population was as a result of decrease of Vd.

Whatever it is, low Vd and short half-life may not remain so long and it is not wise to reduce the interval of administration to prevent subtherapeutic levels, because accumulation may happen due to unpredictable increase in Vd and half-life.

This study has several limitations including small sample size. Considering this study as the first study on Methadone pharmacokinetic following IM administration in critically ill patients, we decided to design as a pilot study. Another limitation of this study is the lack of evaluation of pain relief following methadone administration which makes all observations based on PK perspective. PK/PD studies may improve our knowledge about optimum dosing regimen of Methadone in this setting.

In conclusion, this was the first study to describe pharmacokinetic of Methadone following intramuscular injection in critically ill patients. In this study we described that in spite of high bioavailability, IM administration of Methadone could not reach sufficient serum level of Methadone and the absorption occurs so slowly and unpredictable in geriatric ICU patients. IM injection of Methadone is not a rational strategy for management of acute pain in this population from the PK perspective. Although it's clinical relevance remains to be studied.

In spite of Methadone long elimination half-life, it could not provide minimum effective plasma level more than 4 hours in early dose administrations in geriatric ICU patients. So if the practitioner decides to use Methadone for geriatric ICU patient according to its advantages, it could be used as maintenance therapy and other opioids should be supplemented for breakthrough pain.

In geriatric ICU patients we have to dose Methadone so carefully because the PK parameters may change due to physiological alternations. The normalization of Methadone half-life and Vd during these 6days shows that changes in physiological situation can significantly affect the PK behavior of Methadone.

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