

Research Article

Pethidine Level in Jordanian Women and their Newborns during Labor after a Single Intravenous Dose

Abu Dayyih W^{1*}, Dania El Tannir¹, Eyad Mallah¹, Mohammad Hamad², Nasir Idkaidek³, Riad Awad¹, Abdel Fatah Salem⁴ and Tawfiq Arafat¹

¹Department of Pharmaceutical Medicinal Chemistry and Pharmacognosy, University of Petra, Jordan

²College of Science and Health Professions, King Saud bin Abdulaziz, Saudi Arabia

³Department of Pharmaceutics and Pharmaceutical Technology, University of Petra, Jordan

⁴University for Health Sciences, Hashemite University, Jordan

***Corresponding author**

Wael Abu Dayyih, Department of Pharmaceutical Medicinal, Chemistry and Pharmacognosy, Faculty of Pharmacy and Medical Sciences, University of Petra, Tel: 0096265799555 Ext 8119; Fax: 0096265715561; Email: wabudayyih@uop.edu.jo

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Abstract

Background: Since 1940, pethidine became the most widely used opioid for labor analgesia. However, pethidine administration may cause fetal distress especially if delivery occurred in a short time after administration and due to genetic variations between populations. Therefore, the aim of this study was to develop a validated and sensitive method for determination of pethidine in plasma followed by determination of plasma pethidine level in Jordanian women at different times during and after labor and in the neonatal cord just after delivery.

Methods: Liquid Chromatography tandem mass spectrometry was developed to measure pethidine levels in plasma. Fifteen pregnant females agreed to enroll in the study and each signed an informed consent. All pregnant females received a single intravenous dose of 50 mg pethidine followed by withdrawing of blood samples at certain time points for the measurement of pethidine levels. In addition, umbilical cord was collected for the same purpose.

Results: Due to fetal distress, three out of fifteen subjects (20%) dropped out of the study following pethidine administration and went through Caesarian section. Two of the three withdrawn cases had high maternal pethidine plasma levels. A negative correlation was found between pethidine bioavailability in the newborn and the dose-delivery duration ($p < 0.01$). In addition, there was a negative correlation between maternal's pethidine concentration and Apgar score ($p < 0.05$).

Conclusion: The present study showed that single intravenous dose during labor cannot be considered safe in Jordanian population without an extensive study with larger sample size regarding pethidine route of administration and its metabolism.

INTRODUCTION

Pethidine, 1-methyl-4-phenylpiperidine-4-carboxylic acid ethyl ester, is a strong synthetic opioid analgesic drug belongs to phenylpiperidine group (Figure 1). It is used as an analgesic during labor since 1940 [1]. Since then, pethidine has become the most widely used opioid analgesic drug during labor. It can be administered either orally or parenterally via the intramuscular, intravenous or epidural routes [1-3].

Consequently, pethidine is thought to be an effective and safe analgesic to mothers and their newborns when administered

during labor. In fact, adequate relief of pain during the first and the early portions of the second stage of labor and during the perineum repair help keep the mother cooperative during delivery, increasing normal vaginal delivery and decreasing the need for forceps or suction for extraction of the baby [4,5]. Some studies, however, have reported that pethidine levels might cause fetal distress especially if delivery occurred in a short time after administration [4,5].

In addition, genetic variations in different populations may affect pethidine metabolism and thus its transfer level to fetal blood stream may cause fetal distress [6].

Thus, it is essential to determine pethidine levels in women and their newborns during labor in different populations so as to recommend protocols for pethidine administration in such populations.

Many studies reported various methods for the determination of pethidine in plasma or in pharmaceutical formulation using various instrumentation [7-10]. However, the methods reported for the determination of pethidine in plasma have some disadvantages such as the limit of quantification and the limit of detection are not sensitive enough; the extraction method from whole blood is tedious and the high alkalinity of the mobile phase degenerates the column more often. In addition, there are no studies were conducted to determine pethidine levels in Jordanian women and their newborn during labor. Therefore, the aim of this study was to develop a validated and sensitive method for determination of pethidine level in plasma followed by determination of pethidine level in Jordanian woman's blood at different times during and after labor and in the neonatal cord just after delivery following intravenous bolus injection of pethidine. Furthermore, this study highlighted the possible relationships between pethidine blood concentrations and time of administration and labor, mother's weight, fetal condition, newborn's weight, newborn's sex and Apgar score. The long-term objective, however, is to recommend a protocol for pethidine administration in Jordanian women during labor in order to reduce pethidine-related adverse events in newborns.

MATERIALS AND METHODS

Chemical reagents and instrumentations

The following reagents (providers) were used throughout the study: pethidine (Manufacturer: Martindale), methanol (Fisher), H₂O (Fisher), ethyl acetate (Fisher), diethyl ether (Tedia), Tricarboxylic Acid (TCA) (Acros), formic acid (VWR), ammonia (Fisher), di-chloro-methane (Acros), methyl tertiary butyl ether (Fisher), bisoprololfumarate (RD). The following instruments (providers) were used in the present study: ion trap mass spectrometer, constant solvent delivery system (Ultimate 3000 RS Pump), volume injector, vacuum degasser (Ultimate 300RS), autosampler (Ultimate 3000 RS), column: ACE 5 C₁₈ 50x2.1mm; LCQ Fleet mass spectrometer, computer system (Windows XP, Thermoscientific®, X Calibar®, Data management software).

Method development

Mobile Phase: From a stock solution of 50 mg/ml pethidine, a 5 µg/ml of pethidine was prepared in 1:1 H₂O/methanol. A volume of 200 µl was transferred into insert vial and injected into LC-MS using a mobile phase composed of 40% aqueous phase (30% tri-chloro-acetic acid and ammonia) and 60% of methanol, pH =3. The flow rate was set at 0.20 ml/min with 5 µl the injection volume and temperature of auto sampler was set at 25°C.

Extraction method: The liquid-liquid extraction using methyl tertiary butyl ether had shown the higher intensity, better resolution with no matrix effect and higher recovery. A 250µl volume of plasma-spiked with pethidine was used in order to obtain 1000ng/ml plasma solution in methyl tertiary butyl ether. The solution was centrifuged for 6 minutes at a speed of 4400 rpm. The supernatant obtained was reconstituted in 200µl H₂O/

methanol (2:1), followed by centrifugation and then the 200 µl of the supernatant was transferred into vials containing the mobile phase for determination.

Selection and preparation of the internal standard (bisoprolol): Bisoprolol, 1-{4-[(2-isopropoxyethoxy) methyl] phenoxy}-3-(isopropylamino) propan-2-ol, was used as the internal standard (Figure 2). A standard solution of bisoprolol (5 µg/ml) showed a peak with a good intensity, no tailing and good resolution, in addition that the retention time was in the same range of pethidine.

Standard solutions and QCs: A stock solution of pethidine was prepared by diluting 1ml of the standard 50mg/ml to q.s. 100 ml 1:1 H₂O/Methanol, resulting in 500 µg/ml solution. The latter was used to prepare serial standard concentrations and spiked plasma concentrations containing the following concentrations: 20, 40, 80, 150, 300, 600, and 1000ng/ml. The QC concentration samples were 60, 500, and 800ng/ml.

Autosampler stability: The autosampler stability study evaluates the stability of pethidine during the injection in the autosampler held at 25°C. The validation is performed over duration of 24 hours. A volume of 50µl of the internal standard stock solution was added to 250µl of each QC aliquot.

Freeze and thaw stability: This validation study is based on the evaluation of the stability of the analyte after 3 cycles of melting and freezing the pethidine sample. Three samples of each QC concentration were prepared, extracted and reconstituted and then injected into the LC/MS-MS.

Bench stability: Six samples of each QC concentration were prepared according to the method described above. Three of each was injected at zero time and the others were kept on the bench at 25°C for 6 hours and then re-injected into the LC/MS-MS.

Recovery and matrix effect

QC samples containing different concentrations (60, 500

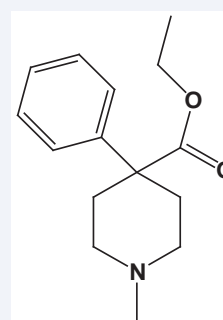


Figure 1 Pethidine structure.

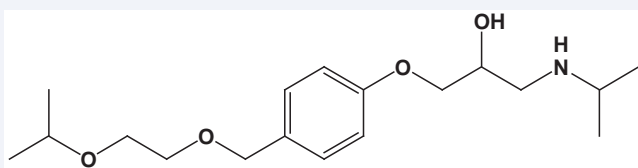


Figure 2 Bisoprolol structure.

and 800ng/ml) were prepared in plasma in 2:1 H₂O/Methanol and containing 50µl of 5µg/ml internal standard solution. These samples were evaluated for percent recovery and matrix effect.

Linearity

Plotting of peak area ratios of standards versus concentration for each sample set and the calibration standard lines were shown to be linear from 20 to 1000 ng/ml for pethidine plasma. R² values were more than 0.996.

Precision

The precision of the assay was measured by intra-day and inter-day percent coefficient of variation over the concentration range from 20 to 1000 ng/ml for pethidine. During the course of the validation, precision was estimated in 10 samples of each quality control concentration and was repeated for 2 consecutive days.

Clinical study

The study was performed in accordance with the relevant articles of the Declaration of Helsinki (1964) as revised in Tokyo (1975), Venice (1983), Hong Kong (1989), Somerset West, RSA (1996) and Edinburgh (2000) with the "Note of Clarification on Paragraph 29" added by the WMA General Assembly, Washington (2002), the "Note of Clarification on Paragraph 30" added by the WMA General Assembly, Tokyo (2004) and the "Note of Clarification on Paragraph 30 added by the 59th WMA general Assembly, Seoul, October 2008. Prior to the initiation of the study, the Ethics Committee (IRB/IEC) at Al-Basher Hospital where the study was carried out approved the study protocol and the informed consent form.

Study population

Fifteen pregnant women enrolled in the study. The average age and weight was 26 ± 6 years and 76 ± 8 kg, respectively. All volunteers read and signed the informed consent. All women were physically and mentally healthy as judged by means of medical and standard laboratory examination. None of the volunteers have any history of alcoholism or drug abuse.

Study design

The study was conducted according to an open, single dose, one period, one treatment in pregnant women in labor. According to the protocol of this study, pregnant women were enrolled in this study if they were already intended to take this analgesic medication. The dosage of pethidine (pethidine HCl) used was 50 mg/ml administered intravenously as the recommendation of Al-Basher Hospital. As safety assessment all pregnant women involved in this study were included in the listing of the safety data. Reason and date for any withdrawal were reported. All adverse events were listed and tabulated by severity, treatment and relationship to the intervention. A list of the reference ranges and units of measurement of the laboratory parameters were determined during the study and documented in each CRF. Any value out of range was assessed as "Not Clinically Relevant" (NCR) or "Clinically Relevant" (CR) on the laboratory printout. If during the course of entry screening, any clinical relevant abnormal value had been observed, this finding was regarded

as an exclusion criterion. Single laboratory values outside the reference range were not regarded as an exclusion criterion provided that: they are not accompanied by clinical symptoms. The context of related laboratory values gives no indication of a pathological process and the investigator regards them as "Not Clinically Relevant" (NCR).

BLOOD SAMPLING AND DRUG ADMINISTRATION

A venous canula was inserted and 2.0 ml blood sample was withdrawn. In addition, a blood sample of 2.0 ml was withdrawn from the umbilical cord after child's birth. Blood samples were placed into heparinized tubes and kept on ice till centrifugation. Samples were processed within 6 hours. After centrifugation, the plasma was collected into an Eppendorf tube and stored frozen at -30°C till analysis. On the day of the sample analysis, a calibration curve was performed with 7 standard points.

Blood sampling was performed at the following times: immediately after labor from mother and 2 hours post drug administration. The precise instructions for drug administration were given to patients by the investigators. All patients, except patient 1, received a single dose of 50 mg/ml of pethidine. Patient 1 received 2 doses of pethidine in 2 hours interval.

Data analysis

The determination of pethidine plasma concentrations were performed by means of LC-MS/MS chromatographic assay method at the laboratories of Jordan Centre for Pharmaceutical Research (JCPR), Amman, Jordan. A validated method for pethidine analysis was developed before the analysis of the patients' samples. The method has been validated for linearity, sensitivity, stability, recovery, precision and accuracy.

The AUC for pethidine had been calculated through Kinetica version 5 software. The relationship of the AUC and the different baseline characters was statistically studied using ANOVA. In addition, Pearson correlation matrix was used to test the correlations between the Apgar score, baby concentration, dose duration, log AUC, log C (baby concentration).

RESULTS AND DISCUSSIONS

Validation

The validation of the method of the present study was accredited in terms of sensitivity, stability, recovery, linearity, intra-day and inter-day precision and accuracy. The accuracy and precision of the LLOQ (20 ng/ml) were 108.9% and 7.3%, respectively. Since these values were within the acceptable range of LLOQ, the method sensitivity is 20 ng/ml (Table 1).

In order to evaluate the linearity of the calibration curve, the latter was plotted on three different days, and the correlation factor (R²) was calculated, for each (Figure 3). The mean of the three ratios (AUC of pethidine/AUC of internal standard) was then plotted against the theoretical concentration ranging from 20ng/ml to 1000 ng/ml. The calibration curve for the each day was plotted and considered valid, when the maximum deviation of the accuracy and LLOQ were within the acceptable limits (Table 1).

The validation of the method of analysis also included

intraday variation by evaluating the results of 10 samples of each QC concentration injected in the same day (Table 1). Similarly, 10 samples of every QC concentration were prepared and injected into the LC-MS/MS, on different days. The accuracy and precision of all exhibited values ranged between 85-110% and 0-10%, respectively.

As for auto sampler stability, the three QC samples ran and showed accuracy values of 90.1, 99.9 and 93.5%, with 4.3, 15, and 3.9% accuracy deviation values for low, mid and high QC, respectively. Furthermore, the bench top stability exhibited accuracy values of 93.8, 96.3, and 96.6% with 3.8, 4.9 and 4.7% accuracy deviation values for low, mid and high QC, respectively. In addition, three cycles of freezing and thawing of the QC samples also resulted in accuracy of 96.5, 100.8, and 97.1% with 4.2, 2.5 and 7.8% precision values for low, mid and high QC, respectively.

The efficiency of the extraction method is expressed by the recovery whereas the effect of the plasma of the efficiency of the method of analysis is expressed by the matrix effect. The recovery of the pethidine was 80.6%, 87.1% and 94.6% for the

QC low, mid and high respectively, whereas the recovery of the internal standard was 85.1%, 98.1% and 100% for the QC low, mid and high, respectively. On the other hand, the matrix effect on pethidine was 94.9%, 104.8% and 101.3% for the QC low, mid and high respectively, whereas the matrix effect on the internal standard was 94.0%, 86.6% and 86.0% for the QC low, mid and high respectively.

Clinical part

Maternal baseline characters: All the subjects have completed 36 weeks gestation on admission to the delivery room. All the mothers were healthy and non smokers except subjects 10 and 12. In fact, according to the subject history taken whether from the subject file or upon questioning, none of the 13 subjects had experienced any chronic disease or chronically taking any medication. Nevertheless, subject 10 developed preeclampsia and gestational diabetes. She had being treated with methyldopa for lowering hypertension, but she was not on any pharmacological treatment for diabetes. The blood sample from this patient was taken at 0 time, but as a result of fetal distress and the patient felt very dizzy, she was transferred for Caesarian section. On the other hand, subject 12 experienced gestational diabetes, and she was on low sugar diet without being treated pharmacologically.

Subject 4 has been withdrawn in less than 30 minutes of pethidine injection. She experienced a severe drop of fetal heart rate and neonatal depression. The first sample for this subject was taken 5 minutes after administration instead. The analytical determination of pethidine in plasma has demonstrated a very high concentration, (42018 ng/ml) after 5 minutes. This concentration exceeds the maximum concentration [11].

Thus, the amount of pethidine transferred to the fetus would have been very high and correlating to the symptoms observed [12].

Neonatal depression, which developed in subject 4, could be secondary to the exceedingly high level of pethidine in the mother's blood. This might be subsequent to a very low, almost non-existent, pethidine metabolism that had resulted in a high amount of pethidine transferred to the fetus and probably caused a very rapid decrease in fetal heart rate. The inter-patient genetic variability in drug metabolism might be a potentially important factor that should be further investigated.

Pethidine maternal pharmacokinetics: Following a single intravenous injection of 50 mg of pethidine, blood sampling was performed at different intervals of time. The concentrations were measured at 0, 120 minutes and just after delivery. Fifteen subjects were included in the study of whom 12 (80%) have completed the study and 3 (20%) were withdrawn. In fact, the withdrawn cases were transferred to the operation room for caesarean section. The plasma pethidine concentrations were determined by LC-MS/MS according to the validated method described before (Table 2). The cases where the blood sampling occurs between 0 and 120 minutes correspond also to the post delivery sample. However, blood sampling could not be taken for subjects number 8 and 14 at 120 minutes because the subjects were in the delivery room at the time, and the sample could not be collected immediately.

Table 1: Example of validation parameters such as sensitivity, calibration curve and QC samples of the validated method.

Condition	Theoretical Conc. (ng/ml)	Measured Conc. (ng/ml)	Accuracy%	Precision%
Sensitivity	20	22 ± 3	109	7.3
Calibration curve				
	20	18	92	
	40	45	112	
	80	88	110	
	150	134	90	
	300	285	95	
	600	585	97	
	1000	1034	103	
QC Samples				
QC 60	60	63 ± 2	106	4.5
QC 500	500	521 ± 28	104	5.4
QC 800	800	802 ± 42	101	5.2

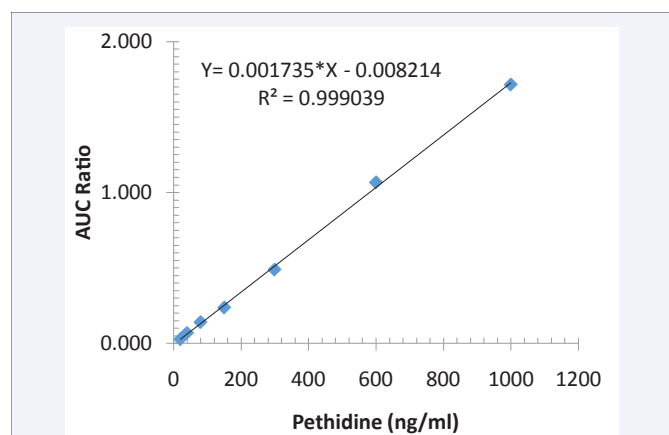


Figure 3 Calibration curve of pethidine in plasma.

Subject 12 has the highest concentration of pethidine (413 ng/ml) at 120 minutes. This may have resulted in the fetal distress and the transfer of the mother to the operation room for Caesarean section delivery.

After a 100 mg intravenous pethidine injection, the mean of $T_{1/2\beta}$ was calculated to be 157 minutes and the maximum concentration (~800 ng/ml) was reached within the first 30 minutes. Nevertheless, among the subjects who had completed the study, 4 subjects (33.3%) had shown a different profile than the normal intravenous profile. The plasma pethidine concentration has been increasing by the time such as in subjects 2, 5, 6 and 12 (Table 2). In some individuals pethidine plasma concentration may increase with time due to a very slow drug metabolism or factors that might interfere with its metabolism [13].

Newborn baseline characters and pethidine pharmacokinetics: The mean weight of the newborns was 3.2 ± 0.4 Kg, and 42% of the newborn were female, and 58% were male (Table 3). The mean Apgar score was 7.8 ± 0.71 . Since all the scores were above or equal to 7, none required antidote to pethidine or medical assistance.

Since the plasma pethidine concentration withdrawn from the umbilical cord reflects the plasma concentration in the newborn, it was decided to take blood from the cord rather than to withdraw blood from the newborn. The plasma pethidine concentrations (ng/ml) for the 12 newborns at the time of

delivery are shown in Table 4. The relationship of the pethidine AUC and the different baseline newborn characters was statistically studied. The statistical results showed that neither the mother's age/weight nor the baby sex/weight was affected by pethidine AUC ($p > 0.05$). The only factor that was affected by the AUC is the Apgar score ($p < 0.05$). As all the mothers have received the same dose and as pethidine is strongly correlated to lowering the Apgar score, consequently, the slower the mother metabolism results in higher transplacental passage resulting in low Apgar score [13].

This elucidates the rapid lowering of the fetal heart rate in subject 4 where the maternal concentration was 42017 ng/ml. It should also be noted that the newborn metabolizes pethidine seven times less than the adult one account of N-demethylation and N-oxidation pathways impairments [14].

Effect of Pethidine of high concentration (C_{max}): The baseline characters including the mother age, mother weight, baby sex and baby weight did not affect the value of the maximum concentration of plasma pethidine reached. In consequence, the pharmacokinetics of pethidine in mother during labor can be comparable to the non-pregnant women. In fact, pethidine half-life of women in labor is not different from that in non-pregnant women, but the volume of distribution in the former is larger, and the clearance is decreased [14].

The placental transfer of pethidine can be reflected by the ratio of umbilical cord pethidine concentration to maternal pethidine blood concentration sampled at the same time. This

Table 2: Pethidine concentrations in pregnant women during labor at different sampling times following a single pethidine injection (50 mg).

Subject	Time (min) following pethidine administration										
	0	5	30	60	75	90	120	140	160	180	213
	Pethidine (ng/ml)										
1	0					257	233				
2							139		200		116
3	0						158			127	
4 (W)	0	42018									
5	0						209				304
6	0			129			258				
7	0				111		88				
8	0									100	
9	0				268		215				
10 (W)	0										
11	0						218	137			
12 (W)			331				413				
13	0					356	138				
14	0								109		
15						266	196				

Table 3: Baseline characters of the newborn related to the cases that completed the study.

	1	2	3	5	6	7	8	9	11	13	14	15
Sex	M	M	M	M	F	M	F	M	M	F	F	F
Weight (Kg)	3.4	3.7	3.2	2.9	3.3	2.8	2.88	2.8	3.4	3.8	3.45	2.9
Apgar score at 1 min	8	7	7	8	8	7	7	8	8	9	8	9

Table 4: Pethidine concentration in umbilical cord at the time of delivery in relation to the time following pethidine administration.

Baby	Time (min) following pethidine injection									
	30	45	50	75	80	90	140	160	185	213
Pethidine (ng/ml)										
1						365				
2	148									
3									100	
5										0
6			166							
7				236						
8							162			
9		179								
11						113				
13					88					
14								54		
15					150					

Table 5: Correlation between newborn pethidine concentration and dose duration on Apgar score.

Variable	Coefficient	Std error	Std coeff	Tolerance	T	p
Pethidine newborn conc	0.023	0.006	0.499	0.606	3.98	0.003
dose duration	0.037	0.008	0.555	0.606	4.427	0.001

could not be performed in this study since in 4 subjects the blood sampling was delayed.

Correlation analysis

Using Pearson correlation matrix, the correlations between the factors Apgar score, baby concentration, dose duration, log AUC, log C (baby concentration) were evaluated (Table 5). The pethidine concentration in the newborn was negatively correlated to the dose duration, so as the time elapsed from intravenous pethidine injection to the sampling increases, the baby concentration decreases. In subject 5, the delivery took place 213 minutes after pethidine administration, and pethidine concentration in the newborn was not detectable. Intravenous administration of pethidine and the associated dose-delivery duration has not been previously addressed. There are published reports, which address the intramuscular administration of pethidine. In one study, the maximum pethidine trapping in the baby was three hours after 100mg i.m. pethidine injection [14-16]. Moreover, after a same dose, the ratio of fetal concentration to maternal concentration increased in the first 5 hours [14].

CONCLUSION

The present study showed that single intravenous dose during labor cannot be considered safe in Jordanian population without an extensive study with larger sample size regarding pethidine route of administration and its metabolism. Consequently, in order to reduce pethidine-related adverse events in newborns, pharmacogenomics studies regarding pethidine metabolism are warranted before recommending a protocol for pethidine administration in pregnant women during labor.

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