# Pharmacokinetic Parameters of Meropenem in the Plasma and Milk of Ewes

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## Abstract

This study had been designed to evaluate the pharmacokinetic parameters of Meropenem in plasma and milk of ewes after intravenous bolus adminsteration, for this purpose, five healthy miking ewes had been received a single intravenous bolus of Meropenem (20 mg/kg) to characterize both of distribution and elimination of Meropenem in plasma and milk, concentrations of Meropenem in plasma and milk had been analyzed by microbiological method and pharmacokinetic data had been analyzed by compartmental and noncompartmental methods, results of mean ± standard deviation for half-life, volume of distribution and total body clearance for plasma samples were 0.67 ± 0.09 h., 0.169 ± 0.01 and 0.3 ± 0.02 L/hr/kg, respectively, the plasma protein binding ratio were 7.27 ± 0.22 %; while the half-life, Cmax and drug penetration ratio for milk samples were 9.56 ± 3.13 h, 3.91 ± 0.99 µg/ml and 0.86 ± 0.23 respectively. In our conclusions; Depending on the approval state of Meropenem for veterinary therapy, we think that the achieved pharmacokinetic parameters of Meropenem in plasma and milk of ewes will candidate it to be one of the preferred parentrally administered antibacterial agents to encounter the acute cases of mastitis that ought to be treated hastily.

***Keywords:*** *Meropenem, Pharmacokinetics, Milk, Ewe.*

## Introduction

Mastitis is among the animal diseases which affect the profitability of rearing animals, it is considered to be one of the expensive diseases in terms of production losses(1); Many studies have been conducted on preventive and microbial aspects of this disease but few studies are based on data of the field farms to estimate production-related losses and treatment costs (2).

Mastitis parentral administration trails had been started at the 70's of the 20th century due to failure of the intra-mammary therapy that related to poor and uneven distribution of antimicrobial agents as a potential result of inflammatory process (3). Studying pharmacokinetics of antibiotics is very important to support the pharmacodynamics in order to achieve the maximal efficacy against bacteria with minimal or no side effects (4).

Meropenem is a semisynthetic Beta-lactam antibiotics belongs to carbapenems subgroup which derived from gram positive bacteria called *Streptomyces cattleya*, it was approved for use widely in 1996; Originally, it was developed to solve the instability of the older member Imipenem toward renal dihydropeptidase (DHP)(5). In general all Carapenems including Meropenem possess a broad spectrum bactericidal effect due to impairment of transpeptidation of peptidoglycan by binding to different types of penicillin binding protein (PBPs)(6). Meropenem shows strong bactericidal effect because it binds to three PBPs in the cell wall of gram positive and gram negative susceptible bacteria(7); Such triple binding may provide an explanation on rapid bactericidal effect of Meropenem(8). There is few pharmacokinetic data about Meropenem in domestic animals and most of them are not far away from the obtained data in human studies, but there is no data about it's kinetic behavior in milk, therefore, our study purpose is to support those data by reassessment of pharmacokinetic profile in ewes and

tracking of Meropenem concentrations in milk in order to provide a preliminary pharmacokinetic data might support the usage of Meropenem as one of the potential antibacterial agent in future veterinary therapy.

## Materials and Methods

The study was conducted at the sheep sheds that belong to the fields of the college of veterinary medicine/ University of Baghdad, Five adult healthy lactating ewes with age of 2-4 years and body weight ranges form 38-48 kg were used as a model for the study, each ewe was subjected for physical examination, complete blood counting and physicochemical examination of milk. Animals were acclimatized for one month and had been fed with balanced food and ad libitum drinking water. A single intravenous bolus dose of 20 mg/kg of Meropenem (Meronem®) manufactured by Astrazeneca, UK, was injected into the left jugular vein; Blood samples about 3 ml had been obtained from right jugular vein and kept in Lithium heparin tubes at 0.083, 0.16, 0.25, 0.3, 0.5 , 0.75, 1, 1.5, 2, 3, 4, 6, 8, 12 and 24 hrs. Each collected blood sample was centrifuged at 3000 rpm for 15 min. in order to obtain clear plasma that kept in -20 ºC till analysis [9]. Milk samples were obtained from both halves (each of them was subjected to the study alone) at 0.25, 0.5, 0.75, 1, 2, 3, 4, 6, 8, 12, 24 and 48 hrs. and kept in -20 ºC till analysis. Microbiological assay were utilized as a method to quantify Meropenem concentrations in different samples; it based on determining of drug potency (formed zone of inhibition in agar diffusion method) against growth of defined isolate of bacteria. Spores prepared according to Sabath method [10] from *Bacillus subtilis* ATCC 6633 that kindly provided by department of biology at college of science/ University of Diyala and utilized as test microorganism to estimate the concentration of Meropenem in blood plasma and milk [11]. Standard curves of Meropenem in plasma and milk had been done in antibacterial-free plasma and milk. The extent Plasma protein binding of Meropenem was determined according to Craig and Suh method [12] which based on calculation of partitioning of Meropenem between two media. Protein binding for each concentration was calculated according to the following formula:

$$Protien\ binding\ (\%) = \frac{Zone\ of\ inhibition\ in\ buffer - Zone\ of\ inhibition\ in\ plasma}{Zone\ of\ inhibition\ in\ buffer} . 100$$

The parameters of pharmacokinetics after administration of Meropenem had been calculated based on Microsoft Excel® spread sheet algorithm [13]; the weighted data ($1/C^2$) of plasma and milk were plotted, where (C) resembles the predicted concentration of Meropenem in plasma and milk. Both compartmental and noncompartmental analysis had been used to analyze the data that obtained from plasma [14]. Aikake information criterion was applied to choose the best model to fit the data of plasma for compartmental analysis [15]. The noncompartmental modeling has been adopted to analyze milk concentrations of Meropenem, where the area under the curve has been calculated by using of lo-linear trapezoidal method [illegible] according to the following:

$$AUC_{(0-\infty)} = AUC_{(0-last)} + \frac{C_{last}}{\lambda_z}$$

Where $AUC_{(0-last)}AUC_{(0-last)}$ resembles the calculated area under the curve, $C_{last}$ is the recorded concentration at the last time while $\lambda_Z$ is the elimination constant of the 1st order kinetics. Both $C_{max}$ and $T_{max}$ were predicted from the milk concentration vs time plotted data, the half-life of Meropenem in milk is estimated by:

$$T_{1/2} = \frac{0.693}{\lambda z}$$

The penetration ratio of Meropenem from plasma to milk was the calculated area under the curve of Meropenem in milk to the calculated area under the curve of Meropenem in plasma

$$AUC_{milk} / AUC_{plasma}$$

## Results and Discussion

Results of the constructed standard curve of Meropenem in plasma showed that the inter-assay coefficient variation (CV %) was 3.36, the determination coefficient ($R^2$) was 0.96, the limit of detection of the assay was 0.19 µg/ml and the low limit of quantification (LLOQ) of Meropenem in plasma was 0.66 µg/ml. while the obtained standard curve of Meropenem in Milk revealed that the inter-assay coefficient variation (CV %) was 3.18%, the determination coefficient ($R^2$) was 0.97, the limit of detection of the assay was 0.14 µg/ml and the low limit of quantification (LLOQ) of Meropenem in plasma was 0.41 µg/ml. According to the achieved R-squared value ($R^2$) Both standard curves of Meropenem that constructed in the plasma and milk showed a clear linearity where the value of $R^2$ for both

curves approached 1, and such result implies a perfect relationship between the used concentrations (dependent variables) and the achieved zones of inhibition (Independent variables) [16]. The coefficient of variation (CV%) is another method to determine the precision of the assay; our study revealed that both calculated CV% values in plasma and milk are lower than 5; such CV% value reflect a good feeling about precision of our standard curves [17]. the limit of detection (LOD) of Meropenem in plasma was 0.19 µg/ml while in milk was 0.14 µg/ml; LOD is precognitive parameter for lowest concentration of the drug that can be detected but not necessarily quantified by the bioassay with reliable difference in comparison to control[18]. On the other hand, the low limit of quantification (LLOQ) is more eligible to determine the precision of the bio-analytical assay; LLOQ is the lowest value at which we can quantify the drug concentration with a high precision and reliability [19]. Our standard curve-based calculations revealed that the LLOQ of Meropenem in plasma was 0.66 µg/ml while in milk was 0.47µg/ml. Both achieved LOQs reflect well precision for our assay since both not exceeded the limit of precision (± 20%) of the coefficient of variation of the assay as recommended by the FDA [20].

we conducted to estimate the ratio of binding of Meropenem to plasma proteins as reported in table (1); we found that the ratio of binding was 7.27%, this finding is compatible with many studies had been done in human and other veterinary species like equine, canine and feline; all these studies reported that Meropenem has a low plasma protein binding ranged from 2-11.87% with no or negligible effect on distribution of Meropenem to different tissues[14 & 21-23]; while EL-Sooud [9] in his study that focused on the pharmacokinetics of Meropenem in ewes reported that the value of plasma protein binding ratio that he estimated by the same method of us was 42.8% which in our evaluation do not get along with his other achieved parameters like distribution and elimination phases of compartmental analysis because EL-Sooud [9] study reported that his trail in Barki sheep were achieved a bi-exponential curve composed mainly from a rapid distributional phase with distribution half-life equal to 0.06 h. and such value reasonably can't achieved with presence of such high protein binding ratio [24]. In general such low ratio of plasma protein binding of Meropenem might be to its zwetterionic charge state that possesses less affinity to bind to plasma protein than acidic or neutral drugs [25 & 26].

The quantitative data that collected from measuring of Meropenm concentrations in plasma after injection of single intravenous bolus dose through determined chronological order were fitted mathematically on compartmental and non-compartmental models; Selection of two compartmental model to fit and calculate our data of plasma concentration-time curve of Meropenem that depicted in figure (1) and listed in table (1) had been established on two criteria; the 1st is shape of the curve who showed a first order and bi-exponential decrement with clear distinguished distribution and elimination phases, while the 2nd is value the calculated Akaike information criterion (AIC) who decide the best model that data should be to fit [27].

The mean of plasma concentration of Meropenem at the zero time was 263.64 µg/ml; the value of the distribution intercept (A) of Meropenem was 206.39 µg/ml, the constant of distribution phase (α) was 9.96 $h^{-1}$ and the distribution half-life ($t_{1/2\alpha}$) was 0.06 h. Meropenem showed a short distribution phase (A) to the interstitial compartment as a normal result of the short half-life of that phase ($t_{1/2\alpha}$) which attributed to the high distribution of Meropenem from central compartment to the peripheral tissues due to low plasma-protein binding ratio that reported previously [28].

The volume of distribution at steady state ($Vd_{ss}$) of Meropenem in plasma was 0.16 L/kg; $Vd_{ss}$ expresses about the equilibrium time between distribution and elimination phases of the drug and characterized by its independence from any elimination process, constant and accuracy [29]; $Vd_{ss}$ had been utilized for determination of loading and maintenance doses in multiple dosage regimens and for interspecies dose extrapolation[30]. The $Vd_{ss}$ of our study that calculated in both compartmental and non-compartmental analysis is relatively small and refer that the distribution of Meropenem was primarily limited to the extravascular compartments including milk [14 & 31]. Our finding about the $Vd_{ss}$ is almost contradicting with EL-Sooud [9] study who reported that the $Vd_{ss}$ in Barki sheep was 0.055 L/kg and such value is also not even approached other species values like dog 0.337 L/kg [14], cat 0.21 L/kg [22] and horse 0.136 L/kg [23]. Such contradiction might be

attributed to miss-calculation by EL-Sooud [9] where his value of $Vd_{ss}$ should be 0.189 L/kg instead of 0.055 L/kg according to the formula that calculate the $Vd_{ss}$ [32]. The area under the concentration-time curve (AUC) is one of pharmacokinetic parameters that measures the exposure time to the drug; the AUC value submitted to the effect dose, absorption and clearance [33].

Our study was reported that the AUC of Meropenem that achieved in plasma was 65.22 (h*µg)/ml and it had been came within the range that achieved by other species who ranged from 53.2 to 90.3 65.22 (h*µg)/ml considering the differences among species that used. The Mean residence time (MRT) is another important pharmacokinetic parameter which resembles the average time that drug molecules spent in the body compartments [34]. As what revealed with the AUC; our study found that the MRT of Meropenem in plasma was 0.54 hr. which was in agreement with other studies in other species who stated the MRT of Meropenem after single intravenous bolus was less than 1 hr. [9, 14, 22 & 23].

There are two important clinical parameters to shape the elimination phase of drug molecules; the elimination half-life ($T_{1/2}$) and the total body clearance (Cl) The elimination pharmacokinetics of Meropenem was not differing from other Beta-lactams where the major feature is a relative rapid renal excretion mostly via tubular secretion and glomerular filtration [21]. Our results reported that the elimination $T_{1/2}$ of Meropenem in plasma was 0.57 hr., while the total body clearance was 0.3 L/hr/kg. Both achieved values of $T_{1/2}$ and $Cl_T$ were came as expected for Beta-lactams generally and Meropenem specifically; where it has a short $T_{1/2}$ with great $Cl_T$, and this combination in addition to the low $Vd_{ss}$ will achieve a quick state of equilibrium between the concentration in central compartment and the extracellular compartments considering their penetration ratio [14].

The results of the pharmacokinetic analysis of Meropenem concentrations in milk of ewes that listed in table (2) reported the Cmax of Meropenem was 3.91 µg/ml and it was achieved at the 6$^{th}$ h. after intravenous administration which gets along with general pharmacokinetic characteristics of Meropenem that indicate to primary concurring distribution into the extracellular fluids within the same time of plasma distribution pattern as we point in figure (2) who graphed the decline in plasma concentration of Meropenem was in harmonization within the rise in milk[35]. Based on our calculations, Meropenem achieved a considerable AUC in milk (56.28 h*µg/ml) as a reflection to the long time that the compartment was exposed to the drug which in turn might be attributed to the delayed residence of Meropenem molecules that empowered by the recorded half-life which was 9.56 hrs. Such long half-life might be presumed to the low measured concentrations of Meropenem in milk; where low concentrations appeared to yield longer terminal half-lives consequently, more flattened curve in comparison to plasma curve, then after large AUC [36].

The capability of Meropenem to penetrate into milk compartment was assessed by penetration ratio which expressed as $AUC_{milk}/AUC_{plasma}$ [37]. Our results about milk penetration ratio of intravenously administered Meropenem were 0.86 which considered good in comparison to other Beta-lactams that administered parentrally in different ruminants; where Ceftriaxone was achieved 0.34 in ewes [38], Ceftizidime 0.16 in does [39], Cephacetrile 0.15, Cephapirin 0.18, Penicillin G 0.2, Cloxacillin 0.26, Ampicillin 0.26 in cows [40] and Amoxicillin 0.48 in cows [41]. Our assumption to explain such high penetration ratio might be due to the used route of administration who primarily ensure even drug distribution to all extravascular compartments, consequently, they accumulate in milk better than other routes and such phenomena is governed by the amount of used dose [42]; and the physicochemical characteristics of the drug like zwitterionic nature and the small molecular size of the drug who might be enhance Meropenem penetration to the milk compartment in comparison to other Beta- lactams [43]. In conclusions; Depending on the approval state of Meropenem for veterinary therapy, we think that the achieved pharmacokinetic parameters of Meropenem in plasma and milk of ewes will candidate it to be one of the preferred parentrally administered antibacterial agents to encounter the acute cases of mastitis that ought to be treated hastily.

**Table (1) compartmental and non-compartmental pharmacokinetic parameters of Meropenem (Single I.V. bolus dose) in plasma of ewes.**

| Parameter | Unit | Plasma | |
|---|---|---|---|
| | | Mean | SD. |
| CMax | µg/ml | N. A. | N. A. |
| AUC | (h*µg)/ml | 65.22 | 4.56 |
| ClT | L/hr/kg | 0.3 | 0.02 |
| TMax | h | N. A. | N. A. |
| λ z | h-1 | 1.2 | 0.38 |
| T1/2 λz | h | 0.57 | 0.09 |
| MRT | h | 0.54 | 0.08 |
| Cp0 * | µg/ml | 263.64 | 112.58 |
| t1/2α* | h | 0.06 | 0.03 |
| t1/2β * | h | 0.53 | 0.19 |
| K10 * | h-1 | 4.06 | 1.29 |
| K12 * | h-1 | 4 | 2.88 |
| K21 * | h-1 | 3.18 | 1.79 |
| A * | µg/ml | 206.39 | 96.1 |
| α * | h-1 | 9.96 | 4.66 |
| B * | µg/ml | 57.25 | 33.03 |
| β * | h-1 | 1.29 | 0.30 |
| VC * | L/kg | 0.075 | 0.05 |
| Vdss * | L/kg | 0.169 | 0.01 |
| Plasma-protein binding | Ratio | 7.27 | 0.22 |

- ·No. of ewes = 5.
- ·All data represent free concentrations of Meropenem.
- ·All data are subjected to weight by 1/C2.
- · (*) calculated by compartmental analysis.

**Table (2) non-compartmental pharmacokinetic parameters of Meropenem (Single I.V. bolus dose) in and milk of ewes.**

| Parameter | Unit | Milk | |
|---|---|---|---|
| | | Mean | SD. |
| AUC | h*µg/ml | 56.28 | 20.13 |
| CMax | µg/ml | 3.91 | 0.99 |
| TMax | h | 6.00 | 1.15 |
| T1/2 λz | h | 9.56 | 3.13 |
| Penetration (AUC milk / AUC plasma) | Ratio | 0.86 | 0.23 |

- No. of ewes = 5.
- All data represent free concentrations of Meropenem.
- ·All data are subjected to weight by 1/C2.

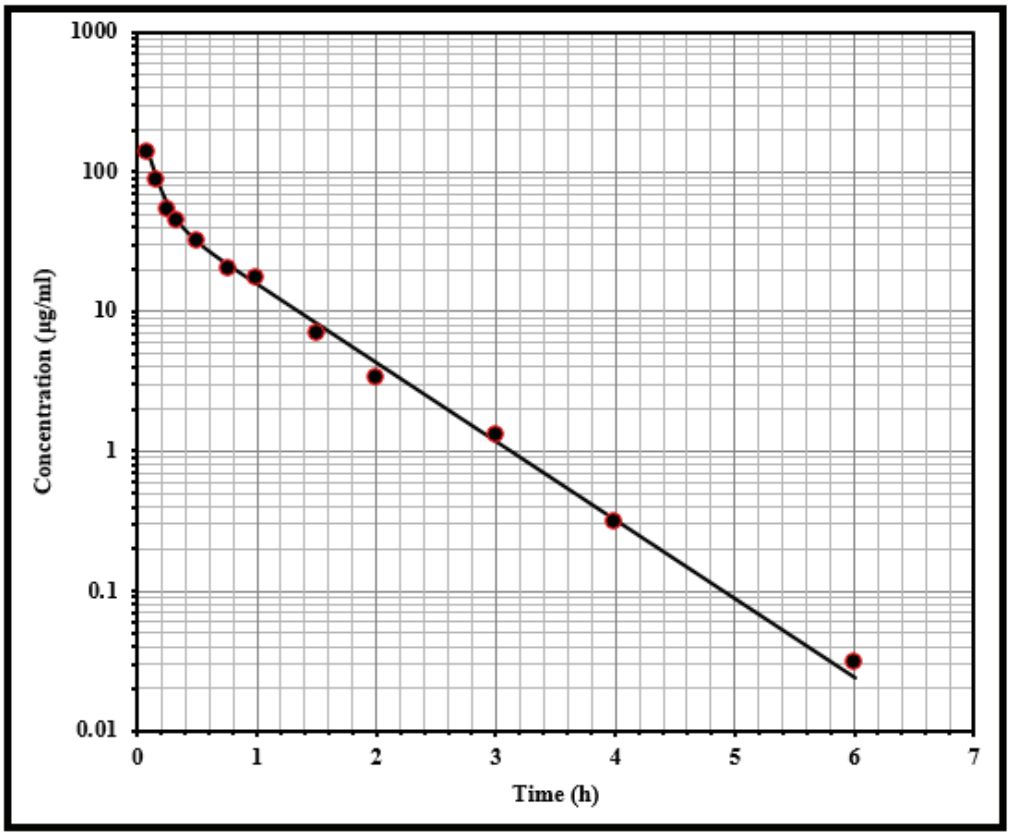


**Figure (1) Two compartmental model of Meropenem in plasma of ewes.**

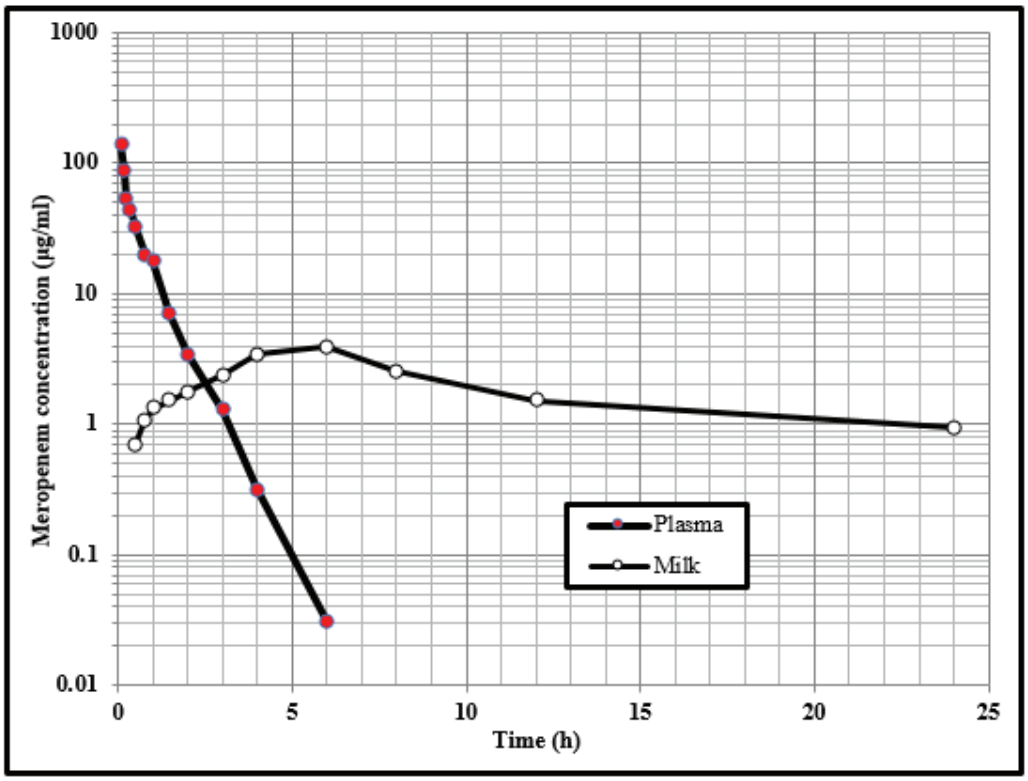


**Figure (2) Non-compartmental analysis of single intravenous bolus for Meropenem in plasma**

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