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Relationship between wound fluid antibiotic concentration and clinical healing time in diabetic foot infections: a meropenem-focused analysis

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ABSTRACT

Aims: The penetration of antibiotics used to treat diabetic foot infection (DFI) into the target tissue is critical for clinical success. This study aimed to evaluate the penetration rates of carbapenem antibiotics into wound fluid, the factors affecting this penetration, and the effects of this penetration on clinical healing time in patients with DFI.

Methods: Twenty patients aged ≥18 years with DFI and open, draining wounds were prospectively included in the study. Thirteen patients received meropenem, four received ertapenem, and three received imipenem. After steady state had been achieved, wound fluid and serum samples were analyzed for antibiotic concentrations using LC-MS/MS.

Results: In accordance with quantitative measurement standards, the analyses focused on the meropenem group (n=13). A linear relationship was observed between serum and wound fluid meropenem concentrations. Wound fluid meropenem concentrations were significantly higher in patients with lower Wagner stages and in those receiving hyperbaric oxygen therapy (HBOT). Patients with comorbid chronic diseases had significantly higher wound fluid meropenem concentrations than those without comorbidities (p=0.034). A correlation was observed between wound fluid meropenem concentrations and clinical healing parameters.

Conclusion: Meropenem penetration into wound fluid during the treatment of DFI is influenced by factors such as comorbidities, wound stage, and HBOT. Monitoring antibiotic concentrations in wound fluid may help optimize treatment, reduce costs, and inform decisions regarding the timing of surgery.

Keywords: Diabetic foot infection, meropenem, wound fluid concentration, pharmacokinetics, Wagner grade

INTRODUCTION

Diabetic foot infection (DFI) is a severe complication of diabetes mellitus that carries a substantial economic burden, impairs quality of life, and represents a leading cause of lower-extremity amputations.[1] Globally, it is estimated that approximately 25% of individuals with diabetes will develop a foot ulcer at least once in their lifetime, with more than half of these lesions subsequently becoming infected.[2] The management of DFI necessitates a multidisciplinary approach that encompasses surgical debridement, appropriate wound care, and systemic antimicrobial therapy.[3]

Clinical success in the treatment of DFIs depends not only on the in vitro susceptibility of the pathogen, but fundamentally on achieving therapeutic antibiotic concentrations at the target site of infection, specifically within wound tissue and fluid. In patients with diabetes, concomitant peripheral artery disease and microvascular dysfunction can substantially impair the target-tissue penetration of systemically administered antibiotics.[4] Consequently, subtherapeutic drug concentrations may occur at the wound site despite adequate serum levels, thereby predisposing to therapeutic failure and the emergence of antimicrobial resistance.[5]

Due to their broad-spectrum activity against common polymicrobial pathogens (gram-positive, gram-negative, and anaerobes), carbapenems represent a cornerstone of empirical therapy in moderate-to-severe DFI.[6] Meropenem is a carbapenem derivative characterized by favorable tissue penetration owing to its low protein binding and large volume of distribution. However, prospective studies evaluating real-time meropenem concentrations in diabetic wound fluid and their correlation with clinical healing times remain limited in the literature.[7,8]

METHODS

Ethics

The study was carried out with the permission of the Gülhane Military Medical Academy Command Clinical Researches Ethics Committee (Date: 24.12.2015, Decision No: 2015-KAEK-59). We obtained an informed consent form from all

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patients for procedure. All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki. This prospective study was conducted among patients hospitalized with a diagnosis of DFI in the department of infectious diseases and clinical microbiology and associated surgical units of a tertiary training and research hospital.

Study Population and Patient Eligibility

The study was conducted between July 18, 2015, and May 31, 2016. During the initial period, patients were evaluated as part of routine clinical care. Following ethics committee approval, prospective patient enrollment and study-specific sample collection were initiated. A total of 20 patients aged 18 years or older with diabetic foot infections and open, draining wounds were included in the study. The inclusion criteria were the presence of an actively exudative wound and a clinical indication for systemic carbapenem therapy (meropenem, ertapenem, or imipenem). Patients with suspected osteomyelitis or those with wounds covered by necrotic tissue that precluded fluid sampling were excluded from the analysis. The Wagner classification system was utilized to assess the ulcers, categorizing them based on wound depth and the presence of infection or necrosis, ranging from grade 0 (intact skin) to grade 5 (whole foot gangrene).

Antibiotic Administration and Sampling Procedure

Intravenous carbapenem therapy was initiated in all patients according to established clinical indications. To ensure that steady-state concentrations were achieved in both serum and tissue, biological sampling was performed at least 72 hours after the initiation of antimicrobial therapy. Thirty minutes after the completion of the initial antibiotic infusion, paired biological samples were collected simultaneously: a serum sample obtained via peripheral venipuncture and a wound fluid sample harvested directly from the wound bed using a sterile syringe or sponge. The collected samples were preserved at -80°C until bioanalysis.

Sample Preparation and Bioanalytical Assay Protocol

Quantification of antibiotic concentrations was performed using an AB SCIEX 3200 QTRAP LC-MS/MS system (AB Sciex, Framingham, MA, USA) coupled to a Shimadzu Nexera HPLC system equipped with a DGU-20A degasser, LC-20AD solvent delivery units, and a SIL-20A autosampler (Shimadzu Corporation, Kyoto, Japan). Although all three carbapenem agents (ertapenem, imipenem and meropenem) were initially evaluated, analytical assay standardization and reliable quantification could only be fully validated and optimized for meropenem. Consequently, the primary pharmacokinetic and statistical analyses were restricted to the 13 patients receiving meropenem who yielded quantifiable drug concentrations.

Preparation of Analytical Standards and Calibration Curves

Two distinct mobile phases were prepared for the liquid chromatography analyses. The first mobile phase was prepared by completely dissolving 1.0 g of ammonium acetate (CH3COONH4) in approximately 500 ml of distilled water using a magnetic stirrer, followed by the addition of 0.1% formic acid, and adjusting the final volume to 1000 ml with distilled water. The second mobile phase consisted of methanol containing 0.1% formic acid. For calibration procedures, a meropenem stock solution (1 mg/ml) was prepared in distilled water, and colchicine solution, used as an internal standard, was prepared in a methanol-water (2:8, v/v) mixture and stored in aliquots at +4°C until analysis.

Clinical Specimen Collection and Pre-analytical Processing

Once steady state concentrations were attained under carbapenem therapy, specimen collection was initiated 30 minutes following the cessation of the intravenous infusion in patients with DFI. Sterile Whatman® filter paper discs were applied to collect wound fluid, with an absorption period of approximately 30-40 minutes to achieve complete saturation. Following collection, the impregnated filter papers were transferred into sterile glass tubes and concurrent serum samples were placed into Eppendorf tubes. All specimens were preserved at -80°C until quantitative determination. Prior to analysis, the LC-MS/MS system was validated using known concentrations of meropenem and colchicine standards.

Quantification of Meropenem Concentrations by LC-MS/MS

During the study, to deproteinize serum samples, 200 µL of acetonitrile was added to 100 µL of serum, and the mixture was vortexed for 1 minute. The samples were centrifuged in a refrigerated centrifuge at +4°C and 5,000 rpm for 5 minutes. After centrifugation, the supernatant was transferred to insert vials for analysis. Wound fluid filter papers were cut to a width of 5 µm in a sterile environment, collected in glass tubes, and 1 ml of acetonitrile was added followed by vortexing for 1 minute. The samples were centrifuged in a refrigerated centrifuge at +4°C and 5,000 rpm for 5 minutes. The supernatant was collected for analysis after centrifugation.

Statistical Analysis

In descriptive statistics, frequencies and percentages were used for categorical data, and the mean, standard deviation, median, minimum, maximum, and range were used for continuous data. The normality of distribution for continuous variables was assessed using the Kolmogorov-Smirnov test. For normally distributed variables, an independent samples Student's t-test was conducted, whereas the Mann-Whitney U test was employed for non-normally distributed data. The correlation between two continuous variables was evaluated using Spearman's rank correlation coefficient. Statistical analyses were performed using IBM SPSS version 22.0 (IBM Corporation, Armonk, NY, USA), and a p-value <0.05 was considered statistically significant.

RESULTS

Among the 13 patients diagnosed with DFI and treated with meropenem, the mean age was 59.6±6.7 years and the mean duration of diabetes was 11.5±6.5 years. Ten patients (76.9%) were male and 3 (23.1%) were female. According to the Wagner classification, 7 patients (53.8%) had grade 3 ulcers and 6 (46.2%) had grade 4 lesions. The mean concentration of meropenem was 14.765±14.123 ng/ml in serum and 4.279±4.893 ng/ml in wound fluid. Other laboratory values for the patients are presented in **Table 1**.

When factors affecting wound fluid meropenem concentrations were analyzed, we evaluated tissue concentrations according to Wagner stages; although drug penetration was higher in patients with lower Wagner stages (stage 3 vs. stage 4),

Table 1. Demographic, clinical, and laboratory findings of the patients

	Mean±SD	Median	Min-max
Age (years)	59.6±6.7	60	49-75
Duration of diabetes (years)	11.5±6.5	10	1-25
HbA1c (%)	8.3±2.4	7.3	5.6-13.9
ESR (mm/h)	90±30	92	47-135
CRP (mg/L)	159±177	103	4-600
Serum meropenem concentration (ng/ml)	14.765±14.123	7700	3780-48900
Wound fluid meropenem concentration (ng/ml)	4279±4893	553	19100-18547

*This table summarizes the demographic characteristics and descriptive statistics of laboratory parameters for patients with diabetic foot infections included in the study. Continuous variables are presented as mean, SD, median, and min-max values according to data distribution. SD: Standard deviation, Min-max: Minimum-maximum, HbA1c: Glycated hemoglobin, ESR: Erythrocyte sedimentation rate, CRP: C-reactive protein

the difference was not statistically significant (p=0.316). Similarly, higher levels of meropenem were detected in the wound fluid of the group receiving hyperbaric oxygen therapy (HBOT) compared with those who did not receive it, but the difference was not statistically significant (p=0.622). Similarly, elevated meropenem levels were noted in female patients and individuals with peripheral vascular disease; however, neither difference was statistically significant (p=0.469). In patients with underlying chronic comorbidities (particularly pronounced in those with renal dysfunction), wound fluid meropenem levels were significantly higher (p=0.034) (Table 2).

Table 2. Comparison of meropenem concentration levels in the wound fluid of patients

	Mean±SD	p*
Gender		
Male	2166±1330	0.469
Female	4913±5440	
Presence of peripheral vascular disease		
No	2393±1277	0.692
Yes	4845±5479	
Wagner stage		
Stage 3	5593±6344	0.316
Stage 4	2746±1983	
Presence of chronic disease other than DM		
No	1423±791	0.034
Yes	5548±5458	
Hyperbaric oxygen therapy status		
Receiving	5262±6058	0.622
Not receiving	2706±1605	

*This table presents a comparative analysis of the impact of various clinical and demographic characteristics on wound fluid meropenem levels. Continuous variables are presented as mean± SD. Intergroup comparisons were performed using the Mann-Whitney U test. A two-tailed p-value <0.05 was considered statistically significant. SD: Standard deviation, DM: Diabetes mellitus

In the meropenem cohort where analytical (quantitative) determination was achievable, a significant positive correlation was identified between serum levels and wound fluid concentrations (Figure).

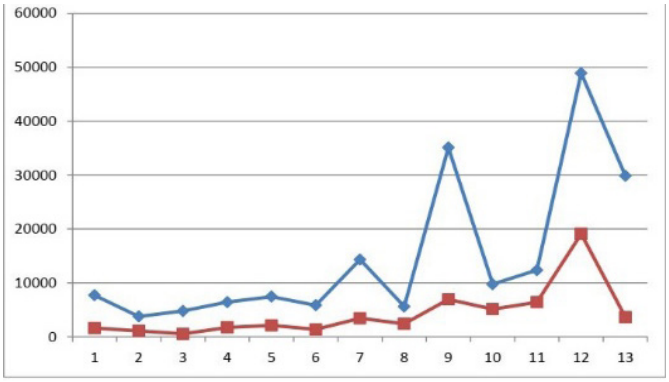


Figure. Comparative concentration profiles of meropenem in serum and wound fluid across patients

This graph illustrates the concurrent changes in serum (blue line) and wound fluid (red line) concentrations of meropenem in treated patients. Examination of the curves reveals a generally parallel relationship between systemic antibiotic levels and concentrations in the target tissue

DISCUSSION

In the management of diabetic foot infections, systemic antibiotic penetration into target tissues is frequently unpredictable and markedly variable due to pathophysiological barriers such as chronic vascular insufficiency, edema, and tissue necrosis.[4] The present study prospectively evaluated the relationship between clinical parameters and wound fluid concentrations of meropenem, a cornerstone agent in both empirical and definitive treatment of DFIs owing to its broad-spectrum efficacy. These data demonstrate a correlation between serum meropenem levels and wound fluid concentrations, indicating that tissue penetration is significantly influenced by underlying comorbidities, alongside observable differences based on Wagner grade and HBOT use.[5,7] In a recent pharmacokinetic study evaluating patients with DFIs, Finazzi et al.[8] reported that meropenem tissue penetration was substantially more variable than that observed in non-diabetic individuals. The positive correlation observed between serum and wound fluid concentrations suggests that the pharmacokinetic profile of meropenem is preserved to a certain extent despite tissue ischemia. Nevertheless, this degree of tissue penetration does not inherently equate to therapeutic efficacy; the severity of local inflammation and the extent of wound bed vascularization remain critical determinants of clinical outcome.[2]

Importantly, tissue penetration of meropenem was considerably higher in patients with less advanced Wagner grades, although this observed difference did not reach statistical significance. Wagner staging serves as an indicator of ulcer depth, tissue necrosis, and bone involvement, with advancing grades characterized by progressive microvascular compromise and worsening tissue hypoxia. As emphasized in the 2023 International Working Group on the Diabetic Foot (IWGDF) guidelines by Senneville et al.,[3] standard dosing regimens may be insufficient to attain target tissue concentrations exceeding the minimum inhibitory concentration (MIC) in patients with advanced DFIs. These observations indicate that antibiotics penetrate wound fluid more effectively during earlier stages when vascular architecture remains relatively preserved, thereby underscoring the critical need for dose optimization and timely surgical intervention in advanced disease.[1,6]

The observation of elevated wound fluid antibiotic concentrations among patients receiving hyperbaric oxygen therapy provides valuable preliminary data to the ongoing

debate surrounding adjuvant modalities in the literature. By promoting angiogenesis and regulating microvascular permeability, hyperbaric oxygen therapy counteracts local hypoxia and restores capillary perfusion in ischemic wound tissues. The elevated meropenem concentrations observed in the HBOT group suggest that this adjuvant modality not only improves tissue oxygenation but may also enhance the delivery of pharmacological agents to the target site. In support of this observation, Armstrong et al.[1] highlighted that multidisciplinary care and the synergy of adjuvant HBOT with antimicrobial therapy optimize local tissue bioavailability, thereby translating into improved outcomes in diabetic foot infections.

The marked influence of underlying chronic comorbidities, particularly altered renal function, on meropenem concentrations represents an expected pharmacokinetic phenomenon given the predominantly renal elimination of the drug. The statistically significantly higher concentrations observed in patients with comorbidities (p=0.034) may be attributed to a prolonged elimination half-life of the drug and, consequently, extended retention within the tissue compartment.[4] In line with this pharmacokinetic rationale, Roberts and Lipman demonstrated that impaired drug clearance in critically ill and comorbid patients substantially prolongs exposure and promotes tissue accumulation.[7] However, while elevated tissue retention may enhance local antibacterial efficacy, it concurrently escalates the risk of systemic toxicity-particularly neurotoxicity-thereby warranting judicious dose titration and close therapeutic monitoring.[9]

Limitations

Several limitations of the present study should be acknowledged. First, although 20 patients were initially enrolled, technical constraints in the bioanalytical quantification of the imipenem and ertapenem arms restricted the final pharmacokinetic evaluation to 13 meropenem-treated patients, thereby constraining overall sample size and the statistical power of subgroup comparisons. Secondly, wound categorization was based solely on the Wagner classification system. While widely used, this system does not fully account for the presence or severity of peripheral ischemia and neuropathy, which are critical variables that can significantly influence local tissue drug concentrations. Utilizing a classification system that incorporates ischemia, such as the University of Texas classification, might have resulted in more homogeneous study groups and should be considered in future research.

CONCLUSION

Meropenem represents an effective therapeutic agent that achieves favorable penetration into wound fluid during the management of DFIs. Nevertheless, clinical and pharmacokinetic success remains intrinsically linked to ulcer severity (Wagner stage), hyperbaric oxygen therapy, and the underlying burden of systemic comorbidities. Larger prospective trials are warranted to translate wound fluid pharmacokinetic dynamics into personalized dosing protocols, thereby moving clinical practice closer to precision antimicrobial therapy in DFIs.

ETHICAL DECLARATIONS

Ethics Committee Approval

This study was approved by the Gülhane Military Medical Academy Command Clinical Researches Ethics Committee (Date: 24.12.2015, Decision No: 2015-KAEK-59).

Informed Consent

Written informed consent was obtained from all individual participants prior to their inclusion in the study. Participants were fully informed about the study's aims, procedures, potential risks and benefits, and their rights-including the right to withdraw at any time without consequence. All participants voluntarily signed a written informed consent form.

Peer Review Process

This manuscript was subject to external peer review.

Conflict of Interest

The authors declare no conflicts of interest related to this study.

Financial Disclosure

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Author Contributions

Concept: YÇ, OD; Design: YÇ, OD; Control: YÇ, OD; Data Collection and/or Processing: YÇ, OD; Analysis and/ or Interpretation: YÇ, OD; Literature Review: YÇ; Provision of Cases/Equipment: YÇ, OD; Article Writing: YÇ, OD; Critical Review: YÇ, OD.

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