Concentrations of single-dose meropenem (1 g iv) in bronchoalveolar lavage and epithelial lining fluid

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The concentrations of meropenem were measured in plasma, bronchoalveolar lavage (BAL) and epithelial lining fluid (ELF) 0.5–8 h after the administration of a single 1 g iv dose of meropenem. Thirty-five patients undergoing bronchoscopy were studied. Mean concentrations in plasma, BAL and ELF, respectively, measured by high performance liquid chromatography, were as follows: 0.5 h: 25.96, 0.14, 5.04 mg/L; 1 h: 14.98, 0.09, 7.07 mg/L; 2 h: 12.01, 0.06, 3.86 mg/L; 4 h: 2.51, 0.04, 2.20 mg/L; 6 h: 0.57, 0, 0.59 mg/L; 8 h: 0.29, 0, 0 mg/L. Throughout the 2 h following infusion, concentrations in ELF exceeded the MIC\textsubscript{90} for all nosocomial and community-acquired respiratory pathogens, including \textit{Pseudomonas aeruginosa} (3.05 mg/L), \textit{Haemophilus influenzae} (0.16 mg/L) and penicillin-resistant \textit{Streptococcus pneumoniae} (0.86 mg/L). These results support the clinical efficacy of meropenem in the treatment of a wide range of pulmonary infections.

Introduction

The introduction of meropenem represents a step forward in the development of carbapenem antibiotics for clinical use. This group of antibiotics represents an attractive option for the treatment of severe bacterial infections, including pneumonia. In addition to retaining the very wide antimicrobial spectrum of this novel antibiotic class, which includes most respiratory pathogens such as \textit{Streptococcus} spp., methicillin-sensitive \textit{Staphylococcus aureus}, \textit{Haemophilus influenzae}, Enterobacteriaceae, \textit{Pseudomonas aeruginosa} and anaerobes,\textsuperscript{1} meropenem has been shown to be significantly less neurotoxic than imipenem, the first available carbapenem. These features clearly indicate that meropenem may be considered an ideal choice in the setting of critically ill patients, especially when concomitant neurological pathologies are present.\textsuperscript{2}

The high frequency of pulmonary infections in such a clinical context makes it necessary to determine the pharmacokinetic profile of meropenem in the pulmonary compartment. In order to evaluate these properties, we measured the concentrations of meropenem in the bronchoalveolar lavage (BAL) and epithelial lining fluid (ELF).

Materials and methods

A total of 35 patients (19 males, 16 females), \textgeq 18 years of age, undergoing elective bronchoscopy, were enrolled in the study after obtaining written informed consent. The indications for bronchoscopy were the following: sarcoidosis (68.5%), pulmonary fibrosis (14.3%), interstitial pneumopathy (11.4%), bronchial asthma (2.9%) and suspected tuberculosis (2.9%). The study received the approval of the Ethics Committee of our institution.

Exclusion criteria were as follows: antibiotic therapy ongoing or in the last 5 days, severely compromised respiratory status, significant renal or hepatic impairment, serious metabolic, cardiovascular, central nervous system and infectious diseases, history of allergy to any of the \(\beta\)-lactams and females who were potentially child bearing or breast feeding.
Dose regimen

This was an open-label study, designed to evaluate the concentrations of meropenem in BAL and ELF following the administration of a single 1 g iv dose injected over 30 min.

Patients were consecutively allocated into six bronchoscopy groups as follows: group 1, 0.5 h post-dose; group 2, 1 h post-dose; group 3, 2 h post-dose; group 4, 4 h post-dose; group 5, 6 h post-dose; group 6, 8 h post-dose. The programme of sampling according to the scheduled timings for BAL and blood was fulfilled with a tolerance of 15 min.

Sample collection and processing

A standard fibre-optic bronchoscopy with BAL was performed after pre-medication with atropine 0.5 mg given intravenously and application of local anaesthesia with 1% lidocaine. A total volume of 150 mL of pre-warmed isotonic saline divided into three aliquots was infused into the bronchial tree, followed by gentle aspiration. To avoid contamination with proximal airway cells and fluids the first aliquot of supernatant was discarded. The aspirate from the last two aliquots was pooled and samples were immediately centrifuged at 4000 g for 5 min. An aliquot of supernatant was frozen at –80°C until pharmacokinetic assay. Urea estimation in BAL was performed to calculate meropenem concentration in ELF. Haemoglobin detection in BAL was performed to evaluate possible blood contamination which could alter meropenem concentration in the lavage. Albumin concentration in BAL was determined using an enzymic UV method with urease and glutamate dehydrogenase.3

Venous blood samples were taken at the end of bronchoscopy to detect meropenem and urea concentrations. After centrifugation, plasma samples were stored at –80°C until assay.

HPLC assay

Determination of meropenem concentrations in plasma and BAL was performed by high performance liquid chromatography (HPLC) on Zorbax SB-CN (Rockland Technologies, Inc.) stable bond column (25 cm × 4.6 mm, inside diameter 5 μm) with a mobile phase of ammonium acetate buffer 50 mM, pH 5:acetonitrile (90:10) at a flow rate of 1.0 mL/min and with UV detection at 296 nm. Samples were extracted by solid phase extraction on C18 cartridge (100 mg, 1 mL, Accubond, J&W Scientific). The lower limit of detection level was 50 ng/mL for plasma samples (volume submitted to extraction 0.5 mL) and 1.25 ng/mL for BAL (volume submitted to extraction 10 mL). The coefficients of variation ranged from 4.42% to 16.61%.

Calculation of antibiotic concentrations in ELF

The urea concentrations in BAL fluid and plasma were determined using an enzymic UV method with urease and glutamate dehydrogenase.3

Apparent ELF volume (ELFV) was estimated by using urea as an endogenous marker of ELF dilution and was calculated by relying on the method described by Rennard et al.4 as follows:

\[ \text{ELF}_V = \text{BAL}_V \times \frac{\text{BAL}[U]}{\text{ELF}[U]} \]

where: BALV is the volume of aspirated BAL fluid, BAL[U] is the concentration of urea in BAL and ELF[U] is the concentration of urea in ELF.

The concentration of meropenem in ELF (ELF[M]) was calculated as follows:

\[ \text{ELF}[M] = \text{BAL}[M] \times \frac{\text{BAL}[U]}{\text{ELF}[U]} \]

where BAL[M] is the concentration of meropenem in BAL.

By substituting the first equation into the second, meropenem concentration in ELF was calculated as follows:

\[ \text{ELF}[M] = \frac{\text{ELF}_V \times \text{BAL}[U]}{\text{BAL}_V} \]

Results

Thirty of the 35 patients enrolled in the study were considered eligible. Among the non-eligible patients, two were excluded because of elevated transaminases and for three others BAL or blood samples were not properly stored. The mean patient age was 45.8 (26–73) years and the mean weight was 71.9 (54.6–104.0) kg.

Mean concentrations of meropenem in plasma, BAL and ELF including site:plasma ratios are summarized in Table I.

The highest plasma concentrations of meropenem were recorded 0.5 h after infusion (mean 25.96 ± 22.16 mg/L), with decreasing levels thereafter, as expected on the basis of the drug elimination half-life and according to data observed in other studies. A similar time-dependent pattern was also recorded in BAL and ELF. The highest meropenem concentrations in BAL were detected at 0.5 h (mean 0.14 ± 0.08 mg/L), while highest levels in ELF were achieved 1 h after infusion (mean 7.07 ± 2.87 mg/L). This discrepancy can be attributed to the fact that drug concentrations in BAL were measured directly by HPLC, while those in ELF were obtained by calculating through the appropriate formula, with predictable intra- and inter-group variations. No antibiotic was detectable in either fluid with this method, after 8 h.

Penetration of meropenem into ELF was calculated as ELF:plasma concentration ratio. Mean level of penetration into ELF was 0.48 ± 0.73 and the highest degree of penetration was achieved at 4 h after infusion (1.04 ± 1.20).

All 30 patients were considered evaluable for safety analysis. Only four (13.3%) patients reported mild adverse events during the 48 h monitoring period. None was considered to be related to meropenem.
Concentrations of meropenem in pulmonary fluids

Discussion

Although meropenem concentration in lung and pleural tissues had been determined in some studies, the most recent published by Byl et al.,6 to our knowledge no data are available regarding its distribution in bronchoalveolar and epithelial lining fluids.

Although rather low antibiotic concentrations were detected in BAL, owing to a dilution effect, in our study meropenem penetration into ELF was very satisfactory, being very similar to that observed by other authors in lung and pleural tissues and in bronchial mucosa (mean penetration in these tissues is, respectively, reported in literature as: 0.40, 0.24, 0.38).7 Furthermore, as compared with the available data on \( \beta \)-lactam penetration into ELF, the mean ratio of ELF to serum concentration for meropenem was higher than that measured for amoxycillin (0.12),8 cefuroxime axetil (0.17)9 and cefdinir (0.12–0.15).10

Meropenem, like other \( \beta \)-lactam antibiotics, shows a mainly time-dependent antibacterial killing. In this study, drug concentrations in ELF remained above the MIC\(_90\) for all common community and nosocomial pathogens for a relatively long time. The time above the MIC for penicillin-resistant \( S. \) pneumoniae (MIC\(_{90}\), 0.86 mg/L), \( H. \) influenzae (MIC\(_{90}\), 0.16 mg/L) and \( P. \) aeruginosa (MIC\(_{90}\), 3.05 mg/L) was about 82%, 94% and 37%, respectively (Figure). In recent studies11 the antibacterial effect provided by the q12h meropenem dosing was found to be comparable to the one engendered by the recommended q8h dosing, thus suggesting some difference between carbapenems and other \( \beta \)-lactams. Other pharmacodynamic parameters, such as the peak/MIC ratio or the AUC/MIC ratio and/or the post-antibiotic effect, which is unexpectedly prolonged for carbapenems, may help to explain the antibacterial dynamics of meropenem.

In conclusion, our results give new information about the penetration of meropenem into pulmonary fluids, which substantially confirms its good distribution into respiratory tissues. Therefore, the overall pharmacological profile of meropenem, including its wide antibacterial spectrum, makes it a suitable agent for the treatment of severe bronchopulmonary infections especially in a nosocomial setting.

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References

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