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CONCISE REVIEW

Meropenem: Focus on its Use in Serious Bacterial Infections

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Abstract: Meropenem is an effective broad-spectrum carbapenem antibiotic frequently prescribed for treatment of severe bacterial infections. We conducted a structured review of the published literature to review the microbiology, clinical efficacy and pharmacokinetics, pharmacodynamics and tolerability of meropenem for the treatment of serious bacterial infections. Robust susceptibility data describes the broad spectrum of action of meropenem against many Gram positive and Gram negative organisms as well as stability against ESBL producing organisms. In clinical trials with other antibiotic comparators such as imipenem/cilastatin and cephalosporins (with and without an aminoglycoside), meropenem has been shown to have comparable efficacy for the treatment of different types of serious bacterial infections including severe community acquired pneumonia, complicated intra-abdominal infections, complicated skin and skin structure infections, bacterial meningitis and complicated urinary tract infections. In clinical studies of meropenem versus ceftazidime and an aminoglycoside, meropenem produced superior results for treatment of nosocomial and ventilator associated pneumonia. Meropenem also has a favourable pharmacokinetic profile enabling distribution into many tissue sites whilst maintaining a good safety and tolerability profile in adult and paediatric patients. Like other beta-lactam antibiotics, distribution into peripheral tissue may be impaired in critically ill patients. Administration can occur by either bolus dosing or intermittent infusion, although poor stability at room temperature complicates possible administration by continuous infusion. Such properties make meropenem a useful treatment for serious bacterial infections as either empiric or directed therapy, with administration by extended infusion appropriate for treatment of infections caused by pathogens with reduced susceptibility.

Keywords: β-lactam antibiotic, continuous infusion, extended infusion, bolus dosing, safety, TDM, pharmacokinetics, pharmacodynamics, clinical outcome

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Introduction

Serious bacterial infections may have high mortality rate if inappropriately treated. Complicating the treatment of prescription of antibiotics for patients with serious bacterial infections are the decreasing rates bacterial susceptibility and the difficulties associated with achieving appropriate antibiotic concentrations at the site of infection. Suffice to say, source control and early and effective antibiotic therapy is essential for facilitating resolution from the infection.[1–4] In the absence of microbiological data to guide antibiotic choice, effective broad spectrum agents that are appropriate in the context of local susceptibility patterns are essential. Given the persisting high morbidity and mortality associated with serious bacterial infections,[1,2,5,6] further information to guide responsible use of effective empiric antibiotic dosing should be considered a clinical imperative to improve outcomes.

Serious bacterial infections frequently have significant sequelae resulting in morbidities including organ dysfunction requiring intensive care unit (ICU) admission which inevitably leads to a prolonged hospital length of stay. Of greater concern is the high mortality rates associated with these infections. Any infection that has the potential to result in such high morbidity or mortality is serious and may include severe community acquired pneumonia (sCAP), nosocomial pneumonia, complicated urinary tract infections (cUTIs), complicated intra-abdominal infections (cIAIs), bacterial meningitis and complicated skin and skin structure infections (cSSSIs). Many of these infections can lead to severe sepsis and septic shock which occur commonly in ICUs and may have mortality rates approaching 50%.[7,8]

Complicating the effective treatment of these serious bacterial infections are the wide pharmacokinetic variations of some antibiotics that can occur in critically ill patients. These changes present significant challenges to effective prescribing for clinicians. Patients with sepsis are known to become hyperdynamic causing increased renal blood flow and increased clearance of many renally cleared antibiotics.[4,9–11] Such patients may also develop a capillary leak syndrome resulting in increased interstitial fluid volumes which causes a corresponding increase in the volume of distribution of many antibiotics.[4,12] Contrastingly, patients may develop end-organ failure. In this case cardiovascular failure can lead to impaired drug distribution and failure of the eliminating organs (kidney and liver) and can lead to reduced drug clearances predisposing to antibiotic toxicities. The difficult-to-predict pharmacokinetics in critically ill patients significantly increases the potential for suboptimal antibiotic concentrations. Given the strong association between appropriate antibiotic therapy in infected critically ill patients and mortality,[1,2,5,6] as well as the development of antibiotic resistance, selection of effective antibiotics as well as dosing strategies that optimize the antibiotic exposure to the bacteria, will lead to improved clinical outcomes and minimise the development of antibiotic resistance.

Depending on local bacterial susceptibility patterns, meropenem is a broad spectrum carbapenem antibiotic suitable for empiric or directed treatment of serious bacterial infections. It is approved by the United Stated Food and Drug Administration (US FDA) for the treatment of the following infections caused by susceptible bacteria, SSSI, IAI and bacterial meningitis.[13] Of note, meropenem is not approved for treatment of pneumonia, although is commonly prescribed for this indication where sufficient clinical need exists.[14–16]

The objective of this paper is to review the pharmacology, microbiology, clinical outcome data, safety and tolerability and place in therapy of meropenem for the treatment of serious bacterial infections.

Search Strategy

Data for this review were identified by searches of Pubmed (1966 to Jan 2010), EMBASE (1966 to Jan 2010) and the Cochrane Controlled Trial Register as well as references from relevant articles. Studies that included information relating to bacterial susceptibility, clinical outcome data, pharmacokinetics and pharmacodynamics, dosing and safety and tolerability of meropenem were eligible for inclusion. Numerous articles were identified through searches of the extensive files of the authors.

Pharmacology

Meropenem is a parenteral, broad-spectrum carbapenem antibiotic that is classified as a member of the β-lactam family of antibiotics. Meropenem has bactericidal activity via cell wall penetration and subsequent inhibition of penicillin binding proteins

(PBP) which are responsible for the elongation and cross-linking of the bacterial peptidoglycan. The inhibition of PBP leads to disruption of the bacterial peptidoglycan and ultimately to bacterial cell death. This mechanism of activity is bactericidal. Unlike imipenem, meropenem is not a significant substrate of human dehydropeptidase-1 (DHP-1) and therefore does not require concomitant administration with cilastatin.[17] In a comparative study with imipenem and biapenem, meropenem showed better affinity for PBP in *E.coli* (PBP-2 and PBP-4) and PBP-2, -3 and -4 in *Pseudomonas aeruginosa*, which was suggested as the reason for an extended spectrum of activity of meropenem against Gram negative species.[18]

Microbiology

Meropenem is active against a broad range of Gram positive and Gram negative bacteria, including Enterobacteriaceae, *P. aeruginosa* and *Acinetobacter spp*.[17] Meropenem has little appreciable activity against atypical organisms and other therapies should be used where these are suspected as causative of infection. Table 1 describes the activity of meropenem against some aerobic Gram positive and Gram negative bacteria and anaerobic bacteria[19,20] in Europe and the USA. European data is from 2007, and USA data is from 2008. The data is drawn from The Meropenem Yearly Susceptibility Test Information Collection (MYSTIC) Program. MYSTIC is a global, antibiotic resistance surveillance network of over 100 medical institutions worldwide monitoring the susceptibility of meropenem and other selected broad-spectrum agents.

Aerobic Gram positive organisms

Meropenem is active *in vitro* against a wide range of Gram positive bacteria, including Methicillin-Susceptible *Staphylococcus aureus* (MSSA), coagulase-negative Staphylococci (CoNS) and *Streptococcus spp*, including β-hemolyticus Streptococci, *Streptococcus pneumoniae* and Viridans group Streptococci. However, there are some Gram positives with intrinsic resistance to meropenem (and generally to β-lactams), mainly Methicillin-Resistant *Staphylococcus aureus* (MRSA) and *Enterococcus faecium and Enterococcus faecalis,* which each have MIC_{90} reported as 32 mg/L, >16 mg/L and 16 mg/L respectively.[17]

Aerobic Gram negative organisms

The spectrum of activity of meropenem against Gram negative species is excellent. Meropenem demonstrates *in vitro* activity against many of the clinically relevant Gram negative pathogens including the non-fermentative bacilli *P. aeruginosa* and *Acinetobacter baumannii*. However, it is not active against *Stenotrophomonas maltophilia* because of intrinsic production of carbapenemase which degrades the meropenem molecule. Meropenem is not hydrolyzed by most of the β-lactamases, including AmpC β -lactamases and extended spectrum β-lactamases (ESBL)[21] and therefore the susceptibility of β-lactamase producers and non–β-lactamase producers to meropenem does not vary significantly.[21] However, increasing rates of bacterial resistance of *A. baumannii, Klebsiella pneumoniae* and *P. aeruginosa* to meropenem are being documented in countries such as Greece[22] and Turkey.[23] In other countries, including the USA, meropenem is no longer sufficiently active against *Acinetobacter* spp.[19] This trend has also been observed in the worldwide meropenem susceptibility surveillance database (MYSTIC), that is showing slow but increasing emergence of bacterial resistance to meropenem.[19,20]

Anaerobes

Meropenem has been shown to be active *in vitro* against many anaerobic bacteria, with susceptibility rates of 100% against organisms such as *Clostridium difficile*, *Clostridium perfringens*, and *Prevotella spp*. *Bacteroides fragilis* is also susceptible *in vitro* to meropenem, but the susceptibility rate clinically is documented to be lower (88.9%) according to data from the manufacturers.[24]

Once identification of the infective pathogen has occurred, the broad spectrum of activity requires that treatment should be de-escalated to an appropriate agent with a narrower spectrum where appropriate.

Resistance Mechanisms

With increasing resistance to many antibiotics worldwide, an understanding of the known mechanisms of resistance to meropenem is important to guide appropriate prescription in severe infections. Even though meropenem is reported to be poorly associated with the development of bacterial resistance *in vitro*,[25] like many other broad spectrum β-lactams, resistance to

Table 1. Susceptibility data of various aerobic Gram positive, Gram negative and anaerobic bacteria to meropenem in USA and Europe.

Organism	$MIC_{50\ (mg/L)}$ (USA)[19] (no. of isolates)	$MIC_{90\ (mg/L)}$ (USA)[19] (no. of isolates)	% susceptible (USA)[19] (no. of isolates)	$MIC_{50\ (mg/L)}$ (Europe)[20] (no. of isolates)	$MIC_{90\ (mg/L)}$ (Europe)[20] (no. of isolates)	% susceptible (Europe)[20] (no. of isolates)
Aerobic gram negative						
Citrobacter spp	0.03 (n = 103)	0.06 (n = 103)	100% (n = 103)	0.03 (n = 147)	0.06 (n = 147)	99.3% (n = 147)
Enterobacter spp	0.03 (n = 215)	0.12 (n = 215)	96.7% (n = 215)	0.03 (n = 539)	0.13 (n = 539)	98.7% (n = 539)
Escherichia coli	≤0.015 (n = 487)	0.03 (n = 487)	98.6% (n = 487)	0.016 (n = 781)	0.03 (n = 781)	99.9% (n = 781)
Klebsiella spp	0.03 (n = 416)	0.06 (n = 416)	94.2% (n = 416)	0.03 (n = 699)	0.06 (n = 699)	99.3% (n = 699)
Proteus mirabilis	0.06 (n = 171)	0.06 (n = 171)	100% (n = 171)	0.06 (n = 244)	0.13 (n = 244)	100% (n = 244)
Serratia spp	0.06 (n = 145)	0.06 (n = 145)	97.2% (n = 145)	0.03 (n = 195)	0.13 (n = 195)	100% (n = 195)
Enterobacteriaceae spp	0.03 (n = 1537)	0.06 (n = 1537)	97.3 (n = 1537)			
Pseudomonas aeruginosa	0.5 (n = 439)	8 (n = 439)	85.4% (n = 439)	1 (n = 748)	16 (n = 748)	79.1% (n = 748)
Acinetobacter spp	8 (n = 127)	>32 (n = 127)	45.7% (n = 127)	1 (n = 166)	16 (n = 166)	74.1% (n = 166)
Aerobic gram positive						
MSSA	0.12 (n = 317)	0.12 (n = 317)	100% (n = 317)	0.13 (n = 555)	0.25 (n = 555)	100% (n = 555)
Coagulase-negative Staphylococci	0.12 (n = 143)	0.25 (n = 143)	100% (n = 143)	0.13 (n = 187)	8 (n = 187)	89.3% (n = 187)
Streptococcus pneumoniae	<0.0015 (n = 125)	1 (n = 125)	80% (n = 125)	<0.008 (n = 79)	0.13 (n = 79)	94.9% (n = 79)
β-hemolytic streptococci	<0.0015 (n = 119)	0.06 (n = 119)	100% (n = 119)	–	–	–
Viridans group streptococci	0.06 (n = 40)	0.5 (n = 40)	90% (n = 40)	–	–	–
Streptococcus spp	–	–	–	0.016 (n = 135)	0.13 (n = 135)	96.3% (n = 135)
Anaerobic bacteria[21]						
Clostridium difficile	2 (n = 8)	4 (n = 8)	100% (n = 8)	2 (n = 8)	4 (n = 8)	100% (n = 8)
Clostridium perfringens	<0.008 (n = 14)	0.25 (n = 14)	100% (n = 14)	<0.008 (n = 14)	0.25 (n = 14)	100% (n = 14)
Bacteroides fragilis	1 (n = 18)	8 (n = 18)	88.9% (n = 18)	1 (n = 18)	8 (n = 18)	88.9% (n = 18)
Prevotella spp	0.064 (n = 18)	0.25 (n = 18)	100% (n = 18)	0.064 (n = 18)	0.25 (n = 18)	100% (n = 18)

meropenem, is becoming more common. Knowledge of resistance can assist the clinician determine clinical scenarios when meropenem should not be commenced, or alternatively, should be ceased due to possible resistance development. Definitive mechanisms of resistance reported in the literature to meropenem include:

β-lactamases

As indicated previously, meropenem is not hydrolyzed by most of the β-lactamases, however it can be inactivated by carbapenemases, a subgroup of β-lactamases. Microbiological testing for these enzymes should be considered important for determining the appropriateness of use of meropenem. The Ambler molecular classification is used to discern amongst the different classes of carbapenemases[26]:

- *Class A carbapenemases*: produced by some species of Enterobacteriaceae and *P. aeruginosa,* and are inhibited by clavulanic acid. These enzymes are rare and only clinically significant in combination with other resistance mechanisms such as decreased permeability and/or presence of efflux pumps.[27]
- *Class B carbapenemases*: encoded by the gene series IMP and VIM, are also known as metallo-β-lactamases and are the most potent class of carbapenemases. These enzymes are capable of hydrolyzing all β-lactams except the monobactams. The metallo-β-lactamases have metallic atoms in the core of their structure, and can be inhibited by ethylenediaminetetraacetic acid (EDTA) but not by common β-lactamase inhibitors such as clavulanic acid, tazobactam or sulbactam. These metallo-β-lactamases have been found worldwide, and are produced by Gram negative species such as Enterobacteriaceae, *S. maltophilia* and *P. aeruginosa*.[27]
- *Class D carbapenemases*: these are oxacillinases (OXA) with weak carbapenemase activity and do not have activity against extended-spectrum cephalosporins and aztreonam. These oxacillinases have been reported in *A. baumannii* infections, but are reported to compromise the activity of carbapenem only marginally.[27]

Reduced affinity for PBP binding sites

Poor binding affinity of carbapenems to PBP binding sites appears problematic mainly to Gram positive species, such as MRSA and *Enterococcus spp*. This low affinity confers intrinsic resistance to meropenem and generally to all β-lactam antibiotics.

Efflux pumps and porins

The overexpression of multidrug efflux pumps as a mechanism of decreased susceptibility to meropenem has been documented in *P. aeruginosa*[28,29] as well as other Gram negative bacteria.[30,31] A decrease in the number of porins in the cell membrane has also been described and causes reduced passive diffusion of meropenem into the bacteria.[32] These two mechanisms of resistance, will affect meropenem activity[33] and can explain poor bacteriological activity with apparently therapeutic dosing.

Pharmacodynamics

Meropenem is a time-dependent antibiotic, where antibacterial activity is related to the time for which the free concentration is maintained above the minimum inhibitory concentration (MIC) during a dosing interval (fT > MIC).[34] This characteristic is maintained in both Gram positive and Gram negative organisms. This is to be contrasted against other antibiotics where bactericidal activity can be related to the ratio of the peak concentration in a dosing interval (C_{max}) to the MIC of the bacteria (C_{max}/MIC) and/or the ratio of the area under the concentration time curve over a 24-hour period to the MIC ($AUC_{0–24}$/MIC).

Meropenem is also known to possess a longer post-antibiotic effect (PAE) than penicillins and cephalosporins. Against Gram negative bacteria, meropenem displays a concentration-dependent long (2–5 h) PAE on *Enterobacter cloacae*, *Escherichia coli*, *K. pneumoniae*, *P. aeruginosa* and *Serratia marcescens*.[35]

The fT > MIC required for optimal bactericidal activity for carbapenems has been reported to be 40% from *in vitro* and *in vivo* animal models.[36] Bacteriostatic effects have been shown in a murine lung infection model to be 15%–20% fT > MIC.[37] In comparison, cephalosporins are reported to require 50%–70% fT > MIC and penicillin 50%–60% fT > MIC for maximal bactericidal activity.[38] The increased % fT > MIC for cephalosporins and penicillins is most

likely because of a reduced PAE.[38] Drug exposures required for maximal clinical outcomes have been described using retrospective human pharmacokinetic data. This data suggests that advantages may exist for maintaining meropenem concentrations for longer periods and at concentrations up to five times the MIC throughout the entire dosing interval ($fT > 5 \times MIC$) in some patient populations, particularly critically ill patients.[39,40] The significant difference between this finding and the *in vitro* and animal *in vivo* data, requires further prospective human studies to clarify the precise pharmacodynamic endpoints for maximal meropenem activity.

Pharmacokinetics

The pharmacokinetics of meropenem have previously been extensively reviewed elsewhere.[17,41]

Distribution

The pharmacokinetic parameters for meropenem observed in healthy volunteers[13,42] are described in Table 2.

As described in Table 2, meropenem has a Vd consistent with the volume of intravascular and interstitial fluid. It therefore, does not penetrate intracellularly or into adipose tissue to any significant extent. Therefore, weight-based dosing of meropenem should be based on lean body weight and not total body weight.[43] Meropenem has negligible protein binding (2%–3%). In healthy volunteer studies and some patient studies, meropenem is reported to penetrate the interstitial fluid of tissues sufficiently well to achieve concentrations sufficient to inhibit susceptible organisms.[13] The C_{max} is reported to occur in tissues (gynaecological tissue, skin, intra-abdominal tissue, peritoneal fluid, bronchial mucosa, fascia and cardiac tissues) within 0.5 to 1 hours post dosing.[13] For other tissues such as lung, inflamed cerebrospinal fluid, bile and muscle, the C_{max} occurs 2–3 hours after administration.[13]

Table 2. Pharmacokinetic parameters of 500 mg and 1000 mg doses of meropenem administered to healthy volunteers.

Parameter	500 mg over 5 mins	1000 mg over 30 mins
C_{max} (mg/L)	52	49
AUC_{0-24} (mg.h/L)	27–32	67–78
Vd (L)	12.5–20.7	12.5–20.7
CL (L/hr)	11.3–19.7	11.3–19.7
CL_{renal} (L/hr)	8.3–15.1	8.3–15.1
$CL_{non\text{-}renal}$ (L/hr)	3.0–4.6	3.0–4.6
$T_{1/2}$ (h)	~1	~1

Metabolism and elimination

Meropenem undergoes non-renal metabolism by dehydroxypeptidase I to form an open beta-lactam ring metabolite, which like the parent compound is renally eliminated. Between 19 and 27% of the parent compound undergoes metabolism.[42] Meropenem displays linear pharmacokinetics over the 250 mg to 1000 mg dose range.[42] It is likely to be primarily renally cleared by filtration and active tubular secretion.[42] The high percentage of renal clearance supports dose adjustment based on accurate assessments of renal function.

Special Patient Populations

Renal impairment

Meropenem undergoes approximately 70% renal clearance, with reduced clearance occurring in renal impairment.[43] Meropenem clearance has been shown to be closely correlated with creatinine clearance and dose adjustments are recommended during different levels of renal dysfunction.[13] For treatment of most serious bacterial infections, a starting dose of 1000 mg should be considered. Therefore, in the presence of normal renal function (defined as creatinine clearance >50 ml/min), a minimum of 8-hourly dosing should be used, however, for a creatinine clearance from 26–50 ml/min the dose can be reduced to 1000 mg 12-hourly, for a creatinine clearance of 10–24 ml/min the dose can be reduced to 500 mg 12-hourly and for a creatinine clearance <10 ml/min a dose of 500 mg 24-hourly can be used.[13] Simulation data has shown that 500 mg 6-hourly dosing achieves equivalent pharmacokinetic-pharmacodynamic endpoints (% fT . MIC) to 1000 mg 8-hourly and 500 mg 8-hourly dosing achieves equivalent endpoints to 1000 mg 12-hourly.[44]

Renal replacement therapy

Little data exists regarding dosing during intermittent haemodialysis and therefore it is recommended that dose administration occurs once daily after dialysis treatment.[13] More data exists for meropenem pharmacokinetics in different forms

of continuous renal replacement therapy (CRRT) such at continuous veno-venous haemofiltration (CVVHF).[45–50] However, the operational characteristics of the CVVHF used in these studies have varied greatly; the membrane surface areas have varied between 0.43–0.9 m^2, the ultrafiltrate flow rates (UFR) between 1–2 L/h, the blood flow rates between 0.6–12 L/hr and different types of membranes used. The major determination for meropenem clearance is UFR with other factors such as membrane surface area and blood flow rate likely to sufficiently describe meropenem haemofiltration clearance. Typical dose reductions are in the order of 33%–50% of the empiric dose. A summary of the published studies of meropenem pharmacokinetics in CRRT is provided in Table 3.

Sepsis patients without renal dysfunction

Patients with serious infections will often develop sepsis, and therefore the pharmacokinetics observed in this patient population is of great relevance. Critically ill patients with sepsis develop physiological changes likely to affect the pharmacokinetics of meropenem. As part of the systemic inflammatory response syndrome (SIRS) that can be caused by an infection, an increased cardiac output and consequent increased renal blood flow leading to increased clearance of renally cleared drugs like meropenem.[4] Similarly, this pathology can lead to the development of leaky capillaries that result in a movement of intravascular fluid into the interstitial space which results in an increased apparent volume of distribution.[4] Additionally, altered fluid distribution in the body can lead to a maldistribution of blood flow causing impaired perfusion of peripheral tissues leading to reduced tissue concentrations. These pharmacokinetic changes were described in a paper by Roberts et al[12] that used an *in vivo* sampling technique called microdialysis to show that tissue concentrations were 30%–50% of observed plasma concentrations in critically ill patients with sepsis. The investigators also found an apparent Vd that was nearly twice as large as that observed in healthy volunteers (22.7 L vs. 12.4 L).[51] Similarly large values were also found by other investigators in critically ill patients.[52,53] Drug clearance was slightly larger in the study by Roberts et al[12] compared with the study by Krueger et al[51] in healthy volunteers although was not clinically significant (13.6 L/hr vs. 12.4 L/hr).

Dosing Modalities

Given the time-dependent antibiotic activity of meropenem and altered pharmacokinetics likely to occur in patients with serious infections, there are dose considerations necessary for optimal antibiotic exposures. As a time-dependent antibiotic, administration as an extended- or continuous intravenous infusion serves to maximize the time that concentrations are maintained above the MIC of the pathogen.[54] However, as a carbapenem, meropenem only requires 40% $f\,T > MIC$, the requirement for longer $f\,T > MIC$ remains debatable, although emerging data suggests

Table 3. Comparative CRRT settings and pharmacokinetic data from studies of meropenem clearance during continuous veno-venous haemofiltration.

Study	Membrane SA (m^2)	BFR (L/hr)	UFR (L/hr)	SC	$T_{1/2}$ (hrs)	Vd (L/kg)	CL_{CVVHF} (L/hr)	Cl_{tot} (L/hr)	CL_{CVVHF}/ SA	CL_{CVVHF}/ BFR	CL_{CVVHF}/ UFR
Thalhammer 1998	0.43	9	165	1.09	2.46	29.90	2.98	8.62	6.93	0.33	0.018
Tegeder 1999	0.9	10	66	1.17	8.7	12.4	1.32	3.10	1.47	0.13	0.020
Ververs 2000	0.9	12	99	0.63	6.3	0.37	0.96	4.57	1.07	0.08	0.010
Giles 2000	0.9	9	102	0.95	5.84	0.35	1.50	3.63	1.67	0.17	0.015
Valtonen 2000	0.7	6	24	NS	7.5	NS	NS	3.27	NS	NS	NS
Krueger 2003	0.9	1	96	0.91	3.63	0.28	1.47	4.98	1.63	1.47	0.015

Abbreviations: SC, sieving coefficient; BFR, blood flow rate; UFR, ultrafiltrate flow rate; $T_{1/2}$, elimination half life; Vd, volume of distribution; CL_{CVVHF}, clearance by haemofiltration; CL_{tot}, total clearance; NS, data not stated.

a longer f T > MIC may be required in patients with serious bacterial infections.[40,41]

Most of the data that presently exists to support extended or continuous infusions is derived from simulation studies.[55–58] This main message from these papers is that with increasing MICs, the utility of extended- and/or continuous-infusion for achieving 40% f T > MIC increases. However, susceptibilities to meropenem generally remain sufficiently high,[59–61] that administration as an intermittent infusion (over 30 mins) remains appropriate for treatment of serious infections.[12] An important retrospective cohort study in this context was performed by Lorente et al which sought to determine the clinical efficacy of continuous (1 g over 6 hrs administered every 6 hrs) versus intermittent infusion (1 g over 30 mins every 6 hrs) of meropenem for the treatment of ventilator-associated pneumonia (VAP) due to Gram negative bacilli.[14] The study was designed as such as continuous infusion is likely to follow the pharmacodynamics of meropenem and sustain meropenem concentrations for a more significant f T > MIC. The authors found that the group receiving meropenem by continuous infusion showed a greater clinical cure rate than the group treated with intermittent infusion (38 of 42, 90.47%, vs. 28 of 47, 59.57%, respectively; $P < 0.001$).

Stability data

One aspect of clinical importance which determines the capacity to administer meropenem as an extended- or continuous-infusion is its physicochemical stability at room temperature. At room temperature the stability of meropenem is limited to approximately 8 hours when dissolved in a 0.9% sodium chloride solution.[62] Further to this, meropenem has reduced stability in 5% glucose solutions.[13] Data from Kuti et al, suggests that when used in the ambulatory setting, if the meropenem solution is maintained next to a cold pack, the stability can be extended to 24-hours.[63] When stored at 5°C, meropenem stability has been documented at 120 hours.[64] It follows that for meropenem to be administered as a continuous infusion in the clinical environment, it should be administered in 0.9% sodium chloride as 3 × 8 hour infusions with longer infusion durations not appropriate unless in the presence of a cold pack. If elevated serum sodium concentrations necessitate administration with 5% glucose, then continuous infusions are not practicable and use of extended infusions over 3-hours could be used if extended infusion durations are desired.[65]

Clinical Outcome Data

Several trials have been published that evaluate the effectiveness and safety of meropenem as empirical therapy in different types of severe bacterial infections. These trials are described in Table 4. Data on complicated intra-abdominal infections (cIAI) is discussed below because of the range of different studies undertaken for this indication.

Nosocomial pneumonia

Three studies have been performed comparing meropenem with other antimicrobial agents for the treatment of nosocomial lower respiratory tract infections.[66–68] In the studies of mereopenem versus ceftazidime plus tobramycin[66] or amikacin,[67] the authors reported improved clinical and bacteriological cures with meropenem monotherapy. The third study by Heyland et al[68] compared meropenem monotherapy versus meropenem plus ciprofloxacin for the treatment of late-onset VAP in critically ill patients. Although the results gave support for meropenem monotherapy for treatment of late-onset VAP in most patients, it also demonstrated the importance of combination therapy for patients infected with *Pseudomonas spp.*, *Acinetobacter spp.*, or multidrug-resistant Gram negative bacilli. In these patients, combination therapy achieved improved bacteriological cure rates with combination therapy ($P = 0.05$) and had improved appropriateness of empirical therapy ($P < 0.001$) compared with those patients that received monotherapy.[68] For nosocomial infections, meropenem has shown conflicting results in pharmacoeconomic analyses depending on the type of analysis performed.[69,70]

Severe Community-Acquired Pneumonia (sCAP)

Three randomised controlled trials have evaluated the efficacy of meropenem in the treatment of another serious bacterial infection, sCAP.[71–73] Each study has demonstrated non-inferiority of meropenem to imipenem/cilastatin[71] and other conventional therapy for sCAP (ceftriaxone + clarithromycin or amikacin + clarithromycin)[72] or ceftazidime.[73]

Table 4. Summary of studies comparing clinical and bacterial cure rates for serious bacterial infections of meropenem versus comparators.

Author	Study design	Meropenem comparator	Main findings
Nosocomial pneumonia			
Sieger et al[66]	Randomised, multicentre (n = 211)	Ceftazidime + tobramycin	Improved clinical ($P = 0.04$) and bacteriological ($P < 0.006$) cure with meropenem for lower RTI
Alvarez-Lerma et al[67]	Randomised (n = 140)	Ceftazidime + amikacin	Improved clinical ($P < 0.05$) and bacteriological ($P < 0.05$) cure with meropenem for VAP
Heyland et al[68]	Randomised (n = 740)	Meropenem + ciprofloxacin (combination)	Similar clinical and bacteriological cure rates late-onset VAP for both groups. If patient infected with *Pseudomonas spp.*or multidrug-resistant Gram negatives, combination therapy resulted in improved bacteriological cure rates ($P = 0.05$)
Severe Community-Acquired Pneumonia (sCAP)			
Bartlonini et al[71]	Randomised, multicentre (n = 144)	imipenem/cilastatin	Meropenem was as effective as imipenem/cilastatin
Romanelli et al[72]	Randomised, open-labelled (n = 204)	Ceftriaxone + clarithromycin or amikacin + clarithromycin	Meropenem or imipenem/cilastatin as effective as the comparators but meropenem more mildly more cost-effective ($60/day)
Finch et al[73]	Pooled data from two clinical trials (n = 393)	Ceftazidime	Meropenem and ceftazidime were effective with clinical cure rates of 91.4% and 90.3% respectively and bacteriological cure rates 94.7% and 92.3% respectively
Complicated skin and skin structure infections			
Nichols et al[83]	Randomised, open-labelled (n = 377)	Imipenem/cilastatin	Both agents effective for treating cSSSI with high clinical cure and bacteriological response rates for both meropenem (98% and 94%), and imipenem/cilastatin (95% and 91%)
Fabian et al[84]	Randomised, double-blinded (n = 1076)	Imipenem/cilastatin	Clinical outcomes were similar with 93.5% success for meropenem and 92.3% for imipenem/cilastatin. Duration of the treatment and frequency of surgical interventions (27% vs. 25% respectively) were also similar
Bacterial meningitis			
Schmutzhard et al[85]	Randomised, multi-centre (n = 56)	Cefotaxime or ceftriaxone	Meropenem clinical cure rate was 100% compared with the cephalosporins 77% for adults
Klugman et al[86]	Randomised (n = 190)	Cefotaxime	Clinical cures of 100% in both meropenem and cefotaxime groups for paediatrics
Odio et al[87]	Randomised, multi-centre (n = 258)	Cefotaxime	Clinical cure rates of 97% in the meropenem and 96% in the cefotaxime group for paediatrics
Complicated urinary tract infections			
Cox et al[88]	Open-labeled, randomised multi-centre (n = 235)	Imipenem/cilastatin	*E.coli* was the most frequent causal pathogen. The two treatments resulted in excellent clinical and bacteriological cure rates for meropenem (99% and 90%) and imipenem/cilastatin (99% and 81%) respectively. Patients receiving meropenem had decreased incidence of adverse drug events (i.e. pruritus, diarrhoea and elevation of hepatic enzymes) (8% vs. 19% respectively)

Abbreviations: RTI, respiratory tract infection; VAP, ventilator associated pneumonia; cSSSI, Complicated Skin and Skin Structure Infections.

Complicated Intra-Abdominal Infections (cIAI)

The efficacy of meropenem versus comparators for the treatment of cIAI has been evaluated by several randomised trials.[74–77] The chosen comparators included imipenem/cilastatin,[74,76,78] cefotaxime plus metronidazole[75,79] and clindamycin plus tobramycin.[77,80,81] In these trials, meropenem demonstrated clinical and bacteriological non-inferiority to imipenem/cilastatin[74,76,78] and clindamycin/tobramycin[77,80] in the treatment of cIAI. A similar rate of adverse events was also observed between the groups, except for the clindamycin/tobramycin comparator group which developed a significantly increased serum creatinine concentration.[80] Meropenem demonstrated clinical superiority against cefotaxime plus metronidazole in one study ($P = 0.03$).[80] Clinical and bacteriological non-inferiority was shown in another study.[82] Therefore, in comparison with cefotaxime plus metronidazole, meropenem is an effective alternative for the management of cIAI.

Complicated Skin and Skin Structure Infections (cSSSI)

The comparative effectiveness of meropenem and imipenem/cilastatin for treatment of cSSSI has been assessed in two randomised multi-centre clinical trials.[83,84] Each has shown equivalence of therapy for treatment of cSSSI.

Bacterial meningitis

Clinical outcomes studies have been performed to assess the clinical utility of meropenem in bacterial meningitis in adults[85] and in paediatrics.[86,87] The data suggests that meropenem may be an appropriate alternative treatment for this indication.

Complicated Urinary Tract Infections (cUTI)

cUTI are also considered a serious bacterial infection and have been subject to one significant study that compared meropenem with imipenem/cilastatin.[88] In this study, the authors concluded that meropenem was an appropriate alternative to imipenem/cilastatin for the treatment of cUTI.

Safety and Tolerability

Meropenem is well tolerated and is considered very safe. Extensive reviews of the safety and tolerability of meropenem have been published previously.[89] An excellent comparison of the safety of meropenem with imipenem/cilastatin, cephalosporins (with and without an aminoglycoside) and clindamycin with an aminoglycoside was performed by Linden et al.[89] The authors included 52 previous studies with a total of over 6000 patients (including >1000 paediatric patients) and found comparable rates of clinician-reported adverse events. The incidence of drug-related adverse events for meropenem was 16% compared with 12%–21% for the comparators. The most frequently observed adverse events were diarrhoea, rash and nausea and vomiting which all occurred in less than 4% patients. In paediatric patients with serious bacterial infections, a similar rate of drug-related adverse events was seen as in the combined analysis.

Drug-related laboratory adverse events were also uncommon for both meropenem and the comparators with increased alanine transferase concentrations (3.7% and 2.4%–5.7% respectively), aspartate transferase concentrations (2.9% and 1.9%–4.6% respectively) and thrombocytosis (1.3% and 1.2%–4.6% respectively) being the most common events. It should be noted that all of the included studies in the analysis by Linden et al[89] typically excluded patients with a known hypersensitivity to β-lactams (or comparator drugs) as well as patients with marked hepatic or renal disease or with a history of seizures. However, other data suggests that the rate of carbapenem cross-hypersensitivity to β-lactams is approximately 10%.[90]

Meropenem has been described to interact with sodium valproate resulting in decreased sodium valproate concentrations. The mechanism for this remains unclear, although the extent of the interaction is significant with a decrease in sodium valproate up to 82%.[91] Where possible, an alternate antibiotic should be used in patients previously receiving sodium valproate therapy.

Place in Therapy

The broad spectrum of antibacterial activity as well as favourable pharmacokinetic profile and safety profile make meropenem an attractive choice for therapy of serious bacterial infections. These attributes

are reinforced by compelling data describing the importance of early and appropriate antibiotic therapy for improving outcomes in critically ill patients with serious bacterial infections.[1–3,5,92] However, whilst such data suggests that meropenem would provide excellent empiric cover, the same data also suggests that it is an appropriate alternative to be kept as a reserve agent for directed therapy to reduce selective pressure that may lead to the development of future antibiotic resistance. Certainly any considerations for empiric use of meropenem should be guided by local susceptibility profiles and the clinical presentation of the patient including recent antibiotic therapies.

Standard directions for administration of meropenem, in the absence of renal dysfunction, recommend administration every 8 hours as a 5 minute or 15–30 minute infusion. However, the short half-life of meropenem in these patients (<1 hour) means that low concentrations may be present for considerable durations of the dosing interval. Present data indicates that despite this, because of the high level of susceptibility of most bacteria to meropenem, that pharmacodynamic targets are still achieved.[12] However, with decreasing susceptibility, the 8 hour dosing interval may become inappropriate and more frequent administration, or administration as an extended- or continuous infusion may be preferred to achieve pharmacodynamic targets associated with maximal bacterial killing. Furthermore, emerging data suggests that in patients with impaired peripheral circulation, such as those with sepsis or septic shock that tissue concentrations are in fact significantly lower than plasma concentrations.[12] Although no data demonstrates the relationship of tissue concentrations to clinical outcome, tissue concentrations may be found to be important because they are the site of most infections.[93] Further research may guide the need for altered dosing to optimize antibiotic concentrations in the infected tissue. In most other clinical situations, meropenem has excellent penetration into body tissues.

In comparison with other antibiotics, meropenem has been shown to be an effective and well tolerated alternative to other agents. In clinical trials with other antibiotic comparators such as imipenem/cilastatin and cephalosporins (with and without an aminoglycoside), meropenem has been shown to have comparable efficacy for the treatment of different types of serious bacterial infections including sCAP, cIAI, cSSSI, bacterial meningitis and cUTIs. In clinical studies of meropenem versus ceftazidime and an aminoglycoside, meropenem produced superior results for treatment of nosocomial and VAP. Accordingly, meropenem is recommended as empiric therapy for various infections by many leading authorities including the American Thoracic Society,[94] the European Society for Clinical Microbiology and Infectious Diseases[95] and the Infectious Diseases Society of America.

Conclusion

Meropenem is an excellent therapeutic option for treatment of serious bacterial infections. Meropenem has a broad spectrum of activity against many Gram positive and Gram negative organisms and stability against ESBL producing organisms. It has a favourable pharmacokinetic profile enabling distribution into many tissue sites and has been shown to be at least as effective as comparator antibiotics for various serious bacterial infections in well designed clinical trials. Meropenem also has a good safety and tolerability profile in adult and paediatric patients. This allows administration by bolus dosing or intermittent infusion, although poor stability at room temperature complicates possible administration by continuous infusion. Such properties make meropenem an excellent treatment for serious bacterial infections as either empiric or directed therapy, with administration by extended infusion appropriate for treatment of infections caused by pathogens with reduced susceptibility.

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