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Meropenem: evaluation of a new generation carbapenem[1]

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Abstract

Meropenem is a new β-lactam antibiotic belonging to the carbapenem class. It differs structurally from imipenem, the first carbapenem to be marketed, by possessing a 1-β-methyl group on the carbapenem moiety and a substituted 2′ side chain. Meropenem is relatively stable to human dehydropeptidase-I (DHP-I), and therefore, unlike imipenem, it does not need to be administered with a DHP-I inhibitor such as cilastatin. Meropenem has an ultra-broad spectrum of antibacterial activity which encompasses Gram-positive and Gram-negative aerobes and anaerobes, including many strains resistant to other antibacterials. Compared to imipenem, meropenem is more active against Enterobacteriaceae and *Pseudomonas aeruginosa* and a little less active against some Gram-positive cocci. Meropenem is susceptible to few clinically important β-lactamases. Meropenem exhibits a linear pharmacokinetic profile which shows predictable age and disease-related changes. Elimination is primarily renal with a half-life of approximately 1 h after intravenous (IV) administration. Meropenem monotherapy has proved efficacious in the treatment of a variety of infections in adults and children and can be administered by bolus IV injection, as well as IV infusion and intramuscular (IM) injection. Prospective, randomised clinical trials have shown it to be as efficacious as comparator regimens in the treatment of lower respiratory tract, intra-abdominal, urinary tract and skin and soft tissue infections, meningitis and septicaemia. Furthermore, meropenem monotherapy has demonstrated efficacy in the empirical treatment of febrile neutropenic cancer patients. Meropenem is well tolerated by the CNS in clinical studies, which reflects animal data, suggesting a low propensity to cause seizures. Thus, meropenem is an important new antibacterial which should prove particularly useful in severe and polymicrobial infections and those caused by organisms resistant to other agents. © 1997 Elsevier Science B.V.

Keywords: Meropenem; Carbapenem; Antibacterial; Imipenem; β-lactamases

1. Introduction

Meropenem is a novel carbapenem antibacterial recently introduced and available in many countries. The first member of this class, imipenem, was launched in the 1980s. These agents share a number of important advantages over other types of antibacterials. In particular, they offer the broadest antibacterial spectra of any class, which includes virtually all clinically important Gram-positive and Gram-negative aerobes and anaerobes. This activity is due in part to the high degree of stability shown by the carbapenems to β-lactamases. This property is becoming increasingly important in view of the increasing incidence of Enterobacteriaceae strains which produce extended-spectrum β-lactamases.

However, there are important differences between meropenem and imipenem. Imipenem is susceptible to metabolism by renal dehydropeptidase-I (DHP-I). Consequently, the drug must be administered with cilastatin, a DHP-I inhibitor. In contrast, meropenem is relatively stable to this enzyme and does not require co-administration with a DHP-I inhibitor. Also, there are differences in the antibacterial spectra of the two agents. Meropenem shows somewhat better activity against Enterobacteriaceae and *Pseudomonas aeruginosa*, while imipenem is more potent against some Gram-positive cocci. Meropenem may be better tolerated than imipenem/cilastatin, particularly by the gas-

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trointestinal tract with regard to nausea and vomiting and the central nervous system. In addition, meropenem, unlike imipenem/cilastatin, can be given by intravenous bolus injection.

Therefore, meropenem monotherapy is an attractive choice for the empirical treatment of moderate or severe bacterial infections. This article reviews the chemical, antimicrobial and pharmacokinetic properties of the drug, and examines the clinical evidence of its therapeutic efficacy.

2. Chemistry

Meropenem, (-)-(4R,5S,6S)-3-[[(3S,5S)-5-(dimethylcarbamoyl)-3-pyrrolidinyl]thio]-6-[(1R)-1-hydroxyethyl] - 4 - methyl - 7 - oxo - 1 - azabicyclo[3,2,0]hept - 2 - ene - 2-carboxylic acid, is among the newer semisynthetic β-lactam antibacterial agent belonging to the carbapenem class (Fig. 1). Meropenem differs chemically from imipenem by possessing a 1-β-methyl group on the carbapenem moiety and a substituted 2′ side chain. The 1-β-methyl substituent provides stability to human renal dehydropeptidase-I (DHP-I) [1], an enzyme that hydrolyses imipenem [2]. Meropenem can therefore be administered as a single agent, unlike imipenem which must be co-administered with cilastatin, a DHP-I inhibitor, to prevent degradation of the molecule and nephrotoxic effects [2]. The 2′ side chain of meropenem provides enhanced activity against *P. aeruginosa* [3].

Meropenem has pK_a values of 2.9 and 7.4, and an octanol water partition coefficient of less than 1×10^{-3} over the pH range 3–9. Meropenem trihydrate is available for parenteral clinical use as a sterile white to yellow crystalline powder, blended with anhydrous sodium carbonate to increase its solubility. The approved trade names for meropenem are Merrem, Meronem, Optinem and Merozen.

3. Antibacterial activity

Studies have shown that meropenem freely penetrates Enterobacteriaceae [4] and *P. aeruginosa* [5].

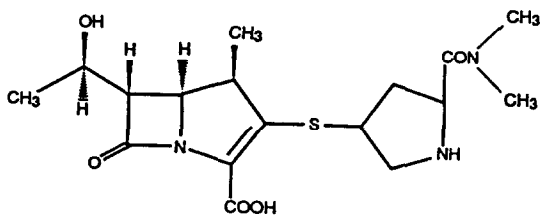

Fig. 1. The chemical structure of meropenem.

Similar to other β-lactam antibacterial agents, meropenem binds covalently to penicillin binding proteins (PBPs) [6]. PBPs are essential for bacterial cell wall biosynthesis and this disruption leads to bacterial cell death. In *Escherichia coli*, the main target of both meropenem and imipenem is PBP2. However, in *P. aeruginosa* meropenem, unlike imipenem, has a high affinity for both PBP2 and PBP3 [4,7]. A comprehensive overview of the antibacterial activity of meropenem and a comparison with imipenem and various other antibacterial agents is provided in the reviews by Edwards [6] and Wiseman et al. [8]. Meropenem has a broad spectrum of antibacterial activity which encompasses the majority of clinically important aerobic, nutritionally fastidious, and anaerobic bacteria (Table 1Table 2). The widely accepted susceptibility breakpoints for meropenem are 4 and 8 mg/l for full and intermediate susceptibility, respectively, and ≥ 16 mg/l for resistance [6]; these remain to be confirmed by NCCLS. The spectrum of activity of meropenem is similar to that of imipenem. However, meropenem is more active in vitro than imipenem against Enterobacteriaceae and other Gram-negative aerobes and a little less active against some aerobic Gram-positive cocci [6].

Meropenem exhibits a high degree of potency against non-fermenters. It is generally 2- to 4-fold more active than imipenem against most *Pseudomonas* spp. and 4-fold more potent against *Burkholderia cepacia* [6]. Indeed, meropenem was the most potent antimicrobial tested in a recent study involving 1991 clinical isolates of *P. aeruginosa*; 98.9% of isolates were fully susceptible to meropenem [9]. Meropenem, in common with most β-lactam agents [10], is not active against *Stenotrophomonas* (*Xanthomonas*) *maltophilia* [8].

The activity of meropenem in vitro against bacterial strains resistant to other antimicrobials has also been evaluated. Meropenem retains activity against penicillin-resistant (PR) *Streptococcus pneumoniae*, although its MIC_{90} in these strains is increased to 1 mg/l [6,11]. Meropenem has demonstrated a high degree of activity against Enterobacteriaceae and *P. aeruginosa* strains with resistance to fluoroquinolones, aminoglycosides or other β-lactams (Table 3). In one study, 95% of 144 Gram-negative bacilli isolates resistant to ciprofloxacin, cefoperazone and/or amikacin were susceptible to meropenem [24]. Another study showed meropenem to be at least 4-fold more active than imipenem against most strains of Gram-negative bacilli with resistance to other β-lactam agents (e.g. piperacillin, ticarcillin) [21]. Meropenem has also demonstrated activity against strains of anaerobic organisms resistant to cefoxitin, clindamycin and metronidazole (Table 4).

Table 1
In vitro antibacterial activity of meropenem and comparators against clinically important Gram-positive and Gram-negative aerobes

Organism	Number of strains	MIC_{90} (mg/l)					
		Meropenem	Imipenem	Ceftazidime	Cefotaxime	Gentamicin	Ciprofloxacin
Gram-positive							
Staphylococcus aureus (MS)	3417	0.25	0.13	>16	4	8	0.5
Staphylococcus epidermidis (MS)	1317	4	1	16	64	16	16
Streptococcus pyogenes	392	<0.06	<0.06	0.25	<0.25	16	1
Streptococcus pneumoniae (PS)	709	0.13	0.06	1	0.25	>16	2
Streptococcus pneumoniae (PR)	143	1	0.25	32	1	16	1
Enterococcus faecalis	1698	8	2	>128	>128	128	4
Listeria monocytogenes	155	0.25	0.25	128	128	2	1
Gram-negative							
Escherichia coli	3683	<0.06	0.5	<1	<0.25	8	0.13
Citrobacter freundii	656	0.13	1	64	32	32	0.5
Klebsiella pneumoniae	1241	0.06	1	1	0.5	4	0.25
Enterobacter cloacae	1201	0.25	2	64	64	32	0.25
Serratia marcescens	764	0.25	2	4	32	64	2
Proteus mirabilis	1398	0.13	4	0.25	<0.25	4	0.13
Proteus vulgaris	377	0.25	4	0.25	1	2	0.06
Salmonella spp.	308	<0.06	0.5	<1	64	1	<0.06
Morganella morganii	567	0.25	4	16	8	4	0.13
Providencia rettgeri	203	0.25	4	4	1	128	8
Providencia stuartii	361	0.5	4	8	1	>128	32
Haemophilus influenzae[a]	1343	0.13	4	0.25	0.06	8	0.016
Neisseria meningitidis	98	0.016	0.13	<0.25	<0.25	8	<0.016
Neisseria gonorrhoeae (PS/PR)	568	0.03	0.25	0.03	0.03	16	0.008
Moraxella catarrhalis	212	0.008	0.13	0.5	0.5	2	0.06
Pseudomonas aeruginosa	3018	4	>8	>16	128	>64	2
Burkholderia cepacia	166	8	32	16	>32	128	8
Acinetobacter calcoaceticus	461	2	2	64	128	64	8

Compiled internationally from 122 laboratories (reproduced with permission [6]).
MS, methicillin-susceptible; PS, penicillin-susceptible; PR, penicillin-resistant.
[a] Including β-lactamase-positive or ampicillin-resistant strains.

Carbapenems, unlike other β-lactam agents, exert a post-antibiotic effect (PAE) with Gram-negative bacilli [8]. Meropenem has also demonstrated a PAE with *Staphylococcus aureus*, *Enterococcus faecalis*, *P. aeruginosa* and *Bacteroides fragilis* [6]. With respect to Enterobacteriaceae, meropenem induced a PAE with 80% (12/15) of strains tested (Zeneca, data on file).

3.1. Resistance

Meropenem is stable to virtually all bacterial serine-based β-lactamases, including the Type-I enzymes elaborated by *Enterobacter*, *Citrobacter*, *Serratia* and *Pseudomonas* spp. [6]. A zinc-dependent plasmid-mediated carbapenemase which confers resistance to meropenem and imipenem has been reported in *P. aeruginosa* [27]. Also, carbapenems may be susceptible to hydrolysis by metallo-β-lactamases produced by *Stenotrophomonas maltophilia*, *Flavobacterium* spp. and, less commonly, by *Aeromonas hydrophilia* and *Bacteroides* spp. [6,28]. Few antibacterial agents are effective against *E. faecium* and methicillin-resistant (MR) staphylococci and these organisms are also resistant to meropenem.

The potential for development of bacterial resistance to meropenem by the usual means of alteration of PBPs and/or production of β-lactamases appears to be low [29]. Meropenem is not a potent inducer of chromosomal Type-I β-lactamases in *P. aeruginosa* [30]. Indeed, relative to imipenem, meropenem may have a lower propensity to induce these enzymes in Enterobacteriaceae and *P. aeruginosa* [31,32].

Some cross-resistance between meropenem and imipenem involving both enzymatic and non-enzymatic mechanisms has been reported [31]. However, Enterobacteriaceae, *P. aeruginosa* and *B. cepacia* strains resistant to imipenem may remain susceptible to meropenem (Zeneca, data on file) [15,16,33].

Table 2
In vitro antibacterial activity of meropenem and comparators against anaerobes

Organism	Number of strains	MIC_{90} (mg/l)			
		Meropenem	Imipenem	Clindamycin	Metronidazole
Bacteroides fragilis	1686	0.5	1	8	2
Bacteroides thetaiotaomicron	518	0.5	0.5	16	2
Bacteroides vulgatus	264	0.5	1	8	1
Bacteroides distasonis	204	1	1	8	2
Fusobacterium nucleatum	87	0.25	0.5	2	2
Peptococcus magnus	128	0.25	0.5	2	2
Clostridium perfringens	391	<0.06	0.25	4	2
Clostridium difficile	230	2	8	32	0.5

Compiled internationally from 122 laboratories (reproduced with permission [6]).

3.2. Activity in combination with other drugs

The activity of meropenem in combination with a number of other antibacterials has been studied. Checkerboard titrations show that a combination of meropenem with vancomycin or teicoplanin was either synergistic or indifferent against MR staphylococci or enterococci (data on file, Zeneca) [34]. In recent tests the combination of meropenem and teicoplanin was synergistic against moderate-level gentamicin-resistant (MLGR) enterococci and showed an additive effect, sometimes close to synergy, against high-level gentamicin-resistant (HLGR) enterococci [35]. The combination of meropenem and gentamicin showed an additive effect, sometimes close to synergy, against MLGR strains. The triple combination of meropenem, teicoplanin and gentamicin was particularly advantageous, demonstrating a marked degree of synergy against both MLGR and HLGR enterococci.

A combination of meropenem (0.13 mg/l) and vancomycin (1 mg/l) showed a more rapid and prolonged bactericidal effect against methicillin-susceptible (MS) *S. aureus* than either drug alone [36]. More recently, meropenem was combined in vitro with vancomycin (54 strains) or teicoplanin (45 strains) against coagulase-positive and coagulase-negative MS and MR staphylococci [37]. Overall, these combinations acted synergistically against 20–30% of MS strains and 20–60% of MR strains. Synergy was observed most frequently when meropenem was combined with teicoplanin.

The combination of meropenem and amikacin displayed synergy in 56% of tests against *P. aeruginosa*, *Acinetobacter* and Enterobacteriaceae [38]. Also, against *B. fragilis* and *Clostridium* spp., synergy was observed with meropenem in 33% of tests with clindamycin and 100% of tests with metronidazole (Zeneca, data on file). Similarly, meropenem (0.12 mg/l) combined with gentamicin (0.12 mg/l) was more rapidly bactericidal against *P. aeruginosa* than either drug alone.

3.3. Concentration-effect relationship

The rate at which β-lactam antibiotics kill bacteria is relatively independent of the drug concentration achieved. Rather, the pharmacological effect of the drug is determined by the amount of time that the drug concentration remains above the minimum inhibitory concentration (MIC) for the pathogen [39]. Data from animal models of infection have shown that meropenem inhibits growth of Gram-negative bacteria when the concentration of meropenem exceeds the MIC for only 20–30% of the dosing interval [40]. In order to achieve a similar pharmacological effect with a penicillin or a cephalosporin in these organisms, the plasma concentration must surpass the MIC for 35–40% of the dosing interval [41]. Extrapolating from pharmacokinetic and in vitro bacterial susceptibility data, the meropenem plasma concentration/time profile following a 1 g 8-hourly dose indicates that one could expect to have a maximal response for organisms that have MICs of 4 mg/l or less (Fig. 2) [42].

4. Pharmacokinetics

Samples of body fluids or tissues can be analysed for meropenem using either microbiological techniques or high pressure liquid chromatography (HPLC) and the correlation between these two methods appears to be very good ($r = 0.9972$) (Zeneca, data on file).

The pharmacokinetic profile of meropenem resembles that of imipenem when administered as imipenem/cilastatin [43]. However, in the presence of renal failure, the clearance of both meropenem and imipenem is reduced but that of cilastatin is reduced still further leading to more accumulation than imipenem [44].

The principal pharmacokinetic properties of meropenem in healthy adults are summarised in Table 5. After intravenous (IV) or intramuscular (IM) administration, the plasma concentrations, as assessed by the

Table 3
In vitro activity of meropenem against aerobes resistant to other antibacterials

Antibiotic resistance pattern	Organism (number of isolates)	Susceptibility to meropenem[a]		Reference
		% of isolates	MIC_{90} (mg/l)	
Resistant to other classes of β-lactam				
Ampicillin	*Haemophilus influenzae* (22)	—	0.06	[12]
Ceftazidime	Gram-negative rods (20)	75[b]	—	[13]
Ceftazidime, cefotaxime, piperacillin and ticarcillin/clavulanate	Enterobacteriaceae (144)	—	0.06–0.5	[14]
Ceftazidime, cefotaxime, piperacillin and ticarcillin/clavulanate	*Pseudomonas aeruginosa* (20)	—	16	[14]
Ceftazidime	*Pseudomonas aeruginosa* (10)	100[c]	—	[15]
Ceftazidime	*Pseudomonas aeruginosa* (57)	40[c]	64	[16]
Ceftazidime	*Pseudomonas aeruginosa*[d]	83	—	[17]
Cefotaxime, ceftazidime and piperacillin	*Acinetobacter calcoaceticus* (-)	—	0.25	[18]
Penicillin	*Streptococcus pneumoniae* (6)	—	1	[12]
	Streptococcus pneumoniae (51)	100	≤1	[19]
Resistant to aminoglycosides				
Amikacin	Enterobacteriaceae (78)	—	≤0.03–0.25	[20]
Amikacin	*Pseudomonas aeruginosa* (64)	94[c]	—	[15]
Amikacin ceftazidime	*Pseudomonas aeruginosa* (29)	66[c]	—	[15]
Gentamicin	*Enterobacter* spp. (10)	—	0.125	[21]
Piperacillin	*Klebsiella* spp. (10)	—	0.06	
Ticarcillin	*Morganella morganii* (10)	—	0.5	
	Providencia spp. (10)	—	2	
	Serratia spp. (10)	—	8	
Tobramycin	Gram-negative bacilli (81)	79[b]	—	[13]
Tobramycin	*Pseudomonas aeruginosa* (29)	90[e]	8	[20]
Resistant to fluoroquinolones				
Ciprofloxacin	Enterobacteriaceae (57)	98[b]	—	[22]
Ciprofloxacin	*Pseudomonas aeruginosa* (22)	73[c]	—	[15]
Ciprofloxacin	*Pseudomonas aeruginosa* (30)	100[b]	—	[22]
Ciprofloxacin	*Acinetobacter* spp. (37)	95[c]	—	[22]
Ciprofloxacin, gentamicin	*Acinetobacter* spp. (25)	—	2	[23]
Fluoroquinolones	Gram-negative bacilli (58)	74[b]	—	[13]
Ciprofloxacin, cefoperazone and/or amikacin	Gram-negative bacilli (144)	95	—	[24]

—, Details not presented.
[a] Recommended breakpoints defining susceptibility to meropenem are: susceptible, ≤4 mg/l; intermediate, 8 mg/l; resistant ≥16 mg/l.
[b] Susceptibility cut-off ≤4 mg/l.
[c] Susceptibility cut-off ≤8 mg/l.
[d] Strains with immediate susceptibility or resistance to ceftazidime (MIC>8 mg/l).
[e] Susceptibility cut-off <8 mg/l.

area under the plasma concentration-time curve (AUC), increase linearly with dose [42] (Fig. 3) and are close to dose proportional. There may be a minor reduction in clearance with increasing dose [45], but this is of little clinical importance at the dosages used clinically. The plasma concentration-time profile of

Table 4
In vitro activity of meropenem against anaerobes resistant to cefoxitin, clindamycin or metronidazole

Antibiotic resistance pattern	Organism (number of isolates)	Susceptibility to meropenem[a]		References
		Proportion of isolates[b] (%)	MIC_{90} (mg/l)	
Cefoxitin	*Bacteroides fragilis* (12)	91	—	[25]
	Bacteroides thetaiotaomicron (10)	100	—	
	Clostridium difficile (17)	100		
Clindamycin	*Bacteroides fragilis* group (25)	—	0.015–0.5	[26]
	Bacteroides spp. (7)	—	0.06–2	
	Fusobacterium spp. (5)	—	0.12–2	
	Clostridium spp. (20)	—	≤0.004–1	
	Peptostreptococcus spp. (9)	—	≤0.004–1	
	Other anaerobes (3)	—	0.06–4	
Clindamycin	*Bacteroides distasonis* (10)	90	—	[25]
	Bacteroides thetaiotaomicron (18)	100	—	
	Clostridium difficile (17)	100	—	
Metronidazole	*Bacteroides fragilis* group (5)	—	0.03–0.5	[26]
	Bacteroides, other spp. (6)	—	0.06–4	
	Fusobacterium spp. (2)	—	1–2	
	Clostridium spp. (3)	—	0.03–4	
	Peptostreptococcus spp. (16)	—	≤0.004–1	
	Other anaerobes (18)	—	0.015–4	

—, Details not presented.
[a] Recommended breakpoints defining susceptibility to meropenem are: susceptible, ≤4 mg/l; intermediate, 8 mg/l; resistant ≥16 mg/l.
[b] Susceptibility cut-off ≤4 mg/l.

meropenem following IV infusion of the drug is shown in Fig. 2. Mean peak plasma concentrations following single IV infusions of meropenem 500 mg and 1 g in healthy volunteers were approximately 25 mg/l and 50 mg/l, respectively [45]. Peak plasma concentrations were twice as high after a single 5-min bolus IV injection of meropenem (500 mg or 1 g) than after a 30-min IV infusion [46]. However, 1 h after dosing, the plasma concentration profiles and other pharmacokinetic parameters associated with the two methods of administration were similar.

Meropenem penetrates well into most body tissues and fluids [47], including the cerebrospinal fluid, and is not highly bound to plasma proteins (approximately 2%) (Zeneca, data on file). The apparent volume of distribution of meropenem after administration of 500 mg or 1 g as a single-dose bolus IV injection or IV infusion ranges from 0.197–0.239 l/kg [46]. Meropenem concentrations achieved in body tissues and fluids after IV administration of 500 mg or 1 g doses are summarised in Table 6. Meropenem is excreted in animal breast milk in very low concentrations but it is not known whether the drug is excreted in human breast milk.

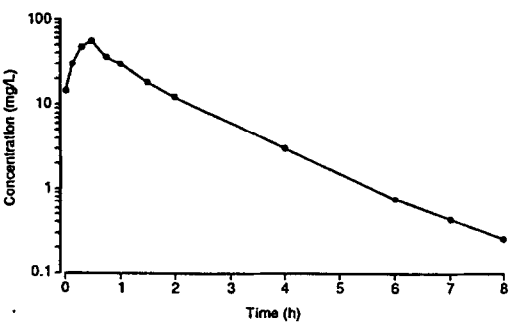

Fig. 2. Plasma concentration-time profile of meropenem after a 30 min IV infusion of 1 g (reproduced with permission [42]).

The plasma elimination half-life of meropenem is approximately 1 h after IV administration [46,46]. The disposition of meropenem administered by the intramuscular route was similar to that of IV meropenem. However, absorption from muscle produces a lower peak concentration which occurs later and has a slightly longer apparent half-life (1.5 h). Comparison of

Table 5
Principal pharmacokinetic parameters of meropenem compiled from seven studies of healthy volunteers (reprinted with permission of Adis International Limited [8])

Parameter	Value
$t_{1/2}$	0.8–1.1 h
Vd_{ss}	12.5–23.0 l
CL	11.0–16.8 l/h
CL_R	8.1–13.1 l/h
Ae	54–79%
Ae_m	19–27%

Ae, amount of drug excreted in the urine; Ae_m, amount of metabolite excreted in urine; CL, total body clearance from plasma; CL_R, renal clearance from plasma; $t_{1/2}$, elimination half-life; Vd_{ss}, apparent volume of distribution at steady state.

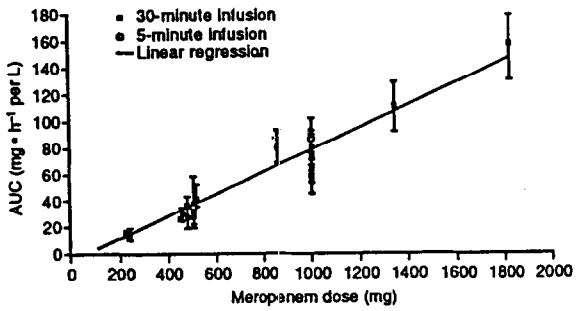

Fig. 3. AUC vs. dose of meropenem (data compiled from several studies; reproduced with permission [42]).

dose-corrected AUC values showed the bioavailability of the IM formulation to be 93.8% (90% confidence intervals 86.6–101.8) [Zeneca, data on file]. These changes are consistent with the change in route of administration. IM administration of meropenem may offer some advantage over the IV route in that it produces more sustained plasma concentrations of meropenem which may exceed bacterial MICs for increased durations, with little accumulation on multiple dosing (Zeneca, data on file).

Meropenem is excreted primarily by the kidney via both glomerular filtration and active tubular secretion. Reduced renal clearance of meropenem was seen when probenicid was co-administered [45], confirming that active tubular secretion plays a role in the excretion of this compound (see Section 9). Excretion of unchanged meropenem in the urine ranges from 54 to 79% of the administered dose. Almost 90% of an IV dose of meropenem is excreted in the urine within 12 h, either as unchanged parent compound (70%) or as the sole microbiologically inactive metabolite (ICI 213689) formed by hydrolysis of the β-lactam ring ($<20\%$) [48].

4.1. Children

Meropenem follows the same, approximately linear, kinetics in children as it does in adults. In a study in 63 children aged 2 months to 12 years who received meropenem 10, 20, or 40 mg/kg IV over 30 min, the mean elimination half-life was 1.13 h, the mean volume of distribution at steady-state was 0.43 l/kg, and the mean clearance was 5.6 ml/min per kg [49]. AUC and peak plasma concentrations increased proportionately with the doubling of the dose from 10 to 20 mg/kg. There was some suggestion of an increase in clearance with the higher dose of 40 mg/kg but this may have been an erroneous result caused by the small patient numbers in each dosage group. The elimination half-life was significantly lower in the group aged 6–12 years compared to the youngest children aged 2–5 months (0.8 versus 1.6 h). Although volume of distribution decreased with increasing age, the differences between these age groups was not clinically significant. As expected for a drug which is primarily eliminated renally, clearance gradually increased from age 2 months to 5 years and then decreased, although none of these changes were clinically or statistically significant.

4.2. Neonates

Meropenem has not been studied clinically in children younger than 3 months of age and thus dosage recommendations cannot be made for this age group. However, some pharmacokinetic data are available. The mean volume of distribution and clearance rate of meropenem were lower and consequently the AUC was larger and the elimination half-life was longer (2.95 versus 2.04 h) in 24 pre-term neonates compared to 14 full-term neonates [50]. This pattern is similar to that seen with all renally excreted drugs in this age group. Volume of distribution was found to increase with increasing body weight, height, and gestational age of the neonate. After correcting for body weight, it was determined that neonates have a larger volume of distribution (0.47 versus 0.24 l/kg) and a lower clearance rate (2.5 versus 3.7 ml/min per kg) of meropenem compared to adults.

4.3. The elderly

Ljungberg and Nilsson-Ehle found that the total body clearance and renal clearance of meropenem in healthy elderly volunteers aged 67–80 years were lower than the corresponding values in adults aged 20–34 years (8.3 versus 12.2 l/h and 5.9 versus 8.2 l/h) [51]. Consequently, AUC and the elimination half-life were significantly increased in the elderly volunteers. The differences in renal function in the elderly were thought to account for the differences in clearance. Nevertheless, no dosage adjustment is recommended for elderly individuals with normal renal function (creatinine clearance >50 ml/min).

4.4. Effect of disease

As would be expected for a drug that undergoes renal excretion, values for total body and renal clearance and the amount of unchanged drug and metabolite excreted in the urine were decreased and the elimination half-life was increased in patients with renal impairment [52–55]. Dosage modification of meropenem based on the patient's creatinine clearance is recommended (Section 5). In ten patients who received meropenem 500 mg, the elimination half-life was reduced by more than 50% during haemodialysis (1.5–2.9 h during haemodialysis compared to 6.8–7 h prior to haemodialysis) [52,55]. It is recommended that meropenem be administered after

Table 6
Mean peak concentration (C_{max}) of meropenem in body tissues and fluids after single-dose IV administration of 500 mg or 1 g (Zeneca, data on file) (adapted with permission [47])

Tissue/fluid	Dose (g)	No. of samples	Mean C_{max} (mg/l or mg/kg)	T_{max} (h)
Plasma and interstitial fluids				
Plasma	10 mg/kg	8	15.6	0.5–1.5
Plasma	1.0	6	23.6	0.5–1.5
Blister fluid	10 mg/kg	8	18.3	0.5–1.5
Blister fluid	1.0	5	26.3	0.5–1.5
Peritoneal exudate	1.0	9	30.2	0.5–1.5
Respiratory tract				
Lung	1.0	2	4.83	>1.5–2.5
Pleura	1.0	3	3.62	>1.5–2.5
Bronchial mucosa	1.0	7	4.53	0.5–1.5
Bronchial secretions	1.0	2	6.39	>1.5–2.5
Bronchial secretions	1.0	8	0.54	>2.5–3.5
Intra-abdominal tissue				
Bile	1.0	7	14.6	>2.5–3.5
Bile	1.0	1	13.1	>1.5–2.5
Gall bladder	1.0	1	3.93	>1.5–2.5
Stomach	1.0	1	2.76	>1.5–2.5
Omentum	1.0	3	2.01	>1.5–2.5
Colon	1.0	2	2.57	0.5–1.5
Cerebrospinal fluid				
Uninflamed meninges	1.0	4	0.18	>1.5–2.5
Inflamed meninges	20 mg/kg	8	1.14	>1.5–2.5
Inflamed meninges	40 mg/kg	5	3.28	>2.5–3.5
Gynaecological tissue				
Endometrium	0.5	7	4.16	0.5–1.5
Myometrium	0.5	15	3.76	0.5–1.5
Cervix	0.5	2	6.95	0.5–1.5
Fallopian tube	0.5	9	3.54	>3.5–4.5
Ovary	0.5	8	2.76	0.5–1.5
Uterus	0.5	3	3.01	0.5–1.5
Skin and skin structure				
Skin	1.0	10	5.30	0.5–1.5
Fascia	1.0	9	8.76	0.5–1.5
Skeletal muscle	1.0	2	6.10	>1.5–2.5
Cardiac tissue				
Cardiac valve	1.0	7	9.66	0.5–1.5
Cardiac muscle	1.0	10	15.50	0.5–1.5
Ophthalmic fluid				
Aqueous humour	1.0	3	1.72	>2.5–3.5
Bone and joint				
Bone marrow	0.5	—	15.4	0.5
Bone tissue	0.5	—	4.0	0.5
Joint fluid	0.5	—	16.6	1.0
Joint tissue	0.5	—	7.2	0.5

T_{max}, time to C_{max}.

haemodialysis and dosage regimens for patients undergoing haemodialysis and haemofiltration have been recommended (Section 5). Currently there is no information on the use of meropenem in patients undergoing continuous ambulatory peritoneal dialysis.

Hepatic impairment does not appear to affect the pharmacokinetics of meropenem and no dosage adjustment is recommended in patients with hepatic dysfunction [56].

Consistent with changes in the pharmacokinetics of other antibacterials used in cystic fibrosis, the elimination half-life and the mean residence time of meropenem 15 mg/kg IV were decreased in eight patients with cystic fibrosis versus the values in eight healthy volunteers (0.74 versus 0.99 h and 1.09 versus 1.39 h, respectively) [57]. As anticipated, the total body and renal clearance rates were higher and the volume of distribution was smaller in the cystic fibrosis group.

5. Clinical pharmacology

The usual dosage of meropenem in adults is 500 mg to 1 g IV three times daily. The dosage depends on the type and severity of infection, the known or suspected susceptibility of the pathogen(s), and the clinical status of the patient. Febrile episodes in neutropenic patients should be treated with 1 g of meropenem three times daily and in meningitis a dosage of 2 g three times daily should be used. Meropenem dosage should be reduced in patients with impaired renal function (creatinine clearance < 51 ml/min) (Table 7). A dosage of 500 mg every 24 h has been recommended in patients undergoing continuous arteriovenous haemofiltration (based on a normal dosage of 1 g 8-hourly). Patients undergoing haemodialysis should receive 500 mg every 48–72 h and after haemodialysis [58]. No dosage adjustment is required in patients with impaired hepatic function.

The recommended dosage for the treatment of most infections in infants and children between 3 months and 12 years of age is 10–20 mg/kg three times daily, depending upon the type and severity of infection, the known or anticipated susceptibility of the pathogen(s), and the patient's condition. Paediatric patients with febrile neutropenia should receive meropenem 20 mg/kg three times daily and a dosage of 40 mg/kg three times daily is recommended for the treatment of meningitis. The adult dosage should be used for children who weigh more than 50 kg. Meropenem has not been studied in children with renal impairment and therefore no dosage recommendations can be made for this patient group. Also at present, there are no dosage recommendations for meropenem in neonates.

In clinical studies to date, the maximum daily dosage of meropenem administered was 6 g in adults and 120 mg/kg in children; the maximum duration of treatment was 52 days in adults and 18 days in children (Zeneca, data on file).

Table 7
Recommendations for meropenem dosage in adults with renal impairment (reproduced with permission of Adis International Limited [58])

CL_{CR} (ml/min)	Dose (mg)	Dosage interval (h)
26–50	500–1000	12
10–25	500	12
<10	500	24
0 (CAVHD)	500	24
0 (haemodialysis)	500	48–72 and after haemodialysis

Based on a 1 g 8-hourly dose in patients with normal renal function. CAVHD, continuous ateriovenous haemofiltration; CL_{CR}, creatinine clearance.

6. Pharmacy

For IV administration, meropenem is available in glass vials containing 250 mg, 500 mg, or 1 g as the trihydrate, blended with the excipient anhydrous sodium carbonate (208 mg sodium carbonate for each g of meropenem) for reconstitution with diluent (5 ml sterile water for injection for each 250 mg meropenem). Meropenem for IM administration is available in glass vials containing 500 mg as the trihydrate, blended with anhydrous sodium carbonate (104 mg) for reconstitution with 2 ml of diluent (sodium carbonate solution 17.34 mg/ml). The IM formulation of meropenem does not contain lignocaine or any other local anaesthetic.

Meropenem powder, when stored in vials at controlled room temperature, is stable for a maximum of 3 years. It is recommended that meropenem solutions be prepared immediately prior to use; however, solutions for IV bolus injection, reconstituted with water for injection, are stable for 8 h at room temperature (15–25°C) and for 48 h when refrigerated (4°C). Meropenem infusions (1–20 mg/ml) for IV administration prepared with 0.9% sodium chloride are stable for 10 and 48 h at room temperature and under refrigeration, respectively. A variety of other diluents (e.g. 5% glucose, Ringer's lactate) are suitable for preparing meropenem infusions. However such solutions should be stored for shorter periods, ranging from 2 to 8 h at room temperature and 8–48 h at 4°C, depending on the diluent used. Correctly prepared solutions of meropenem for IM injection maintain satisfactory potency for 1 h at room temperature and for 4 h when refrigerated. Solutions of meropenem should not be frozen.

6.1. Laboratory considerations

Bioassay, ultraviolet, and HPLC techniques revealed meropenem susceptibility discs stored at −80°C, −20°C, and 4°C to be stable for 24 months (data on file, Zeneca). Imipenem susceptibility discs are stable for only 12 months under similar storage conditions. Meropenem is more stable than imipenem in both broth and agar media. The activity of meropenem was not significantly affected by inoculum concentrations or the pH or composition of the culture media (Zeneca, data on file). Meropenem, in common with imipenem, may be adversely affected by the presence of thioglycollate in culture broth or cysteine (contained in IsoVitaleX) in GC culture media. MICs of meropenem are not affected by additives within haemophilus test medium (HTM) (Zeneca, data on file).

6.2. Mode of use

Meropenem for IV use may be administered by either bolus IV injection (over approximately 5 min) or by short IV infusion (over 15–30 min). In contrast, imipenem/cilastatin for IV use should only be administered by infusion at a rate of 1 g over 40–60 min. Meropenem for IM use should be administered by deep injection into a large muscle mass, e.g. the gluteal.

7. Clinical experience

The therapeutic potential of meropenem has been investigated in an extensive international clinical trials program involving over 6000 patients. The results have shown meropenem to be effective and well tolerated in a range of bacterial infections in adults and children [8,59,60].

7.1. Lower respiratory tract infections

Meropenem has been shown to be as effective as imipenem/cilastatin and ceftazidime (with or without an aminoglycoside) in patients with lower respiratory tract infections (LRTIs). Meropenem has achieved clinical success rates of 81–100% in this setting (Table 8).

In one study, meropenem (1 g three times daily) was as efficacious as ceftazidime (2 g three times daily) plus amikacin (15 mg/kg per day) in the treatment of patients with serious bacterial infections, including LRTIs [65]. Meropenem was administered by IV bolus injection in 44/116 patients (38%). In patients with severe nosocomial pneumonia, the clinical response rate at the end of treatment with meropenem was 30/37 (81%), compared with 23/32 (72%) with ceftazidime-amikacin. The bacteriological eradication rates were similar with the two regimens (71 versus 76%).

Meropenem has also been compared with imipenem/cilastatin in the treatment of hospital-acquired LRTIs. In one study, both drugs were administered at a dosage of 1 g three times daily in patients with nosocomial exacerbations of chronic obstructive pulmonary disease and achieved very similar clinical and bacteriological success rates at the end of treatment (98 versus 96% and 88 versus 89%, respectively) [66].

Another recent study confirmed the dose-equivalence of meropenem and imipenem/cilastatin. The two agents were each administered at a dosage of 1 g three times daily to critically ill patients (mean APACHE II scores 14.9 versus 14.4) with serious bacterial infections, many of whom had received previous unsuccessful antibacterial therapy [71]. Ninety-three of 204 (46%) patients in this study had nosocomial LRTIs. The rates of satisfactory clinical and bacterial response achieved by meropenem and imipenem/cilastatin in the evaluable patients with nosocomial LRTIs at the end of treatment were similar; 75 versus 75% and 48 versus 52%, respectively.

Meropenem has been successfully used in lower dosages for the treatment of community-acquired LRTIs (mainly pneumonia) severe enough to require hospitalisation. One study compared meropenem 0.5 g three times daily with ceftazidime 1 g three times daily [69]. At the end of treatment, the rates of satisfactory clinical response with two agents were similar (93 versus 95%), although a higher percentage of meropenem recipients were cured (64 versus 53%). Therefore this lower dosage of meropenem appears useful for the treatment of pneumonia in hospitalised patients who do not require treatment in an intensive care unit.

Another recent study compared meropenem 0.5 g twice daily with the same dosage of imipenem/cilastatin (both administered IM) in the treatment of moderately-severe community-acquired LRTIs [68]. The clinical success rate was higher with meropenem than with imipenem/cilastatin (96 versus 91%), the difference approaching statistical significance ($P = 0.054$). In the same study, patients with severe community-acquired LRTIs received meropenem 0.5 g three times daily or ceftazidime 1 g three times daily (both administered IM). These regimens produced equivalent clinical and bacteriological response rates (93 versus 92% and 91 versus 91%, respectively).

Because it has in vitro activity against *P. aeruginosa* and *B. cepacia*, meropenem is a candidate for treating pulmonary infections in cystic fibrosis [72]. In a study involving 40 patients (81 episodes of infection), a satisfactory clinical response was observed in 98% of 60 infectious episodes treated with meropenem (125 mg to 1.25 g three times a day depending on the weight of the patient) compared to 90% of 21 episodes treated with ceftazidime (250 mg to 2.5 g three times daily) [70].

In addition, 156 patients have been treated with meropenem on a named-patient basis for a total 272 episodes of infective pulmonary exacerbations of cystic fibrosis, the majority of which were caused by *P. aeruginosa* (Zeneca, data on file). Most patients received a dosage of meropenem 2 g (or 40 mg/kg) three times daily. In the majority of cases meropenem was combined with another antibiotic, usually an aminoglycoside. In 83% of evaluable cases, meropenem therapy resulted in improvements in the clinical status of the patient. Preliminary results from a study in the Danish Cystic Fibrosis Centre provide further evidence of the usefulness of meropenem in this patient population [73].

7.2. Intra-abdominal infections

Intra-abdominal infections are frequently polymicrobial and thus require treatment with an antibacterial regimen that is effective against both aerobic and

Table 8
Summary of clinical and bacteriological results from comparative studies with meropenem in adults with lower respiratory tract infections

Diagnosis	Meropenem				Comparator drug				
	No. of patients evaluated	Dosing regimen	Clinical success[a] (%)	Bacteriological success[b] (%)	No. of patients evaluated	Dosing regimen	Clinical success[a] (%)	Bacteriological success[b] (%)	Reference
Pneumonia[c]	56	0.5 g bid for 14 days	88	96	54	Imipenem/cilastatin 1 g bid for 14 days	93	93	[61]
Chronic bronchitis, infected bronchiec-tasis, other infections[c]	59	IV 0.5 g bid for 7–14 days	86	63	56	IV Imipenem/cilas-tatin 0.5 g bid (3–14 days)	89	63	[62]
Pneumonia[c]	28	0.5 g/day for 3–14 days	89	70	29	Imipenem/cilastatin 1 g/day	79	75	[63]
Nosocomial pneu-monia	40	IV 1 g tid	—	88*	50	IV ceftazidime 2 g tid + tobramycin	—	61	[64]
Severe hospital- ac-quired LRTIs	37	IV 1 g tid	81	71	32	IV ceftazidime 2 g tid + amikacin 15 mg/kg per day	72	76	[65]
Nosocomial AECB	82	IV 1 g tid for 8.9 days (m)	98	88	82	IV imipenem/cilas-tatin 1 g tid for 9 days (m)	96	89	[66]
Community-ac-quired pneumo-nia	8	IM 0.5 g bid for 5–14 days	100	—	10	IM imipenem/cilas-tatin 0.5 g bid for 5–14 days	70	—	[67]
Community-ac-quired AECB	8	IM 0.5 g bid for 5–14 days	100	—	6	IM imipenem/cilas-tatin 0.5 g bid for 5–14 days	67	—	[67]
Moderately severe community-ac-quired LRTIs	153	IM 0.5 g bid for 5–14 days	96	91	148	IM imipenem/cilas-tatin 0.5 g bid for 5–14 days	91	86	[68]
Severe community acquired LRTIs	43	IV 1 g tid	93	100	39	IV ceftazidime 2 g tid + amikacin 15 mg/kg per day	79	87	[65]
Severe community-acquired LRTIs	85	IM 0.5 g tid for 5–14 days	93	91	36	IM ceftazidime 1 g tid for 5–14 days	92	91	[68]
Community-ac-quired LRTIs (mainly pneumo-nia)	84	IV 0.5 g tid for 8.7 days (m)	93	96	79	IV ceftazidime 1 g tid for 9 days (m)	95	94	[68]
Pseudomonal pul-monary infection in cystic fibrosis	27 (54 episodes)	IV 0.125–1.25 g tid for 15 days (m)	98	—	13 (21 episodes)	IV ceftazidime 0.25–2.5 g tid for 15 days (m)	90	—	[70]

AECB, acute exacerbation of chronic bronchitis; m, mean.
[a] Cure and improvement.
[b] Eradication or presumed eradication.
[c] Not specified whether hospital or community-acquired.
*$P = 0.01$ vs. ceftazidime and tobramycin.

Table 9
Summary of clinical and bacteriological results from comparative clinical studies with meropenem in intra-abdominal infections (the intravenous route of administration was used in all studies)

Meropenem				Comparator drug				Reference
No. of patients evaluated	Mean dosing regimen	Clinical success[a] (%)	Bacteriological success[b] (%)	No. of patients evaluated	Mean dosing regimen	Clinical success[a] (%)	Bacteriological success[b] (%)	
88	1 g tid for 7.5 days	92	93	89	Clindamycin 0.9 g tid + tobramycin 5 mg/kg/day for 7.0 days	89	90	[75]
70	1 g tid for 6.5 days	91	90	78	Cefotaxime 2 g tid + metronidazole 500 mg tid for 6.0 days	100	92	[76]
99	0.5 g tid for 5.4 days	98	95	90	Imipenem/cilastatin 0.5 g tid for 5.1 days	96	96	[77]
82	1 g tid for 7.8 days	96	84	88	Imipenem/cilastatin 1 g tid for 8.3 days	94	81	[78]
28	1 g tid for 7.7 days	100	90	31	Imipenem/cilastatin 1 g tid for 8.6 days	97	100	[79]

[a] Cure and improvement.
[b] Eradication or presumed eradication.

anaerobic pathogens. Since meropenem is active against most clinically significant aerobes and anaerobes, it would appear to be an attractive choice for monotherapy [74]. In trials, meropenem has demonstrated equivalent efficacy to that of standard combination regimens and imipenem/cilastatin (Table 9).

In comparative studies, meropenem (1 g three times daily) has displayed rates of clinical response (91–92%) and bacteriological eradication (90–93%) equivalent to those achieved with either cefotaxime (2 g three times daily) plus metronidazole (500 mg three times daily) or clindamycin (0.9 g three times daily) plus tobramycin (5 mg/kg per day) [75,76].

To date, three studies have compared equal doses of meropenem and imipenem/cilastatin in the management of intra-abdominal infections. In two studies, both agents were used at a dosage of 1 g three times daily and produced similar clinical (96–100% versus 94–97%) and bacterial (84–90% versus 81–100%) efficacy rates at the end of treatment [78,79]. Another study used meropenem at a lower dosage (0.5 g three times daily) and demonstrated clinical and bacteriological success rates of 98 and 95%, respectively [77].

In another study mentioned previously which compared meropenem and imipenem/cilastatin (both 1 g three times daily) in critically ill patients, a total of 82 patients were recruited with serious intra-abdominal infections [71]. The two antibiotics produced similar rates of satisfactory clinical response (82 versus 81%, respectively). In patients with polymicrobial intra-abdominal infections, the satisfactory clinical response rate with meropenem was 80%, compared to 70% with imipenem/cilastatin. Both drugs achieved bacteriological response rates of 67–68% in intra-abdominal infections. This extensive clinical evidence suggests that 1 g three times daily is the optimal dosage of meropenem for the treatment of severe intra-abdominal sepsis, which is commonly accompanied by diffuse peritonitis. A dosage of 500 mg could be considered for less severe infections, e.g. appendicitis. Interestingly, four of the studies discussed above allowed for presumptive therapy, that is one to two doses of meropenem could be administered prior to surgery in patients who displayed signs of intra-abdominal infection [75,76,78,79].

7.3. Meningitis

Meropenem is a promising alternative for the treatment of meningitis. It is active against the common causative pathogens [6], including penicillin-resistant *S. pneumoniae* [11], and penetrates well into the CNS when the meninges are inflamed [80]. Meropenem was at least as effective as comparator agents in eradicating *Haemophilus influenzae*, *Neisseria meningitidis*, *S. pneumoniae*, *E. coli* and *P. aeruginosa* from the CSF in an experimental animal model of meningitis [81]. At lower dosages meropenem was significantly more effective than ceftriaxone against penicillin-resistant *S. pneumoniae* ($P < 0.01$) and more potent than ceftazidime against *P. aeruginosa* ($P < 0.016$).

In comparative clinical studies in meningitis, meropenem (up to 6 g/day in adults and 120 mg/kg daily in children) proved as effective as cefotaxime (225–300 mg/kg daily up to a maximum of 12 g/day) or ceftriaxone (100 mg/kg initial dose, followed by a single daily dose of 80 mg/kg up to a maximum of 4 g/day) [82,83]. Dexamethasone was administered concurrently to 91% of patients in these studies. Meropenem produced a clinical cure and bacteriological eradication in 100% of adult and paediatric patients. Interestingly, two case reports have suggested that meropenem may also prove useful in the treatment of meningitis caused by cephalosporin-resistant *P. aeruginosa* [84,85].

Importantly, there have been no significant differences between meropenem and comparator antibiotics with respect to central nervous system (CNS) tolerability. Imipenem/cilastatin has been associated with an increased risk of seizures in children with meningitis [86], as well as patients with renal impairment [87], and is not approved for the treatment of CNS infections.

7.4. Septicaemia

Meropenem monotherapy has been compared with ceftazidime with or without amikacin in the empirical treatment of septicaemia (Table 10) [88]. Patients with septicaemia arising from a urinary tract infection or LRTI were randomised to receive meropenem 500 mg three times daily or ceftazidime 250 mg to 1 g three times daily. Those with multiple sites of infection received either meropenem 1 g three times daily or ceftazidime 2 g three times daily with or without amikacin 15 mg/kg per day. Overall, a satisfactory clinical response was seen in 92% of meropenem recipients, compared with 94% of those who received the comparator regimen at the end of treatment. Bacterial eradication was achieved in all patients in this study, the most common pathogens being Gram-negative aerobes (mainly *E. coli*) and *S. pneumoniae*.

7.5. Febrile neutropenia

Febrile episodes in neutropenic patients pose a great challenge for antibiotic therapy. Since the antimicrobial spectrum of meropenem includes almost all clinically important pathogens, it offers the opportunity for empirical monotherapy in this setting. Meropenem monotherapy (1 g three times daily) proved at least as effective as ceftazidime monotherapy (2 g three times daily) in a total of 304 evaluable episodes of fever in patients with haematological malignancies and who were profoundly neutropenic [92]. All patients treated

Table 10
Summary of clinical and bacteriological results from comparative clinical studies with meropenem in urinary tract infections (UTIs), skin and skin structure infections and septicaemia

Diagnosis	No. of patients evaluated	Dosage regimen	Clinical success[a] (%)	Bacteriological success[b] (%)	No. of patients evaluated	Comparator dosage regimen	Clinical success[a] (%)	Bacteriological success[b] (%)	Reference
Moderately severe UTI	126	IM 0.5 g bid	97*	75	122	IM imipenem/cilastatin 0.5 g bid	90	75	[69]
Complicated UTI	95	IV 0.5 g tid for 7.5 days (m)	99	90	82	IV imipenem/cilastatin 0.5 g qid for 7.3 days (m)	99	81	[89]
Severe UTI	78	IM 0.5 g tid	96	73	35	IM ceftazidime 0.5 g tid	94	75	[69]
Complicated UTI	112	IV 0.25-0.5 g tid for 3–10 days	96	68	107	IV ceftazidime 0.25–0.5 g tid for 3–10 days	94	72	[90]
Complicated UTI	15	IV 1 g tid	87	56	25	IV ceftazidime 2 g tid + amikacin 15 mg/kg/day	100	100**	[65]
Skin and soft tissue infections	123	IV 0.5 g tid for 7.1 days (m)	98	94	126	IV imipenem/cilastatin 0.5 g qid for 7.3 days (m)	95	91	[91]
Septicaemia	61	IV 0.5–1 g tid for 9.8 days (m)	92	100	70	IV ceftazidime 0.25–2 g tid + amikacin 15 mg/kg/day for 9.6 days (m)	94	100	[88]

[a] Cure or improvement.
[b] Eradication or presumed eradication.
* $P < 0.05$ versus imipenem/cilastatin.
** $P = 0.001$ versus meropenem.

with meropenem or ceftazidime survived the first 72 h of therapy. Subsequently, clinical success was achieved without modification of the empirical regimen in 44% of meropenem recipients compared with 41% of ceftazidime recipients. These response rates appear relatively low, but reflect the use of the stringent definitions of failure proposed by the immunocompromised host society (IHS).

Importantly, initial empirical therapy with meropenem proved as effective as the combination of ceftazidime plus amikacin in a large collaborative trial in over 1000 adults and children [93]. Most of these patients had haematological malignancies and a relatively long duration of neutropenia (median 13–15 days) and were therefore at particularly high risk of life-threatening infection. Overall success rates (according to the IHS definition) of 56 and 52% were achieved with meropenem and ceftazidime/amikacin, respectively. The rates of defervescence were similar in the two groups of patients. Both of the regimens used in this study were well tolerated. In particular, there were no reports of seizures and the incidence of vomiting was very low (0.002% in each treatment group). Trials with imipenem/cilastatin in this patient group have reported incidences of nausea or nausea and vomiting of 8–21%, depending on the dosage used and the rate of infusion [94–96].

7.6. Other infections

Meropenem has been evaluated in a variety of other infections (Table 10). It has demonstrated clinical efficacy equivalent to that of imipenem/cilastatin in the treatment of severe or complicated urinary tract infections (clinical efficacy 97–99% for meropenem vs. 90–99% for imipenem/cilastatin) [68,89]. Indeed, in one study involving patients with complicated urinary tract infections, meropenem 500 mg three times daily proved as efficacious as imipenem/cilastatin 500 mg four times daily [89]. Meropenem also showed efficacy similar to that of ceftazidime with or without amikacin in this setting [65,68,90].

Meropenem has also proved effective in skin and skin structure infections. In one large study, 98% of 123 patients treated with meropenem 500 mg three times responded clinically compared to 95% of 126 patients treated with imipenem/cilastatin 500 mg four times daily [91]. Meropenem was highly efficacious against Gram-positive pathogens; 96% (152/159) of pretreatment Gram-positive isolates were eradicated (or presumed eradicated) compared to 88% (129/147) of those treated with imipenem/cilastatin.

Gynaecological infections also respond well to meropenem. The results of a recent study in 475 women, in whom the most common diagnosis was postpartum endometritis, showed meropenem (500 mg three times daily) to have similar efficacy to the combination of clindamycin (900 mg three times daily) plus gentamicin (initial dose 2 mg/kg followed by 1.5 mg/kg three times daily) [97].

7.7. Infections in children

Meropenem possesses many properties which make it a useful agent for the treatment of infections in paediatric patients. Combinations of antibiotics have been widely used in the past to ensure adequate antibacterial coverage. However, monotherapy with a broad-spectrum agent such as meropenem may be preferable in these patients, because of potential problems of IV access and fluid overload associated with combination regimens [59]. Furthermore, meropenem, unlike imipenem/cilastatin, may be administered by IV bolus injection, further reducing the risk of fluid overload.

Clinical studies have shown meropenem to be as effective as commonly-used combination regimens in infants and children [59]. A recent multicentre randomised study in hospitalised children compared meropenem monotherapy (10–20 mg/kg three times daily) with cefotaxime (100–150 mg/kg/day), administered with or without amikacin or metronidazole depending on the site of the infection and local standards of clinical practice [60]. A total of 170 children aged between 3 months and 12 years were recruited. The most common infections in these children were LRTIs (mainly community-acquired) and urinary tract infections. A satisfactory clinical response at the end of treatment was achieved in 98% of meropenem recipients, compared with 93% of those who received a cefotaxime-based regimen. The rates of bacteriological response were also similar (89 versus 90%). Meropenem was administered by IV bolus injection in over 50% of patients in this study and was well tolerated.

7.8. Approved therapeutic indications

Currently, approved therapeutic indications for meropenem in adults and children show some national variations, but include the following infections, caused by single or multiple susceptible bacteria: LRTIs, intra-abdominal infection, meningitis, septicaemia, urinary tract infections, gynaecological infections, skin and skin structure infections, and presumed bacterial infections in neutropenic patients. Meropenem, because of its ultra-broad spectrum of activity, is also indicated for the empirical treatment of these infections, i.e. before the causative pathogen has been identified.

8. Toxicology

Meropenem was well tolerated in animal toxicology studies when given by both the IV and IM routes (Zeneca, data on file). Meropenem has shown good renal tolerability [98] and low seizure-inducing potential in animal models [99–102]. No unexpected effects appeared during chronic toxicity studies of meropenem in rats and dogs, reproductive toxicity studies, and mutagenicity tests (Zeneca, data on file).

8.1. Human toxicity

8.1.1. Symptomatic adverse events

Norrby et al. [103] have reviewed tolerability data from 3220 patient-exposures to meropenem in clinical trials. Adults received meropenem 500 mg or 1 g IV three times daily (2 g IV three times daily for meningitis) and the dosage was adjusted according to creatinine clearance in those with renal impairment. Dosages of IM meropenem were 500 mg every 12 or 8 h. Children received meropenem 10, 20, or 40 mg/kg IV three times daily. Overall, the incidence of adverse events considered to be possibly, probably, or definitely drug-related was 20% in meropenem-treated patients and 17% in those who received a comparator antibiotic. The most common drug-related adverse events in the meropenem group were inflammation at the injection site (2.0%), diarrhoea (1.9%), nausea/vomiting (1.0%), and rash (1.0%). There were no clinically significant differences between meropenem and the comparator antibiotics with respect to the frequency of any adverse reaction. The incidence of withdrawal from treatment because of adverse events was similar for meropenem (1.4%) and for comparator antibacterials (1.8%).

In these studies, evidence for nephrotoxicity was evaluated by reviewing increases from baseline in plasma levels of creatinine of ≥ 10 μmol/l or urea (or blood urea nitrogen) of ≥ 1.5 mmol/l. Increases in creatinine clearance were also reviewed in patients whom the estimated creatinine clearance was less than 51 ml/min. These evaluations indicated that meropenem is not nephrotoxic in clinical use and that the drug compares favourably in this regard with other agents [103].

The tolerability profile of meropenem in elderly patients (>65 years) was not significantly different to that in younger adults [103].

The adverse events reported in a total of 547 children treated with meropenem or comparator agents are summarised in Table 11. There was no clinically significant difference between the tolerability profile of meropenem in these children and that in adults [103]. Furthermore, there was no relationship between the nature or incidence of adverse effects in paediatric patients and the dose of meropenem administered.

Table 11
Incidence of drug-related adverse events reported in children treated with meropenem

Adverse events[b]	Meropenem[a] ($n = 316$)		Comparator[a] ($n = 231$)	
	Children (%)	Adults (%)	Children (%)	Adults (%)
Thrombocytosis	4.4	1.9	2.6	2.4
ALT increased	3.4	5.3	1.9	4.9
AST increased	2.8	4.3	1.5	4.3
Eosinophilia	2.9	0.7	2.2	0.8
Diarrhoea	1.3	1.9	1.3	1.6
PTT increased	1.9	0.4	0	0.5
Nausea and vomiting	0.6	0.8	0	0.8
Urticaria	0.6	0.2	0	0.2
Hyperlipidaemia	1.4	0	0	0
Leucopenia	0.9	0.1	0	0.3
Oral moniliasis	0.3	0.2	2.6	0.1
ALP increased	0.4	2.3	0.5	2.3
LDH increased	0.7	1.8	1.1	1.7

Incidence of same events in adults are shown for comparison (reproduced with permission [103]).
[a] Total populations are shown but numbers for laboratory parameters vary from test to test.
[b] Adverse events reported in more than one child.

The frequency of nausea and vomiting attributable to meropenem does not appear to be correlated either with the rate at which the drug is infused or the dosage [103]. Indeed, the good tolerability of meropenem administered by IV bolus injection has been demonstrated in several studies [65,76,103]. On the other hand, speed of infusion and high daily dosages have been linked to nausea and vomiting with imipenem/cilastatin [94–96,104].

Imipenem/cilastatin is known to be potentially seizuregenic, possibly as a result of its blockade of gamma aminobutyric acid receptors [100]. In particular, imipenem/cilastatin has been associated with seizures in patients with meningitis (7/21 patients in one study [86]). As a result, the drug is not licensed for use in this indication. Meropenem has demonstrated a lower propensity to cause seizures in animal and clinical studies [83,99–103,105]. The total incidence of seizures reported in 3911 patients treated with meropenem, including patients with meningitis, was low (0.38%) and similar to that associated with comparator

cephalosporin-based treatment regimens [103]. Only two seizures (0.05%) were considered to be possibly related to meropenem treatment, neither of which occurred in patients with meningitis. Therefore, meropenem is sufficiently well tolerated by the central nervous system to allow its use in high doses to treat meningitis.

IM administration of meropenem, as with other β-lactam antibiotics, may cause symptomatic local reactions at the injection site such as discomfort and occasionally pain or inflammation. However, the incidence of systemic adverse events appears to be lower for IM compared to IV administration, although the types of reactions encountered are similar [103]. The effect of meropenem administration (500 mg i.v. for 7 days) on the intestinal microflora was investigated in 10 healthy volunteers [106]. No microbiologically active meropenem was detected in the faeces and only minor changes in the intestinal microflora were observed. In all cases, bacterial populations returned to base line values within two weeks after meropenem was discontinued. No *Clostridium difficile* isolates were identified and no new colonisation with meropenem-resistant strains was observed.

8.1.2. Biochemical adverse events

As regards haematological and biochemical adverse events, no clinically relevant differences have been noted between meropenem and comparator antibiotics [100]. Mild, and usually transient, increases in hepatic enzymes have been the most common adverse biochemical events reported with meropenem. IM injection of meropenem may cause tissue damage which is associated with small increases in creatine phosphokinase. However, the increases observed were not considered to be clinically important. Overall, the biochemical and haematological tolerability profile of meropenem appears to be similar to that of third-generation parenteral cephalosporins (ceftazidime, cefotaxime, ceftriaxone), and imipenem/cilastatin.

8.2. Contraindications/precautions

Meropenem is contraindicated in patients who have exhibited hypersensitivity to the product. Individuals who have a history of hypersensitivity to carbapenems, penicillins, or other β-lactam antibacterial agents may also be hypersensitive to meropenem.

In common with other antibacterials, treatment with meropenem may result in overgrowth of non-susceptible organisms. As with other agents, pseudomembranous colitis has also been reported with meropenem. Meropenem is active against *P. aeruginosa* but, as with other antibiotics, caution may be required when the drug is used as monotherapy to treat documented or suspected *P. aeruginosa* LRTIs in critically ill patients. It is recommended that regular sensitivity testing is performed when treating *P. aeruginosa* infection.

The safety of meropenem during pregnancy or lactation has not been established. Although meropenem did not show teratogenic effects in animal studies, the drug should not be used during pregnancy unless the risk/benefit ratio for the foetus is favourable. Similarly, meropenem should not be administered to women who are breast-feeding unless the potential benefit justifies the potential risk to the baby.

The efficacy and tolerability of the IM formulation have not been studied in patients with severe renal insufficiency (creatinine clearance ≤ 25 ml/min) or children and therefore the IM route of administration cannot be recommended for these patients. Meropenem is also not recommended for use in infants less than 3 months of age or children with impaired renal or hepatic function due to the absence of clinical experience in these patient groups.

9. Drug interactions

There are no specific data available with regard to adverse drug interactions with meropenem, although the drug has been administered with many other medications without adverse pharmacological interactions. Due to its low protein binding, meropenem would not be expected to displace other drugs from plasma protein binding sites.

The active tubular secretion of meropenem is blocked by probenecid and thus the plasma elimination half-life and plasma concentrations of meropenem may be elevated when the two drugs are administered concomitantly. However, since plasma concentrations of meropenem are adequate following administration of the drug alone, the concomitant administration of probenicid is not recommended (meropenem data sheet).

10. Conclusion

Meropenem has an exceptionally broad spectrum of antibacterial activity and predictable pharmacokinetics. It has been shown to be as effective and well tolerated as comparator antibacterial agents in a range of bacterial infections in adults and children. On the basis of microbiological, pharmacokinetic and clinical data it would seem reasonable to assume that meropenem is equivalent to imipenem on a gram per gram basis. Unlike imipenem, meropenem does not require co-administration with a DHP-I inhibitor and may be used to treat bacterial meningitis because it has not been associated with an increased incidence of seizures. In addition, meropenem can be administered by bolus IV

injection over 5 min, an advantage in fluid-restricted patients and in children. Meropenem may have a particular role as empirical monotherapy in severe infections and in the treatment of polymicrobial infections. Also, meropenem may be useful in infections caused by bacteria resistant to other antibiotics.

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