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Meropenem versus imipenem/cilastatin in intra-abdominal infections requiring surgery

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In a multicentre, open, randomised study, the efficacy and tolerability of intravenous meropenem (1 g every 8 h, infusion or bolus) was compared with that of intravenous imipenem/cilastatin (1 g every 8 h, infusion) in 232 hospitalised patients with moderate to severe intra-abdominal infections.

At the end of therapy, a satisfactory clinical response (cure or improvement) was seen in 79/82 (96%) evaluable meropenem patients and 83/88 (94%) imipenem/cilastatin patients; this was still seen at follow-up (57/63; 90% and 58/66; 88%, respectively). A satisfactory bacteriological response (elimination or presumed elimination) was seen in 69/82 (84%) meropenem patients and 71/88 (81%) imipenem/cilastatin patients at the end of therapy and in 52/62 (84%) and 55/70 (79%), respectively, at follow-up. There was a high level of clinical cure or improvement (95% for both treatment groups) in the 120 patients (60 in each group) who had polymicrobial infections.

A similar incidence of adverse events was seen in each group: 45/116 patients in the meropenem group (72 events) and 42/116 patients in the imipenem/cilastatin group (65 events); the adverse event profiles were also similar, with injection site inflammation and elevated transaminases the most frequent in both groups. The results of this study indicate that monotherapy with meropenem was as effective and as well tolerated as the combination of imipenem/cilastatin in the treatment of moderate to severe intra-abdominal infections.

Introduction

In patients with intra-abdominal infections, the serious consequences of delaying treatment necessitates the initiation of empirical therapy with antibiotics chosen to reflect the likely causative organisms. The vast majority of cases also require surgery. Cultures have demonstrated the polymicrobial nature of many intra-abdominal infections and the presence of both aerobic and anaerobic organisms in almost half of these infections requires that antimicrobial regimens have a broad spectrum of activity (Hackford, 1990). Traditionally, antimicrobial therapy consists of combinations of antibiotics to achieve sufficient cover. Metronidazole or clindamycin together with a β-lactam antibiotic (e.g.

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cefotaxime) and/or an aminoglycoside are commonly used in such combinations (Hackford, 1990).

Carbapenems are a new class of β-lactam antimicrobial with a very broad spectrum of activity. The only commercially available carbapenem is a formulation of imipenem in combination with the dehydropeptidase-I (DHP-I) inhibitor, cilastatin given to block extensive renal metabolism and prevent nephrotoxicity (Benfield & Chrisp, 1992).

Imipenem/cilastatin has high in-vitro activity against the *Bacteroides fragilis* group and most other anaerobic organisms, is active against enterococci, *Staphylococcus aureus* and aerobic Gram-negative bacilli (Wilson & Mosimann, 1992), and has been used successfully in intra-abdominal infections (Christen, Buchmann & Geroulanos, 1987; Norwegian Study Group, 1987; Geroulanos *et al.*, 1990; Poenaru, De Santis & Christou, 1990; Solomkin *et al.*, 1990; Eckhauser *et al.*, 1992; Eklund *et al.*, 1993).

Potential problems with imipenem/cilastatin include an association with seizures (usually in patients with pre-existing renal impairment and/or central nervous system disorders (Guess *et al.*, 1990) and nausea and/or vomiting which may limit tolerability and necessitate a slower infusion rate (Calandra *et al.*, 1988*b*; Buckley *et al.*, 1992).

Meropenem is a new carbapenem with high in-vitro activity against a wide range of organisms, both Gram-positive and Gram-negative, including *Pseudomonas aeruginosa* and anaerobes. Meropenem also has activity against several subpopulations of bacteria which are resistant to other antimicrobials, such as tobramycin, ciprofloxacin, norfloxacin and ceftazidime (Edwards, 1991); and it has a similar but potentially wider spectrum of activity than imipenem (Bauernfeind, Jungwirth & Scheighart, 1989; Cornaglia *et al.*, 1992; Morandotti *et al.*, 1992).

The aim of the present study was to compare the clinical and bacteriological efficacy and safety of empirical monotherapy with intravenous meropenem with the intravenous combination imipenem/cilastatin in hospitalised patients with intra-abdominal infections. The pharmacokinetic properties of meropenem and imipenem administered as imipenem/cilastatin are comparable, following single and multiple dose administration (Nilsson-Ehle *et al.*, 1991; Drusano, Yuen & Standiford, 1992) and, therefore, the same dosing regimen (1 g every 8 h) was employed for both antibiotics.

Methods

Study design

This study was conducted at 12 centres in six European countries as a randomised, open, parallel group comparison of meropenem and imipenem/cilastatin in the surgical management of intra-abdominal infections.

Patients were included in the study if they were ⩾18 years old and hospitalized with evidence of a systemic inflammatory response (such as pyrexia, elevated white cell count, hypotension, increased heart and respiratory rates, altered mental status) and physical signs consistent with abdominal infection (which included abdominal tenderness, presence of localised or diffuse abdominal wall rigidity, abdominal mass, or ileus). The diagnosis was confirmed at operation by the presence of pus, inflammation, intestinal perforation, abscess or other signs of infection.

Exclusion criteria included: pregnancy or breastfeeding; antibiotic treatment within the three days before study entry (unless the organism was shown to be resistant or still present); hypersensitivity to any β-lactam antibiotics; hepatic failure or hepatic coma;

neutropenia; and endocarditis. Patients were also excluded if they had a history of central nervous system (CNS) disease (e.g. seizures, epilepsy, brain disorders or confusional states).

Reasons for withdrawal from the study included: the occurrence of a serious or unexpected adverse event; pre-treatment pathogens shown to be resistant to allocated treatment; any two doses missed within the first 48 h, or two consecutive doses missed during treatment; deterioration of the patient's condition due to infection; or no pathogens isolated from pre-treatment cultures.

The study was carried out in accordance with the Declaration of Helsinki (revised Venice 1983) and all patients gave written or oral consent; local Ethics Committee approval was obtained from all study centres.

Dosage

Patients were randomised to receive either meropenem or imipenem/cilastatin, each of which was given iv at a dosage of 1 g every 8 h; meropenem was given either as a bolus injection (over not less than 5 min) or infused over 20 to 30 min and imipenem/cilastatin was infused over 30 to 60 min to avoid the nausea and vomiting associated with more rapid administration (Wang *et al.*, 1985; Norrby *et al.*, 1987). In each group, a single dose of antibiotic was allowed before surgery. Since both meropenem and imipenem/cilastatin are chiefly eliminated renally, reductions in dose and/or frequency of both study drugs were made according to the degree of renal impairment in both treatment groups.

The recommended duration of therapy was five to 10 days (maximum 28 days) unless a successful response was reported between 2 and 5 days; no other concurrent antibiotics were allowed, and concomitant medications and/or interventions were recorded.

Evaluations

Clinical examinations were performed pre-therapy (within three days before the start of treatment), daily from Day 2 until the end of therapy, and at 2–4 weeks post-therapy (follow-up). Patients were evaluated for clinical efficacy as follows:

(a) *Cured*: complete resolution of local and systemic signs and symptoms of infection at the end of the treatment period without the addition of other antibiotics or recurrence of symptoms; (b) *Improved*: significant improvement in local symptoms and systemic signs without complete resolution of infection but allowing study treatment to be stopped; (c) *Unchanged/worse*: no improvement or deterioration of signs or symptoms; (d) *Unevaluable*: any patient receiving less than 48 h treatment; misdiagnosis; any patient receiving concurrent antibiotics; or major protocol violations; (e) *Relapse*: infection cleared at the end of therapy, followed by local or general signs of recurrent infection at follow-up.

The overall clinical response was assessed at the end of therapy and at follow-up. Cured and improved were considered satisfactory responses, whereas unchanged/worse and relapse were considered as unsatisfactory responses. Patients were considered evaluable if they were both clinically evaluable and had at least one micro-organism that was sensitive to both of the study drugs isolated from the intra-abdominal site pre-treatment.

Appropriate specimens from the infected abdominal site, such as peritoneal fluid, abscess fluid or pus, and blood cultures were obtained for bacteriological culture not more than three days pre-treatment or after one dose of antibiotic during surgery and repeated (if indicated), during treatment, immediately post-treatment, and at 2–4 weeks post-treatment where possible. Bacteriological response at end of treatment and follow-up was categorised as: (a) *Success*: all causative pathogens eradicated; (b) *Presumed success*: no further culture available due to clinical improvement; (c) *Partial success*: one or more, but not all of the organisms of a polymicrobial infection eradicated, associated with clinical improvement or cure; (d) *Failure*: persistence of causative pathogen; (e) *Presumed failure*: not confirmed by culture but associated with no clinical improvement in condition; (f) *Partial failure*: one or more, but not all of the organisms of a polymicrobial infection eradicated and associated with clinical failure; (g) *Superinfection*: a new pathogen arising during or at end of therapy, requiring antibiotic or surgical treatment; (h) *Unevaluable*: no pre-treatment pathogens isolated, no culture obtained, all pathogens resistant to the study drug, concomitant antibiotics given; (i) *Relapse*: initial eradication of pathogens at end of treatment followed by return of the causative pathogen at follow-up assessment requiring antibiotic or surgical treatment.

Biochemical and haematological monitoring and urinalysis were performed up to 3 days pre-treatment, between days 2 and 4, at least once weekly during treatment and at the end of treatment. If a clinically significant abnormal result was obtained, tests were repeated until the parameter returned to normal. Adverse events and local tolerance were recorded daily. After isolation and identification of pathogens to genus and species level, susceptibility testing was performed according to the standard accepted disc sensitivity criteria and measurements of minimum inhibitory concentrations (MICs) were made. Resistance to meropenem was defined as MIC >8 mg/L or zone size of $\leqslant 10$ mm; corresponding values for imipenem/cilastatin (according to NCCLS criteria) were $\geqslant 16$ mg/L or $\leqslant 13$ mm, respectively.

Statistical methods

A χ-squared test (not continuity corrected) was used to compare the numbers of patients in each group showing a satisfactory response for the two primary efficacy endpoints (clinical response in bacteriologically evaluable patients; bacteriological response). An intention-to-treat analysis was performed on the clinical response data for all patients. A 95% confidence interval (CI) for the difference in proportions was calculated using a normal approximation to the binomial (not continuity corrected). Formal statistical analyses were not performed either on patients returning for a follow-up assessment, or on safety variables.

Results

Demographics

Of the 232 patients who were recruited, 116 patients received meropenem and 116 patients received imipenem/cilastatin.

The groups were comparable in terms of demographic characteristics at baseline for all patients recruited and for those patients that were both clinically and bacteriologically

evaluable (Table I). On entry to the study, the majority of patients were judged by the investigator to be in a good to fair condition (78% of meropenem patients and 76% of imipenem/cilastatin patients), the remainder being considered either in poor clinical condition or critically ill. All patients received their treatment via a peripheral or central vein.

The majority of patients had not received any prior antibiotic therapy (78% in the meropenem, 79% imipenem/cilastatin). The remaining patients in each group had received antibiotics within 3 days before study entry but their infection was not controlled, nor a resistant organism isolated.

Approximately two thirds of patients had concurrent abnormalities, mainly gastrointestinal/hepatobiliary disorders (34 meropenem, 37 imipenem/cilastatin), cardiovascular disorders (32 meropenem, 26 imipenem/cilastatin) and neoplasms (14 meropenem, 10 imipenem/cilastatin). The commonest intestinal/hepatobiliary disorders were cholelithiasis (9 meropenem, 11 imipenem/cilastatin), inflammatory bowel disease (5 meropenem, 4 imipenem/cilastatin) and diverticulitis (6 meropenem, 4 imipenem/cilastatin). Colorectal neoplasms were the most common neoplasms reported (7 in each treatment group). The two treatment groups were well matched for underlying concurrent abnormalities.

Patient numbers

Of the 232 patients recruited to the study, 170 were both clinically and bacteriologically evaluable (82 meropenem; 88 imipenem/cilastatin). Sixty-two patients were excluded from the analysis of efficacy (Table II). Eight meropenem patients and five imipenem/cilastatin patients were judged protocol deviators (e.g. less than 48 h treatment, resistant pathogens or misdiagnosis) and 49 patients (26 meropenem, 23 imipenem/cilastatin) were bacteriologically unevaluable, because no organisms were cultured from pre-treatment samples, or no cultures were obtained. All patients were evaluated for safety.

Table I. Summary of demographic characteristics

	Meropenem		Imipenem/cilastatin	
	All patients ($n = 116$)	Evaluable patients ($n = 82$)	All patients ($n = 116$)	Evaluable patients ($n = 88$)
Sex				
male	71	50	67	54
female	45	32	49	34
Age (years)				
mean	55	57	54	55
range	18–92	18–92	18–88	18–88
Race				
caucasian	113	81	110	83
oriental	2	0	5	5
other	1	1	1	0
Mean weight (kg)				
males	75·1	75·2	70·3	70·1
females	60·8	61·5	64·6	62·8

Table II. Reason for exclusion from clinical and bacteriological assessments

Reason	Meropenem	Imipenem/cilastatin
Misdiagnosis	0	1
Previous trial entry	0	1
Randomisation error	3	1
Pre-therapy pathogens resistant	2	0
Less than 48 h treatment	2	2
Surgery after 3 doses of study drug	1	0
No pre-therapy pathogens isolated	26	23
Total	34	28

Infection types

Most of the 170 evaluable patients presented with community-acquired abdominal infections; 20 patients in the meropenem group and 11 in the imipenem/cilastatin group had hospital-acquired infections, chiefly as a result of previous surgery. Nineteen meropenem patients and 11 imipenem/cilastatin patients had undergone surgery in the two months before the study.

The infections were graded by the investigators as moderate in severity in 66% of meropenem patients and 67% of imipenem/cilastatin treated patients, severe in 26% and 25% respectively, and mild in the remainder.

The intra-abdominal infections were of various aetiologies which are summarised in Table III. The intra-abdominal infections were described in relation to the anatomical site of origin, including the following organ systems; stomach/duodenum, biliary tree (including gallbladder and hepatic ducts), small bowel, appendix, colon, liver, and pancreas (peripancreatic abscesses). They were also categorised, on the basis of operative findings, as abscess and/or peritonitis. The two treatment groups were comparable in terms of their underlying pathology, although more patients in the imipenem/cilastatin group had diffuse peritonitis than in the meropenem group. However more patients in the meropenem group presented with infections following previous elective/emergency surgery in the previous two months; such infections are often more difficult to treat.

Patients in the two treatment groups received similar concomitant adjunctive interventions. Eighty-six percent of meropenem patients had wound drains compared with 88% in the comparator group; 28% of meropenem patients received ventilatory support compared with 30% of imipenem/cilastatin patients; 35% and 36% respectively received parenteral nutrition and 58% of patients in the meropenem group had indwelling urinary catheters compared with 51% in the imipenem/cilastatin group.

The most common organisms isolated at the time of surgery were streptococcus *viridans* (*Streptococcus milleri* being the most predominant), enterococci, *Escherichia coli* and *B. fragilis* group (*B. fragilis* sp. being the commonest) (Table VI). Sixty patients in each treatment group had polymicrobial intra-abdominal infections.

Three patients in the meropenem group and six in the imipenem/cilastatin group were classified as septicaemic (i.e. had both clinical signs of septicaemia and positive blood cultures).

Efficacy

The mean duration of therapy was 7·8 days in the meropenem group and 8·3 days in the imipenem/cilastatin group.

At the end of therapy, a satisfactory clinical response (cure or improvement) was seen in 79/82 (96%) meropenem patients and 83/88 (94%) imipenem/cilastatin patients (Figure 1). The between-group difference (2·02%) was not statistically significant ($P = 0·534$, 95% CI −4·3%, 8·3%). Of those patients that returned for follow-up assessment, 57/63 (90%) meropenem patients and 58/66 (88%) of imipenem/cilastatin patients had a satisfactory response. The clinical response at the end of treatment by site of infection is shown in Table IV. The intention-to-treat analysis gave essentially the same result indicating no bias due to exclusion of patients.

Characteristics of the patients whose intra-abdominal infections were unchanged/worse following study treatment are shown in Table V. In the meropenem group, all three clinical failures were aged 65 years or more, had polymicrobial infections, and had received up to nine doses. Two of the three patients had had previous intra-abdominal surgery. In the imipenem/cilastatin group, the five clinical failures were aged between 26 and 78 years and had received up to 42 doses; none of these failures had received previous intra-abdominal surgery. All other patients (17 meropenem, 11 imipenem/cilastatin) who had undergone surgery in the two months before the study had satisfactory clinical responses. All nine patients with septicaemia (three meropenem, six imipenem/cilastatin) were considered clinically cured at the end of treatment and at follow-up.

Table III. Clinical features of intra-abdominal infections at entry to the study

	All patients		Evaluable patients	
	Meropenem ($n = 116$)	Imipenem/cilastatin ($n = 116$)	Meropenem ($n = 82$)	Imipenem/cilastatin ($n = 88$)
Peritonitis[a]				
diffuse	26 (4)	36 (5)	19 (3)	30 (6)
local	60 (19)	49 (14)	42 (17)	35 (12)
none	30 (21)	31 (22)	21 (18)	23 (19)
Anatomical site of infection				
stomach/duodenum	3	6	1	4
bilary tract/liver				
cholecystitis	5	5	1	2
cholangitis	16	19	12	14
pancreas	1	1	1	1
appendix (complicated)	22	17	21	16
appendix (uncomplicated)	18	14	5	9
appendix (unclassified)	2	5	2	4
small/large bowel	22	22	16	19
previous surgery	22	17	19	11
others	5	10	4	8
Infection severity				
mild	21	16	7	7
moderate	69	69	54	59
severe	26	31	21	22

[a]Number in parentheses indicates number of patients who also had abscesses.

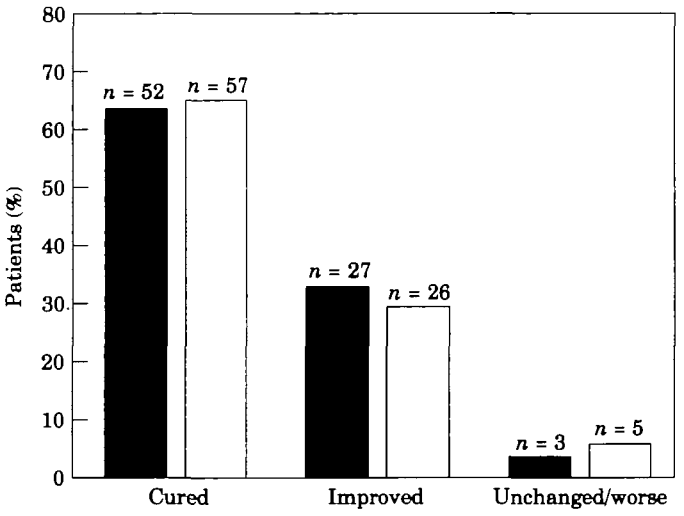

Figure 1. Clinical response at the end of treatment: ■, meropenem ($n = 82$); □, imipenem/cilastatin ($n = 88$).

Satisfactory bacteriological response (success or presumed success) at the end of therapy occurred in 69/82 (84%) meropenem patients and 71/88 (81%) imipenem/cilastatin patients (Figure 2); the difference (3·46%) was not statistically significant ($P = 0·554$, 95% CI −8·0%, 14·9%). Response rates at follow-up were very similar with bacteriological success or presumed success seen in 52/62 (84%) meropenem patients and in 55/70 (79%) imipenem/cilastatin patients.

In the meropenem group, unsatisfactory bacteriological responses at the end of therapy in 5/13 patients were due to new organisms arising during the study (11 new organisms

Table IV. Satisfactory clinical response rate at the end of treatment

	Meropenem ($n = 82$)		Imipenem/cilastatin ($n = 88$)	
	n	%	*n*	%
Peritonitis				
diffuse	18/19	95	27/30	90
local	40/42	95	34/35	97
none	21/21	100	22/23	96
Anatomical site of infection				
stomach/duodenum	1/1		3/4	
cholecystistis	1/1		2/2	
cholangitis	12/12		14/14	
pancreas	1/1		0/1	
appendix (complicated)	21/21		16/16	
appendix (uncomplicated)	5/5		9/9	
appendix (unclassified)	2/2		4/4	
small/large bowel	15/16		16/19	
Previous surgery	17/19		11/11	
Other	4/4		8/8	
Total	79/82	96	83/88	94

Table V. Characteristics of patients whose intra-abdominal infections were clinically unchanged/worse following study treatment

Primary diagnosis	Causative organisms identified at entry	Previous surgery
Meropenem		
Diffuse peritonitis (caecum/colon)	*E. coli*, *Acinetobacter lwoffi*, *Klebsiella pneumoniae*, *P. aeruginosa*, *Proteus mirabilis*, *Enterococcus faecalis*, *Enterococcus faecium*, *Clostridium* sp.	No
Local peritonitis /cholecystitis /intra-abdominal abscess	*Bacteroides merdae*, *E. coli*, *K. pneumoniae*, *P. mirabilis*, *Peptococcus* sp., *Peptostreptococcus* sp., β-haemolytic streptococcus, non-haemolytic streptococcus	Yes
Local peritonitis /anastomotic dehiscence	*E. coli*, *Klebsiella oxytoca*	Yes
Imipenem/cilastatin		
Diffuse peritonitis /perforated small bowel	*E. coli*	No
Local peritonitis /intra-abdominal abscess/diverticulitis	*Clostridium innocuum*, *Clostridium tyrobutyricium*, *E. coli*, *Eubacterium lentum*, *Enterococcus avium*	No
Diffuse peritonitis /perforated sigmoid	*P. aeruginosa*[a], *Candida albicans*[a]	No
Pancreatic abscess	*E. faecalis*[a]	No
Diffuse peritonitis /perforated duodenal ulcer	*Clostridium sporogenes*, *S. aureus*	No

[a]New organism arising during the study.

isolated), compared with 9/17 failures in the imipenem/cilastatin group (24 new organisms isolated). In the meropenem group, seven of the 11 new organisms were Gram-positive aerobes, two were Gram-negative aerobes, one was an anaerobe and one was a yeast. In the imipenem/cilastatin group, of the 24 new organisms cultured, nine were Gram-positive aerobes, eight were Gram-negative aerobes, six were anaerobes and one was a yeast.

In the 120 patients with polymicrobial intra-abdominal infections (60 meropenem; 60 imipenem/cilastatin) there was a high level (95%) of clinical cure or improvement in both treatment groups. A satisfactory bacteriological response was achieved in 49/58 (85%) meropenem patients compared with 46/58 (79%) imipenem/cilastatin patients; this difference was not statistically significant.

In addition, the bacteriological response for each bacterial species was evaluated. A similar distribution of Gram-positive aerobic bacteria (30%), Gram-negative aerobes (39%) and anaerobes (31%) was found throughout the study population. The percentages of causative organisms with a satisfactory response are given in Table VI. The commonest organisms, *E. coli* and *B. fragilis* group, were eradicated or presumed eradicated in 44/48 (92%) and 27/28 (96%), respectively, of the meropenem patients and 48/51 (94%) and 20/21 (95%), respectively, of the imipenem/cilastatin group.

All new organisms arising during the study were assessed to evaluate the tendency of the study drug to select out certain bacterial or fungal strains. Superinfections were defined as those requiring further antimicrobials or surgery, whereas colonisation required no further therapy. Nineteen meropenem and 24 imipenem/cilastatin patients had superinfections and/or colonisations at one or more sites. There were fewer superinfections in the meropenem group compared with the imipenem/cilastatin group (5/82 vs 12/88), whereas the number of colonisations was similar (16/82 vs 16/88). In the meropenem group four of the five superinfections were from drain sites and one was in the blood. One of the patients with a drain site superinfection also had *Candida* sp. isolated in the blood. In the imipenem/cilastatin group, four superinfections were from drain sites, four were from samples taken during further surgery (two of these four patients also had organisms isolated in the blood), one from abscess needle puncture and three in the urine. There was no difference in the incidence of fungi/yeasts cultured from the treatment groups.

Sensitivity testing of the colonising or superinfecting organisms isolated from intra-abdominal sites against both study drugs revealed ten strains to be resistant to meropenem and nine to imipenem, the resistant organisms being: enterococci, *S. milleri* and a coagulase-negative staphylococcus (presumed methicillin resistant).

Safety

Overall, 72 adverse events were experienced by 45/116 (39%) meropenem patients and 65 adverse events were experienced by 42/116 (36%) imipenem/cilastatin patients.

In the meropenem group, 33 patients (28%) experienced adverse events that were considered to be drug-related, compared to 29 patients (25%) in the imipenem/cilastatin group. Incidences of adverse events occurring in more than one patient are shown in Table VII. Most adverse events were mild or moderate in intensity.

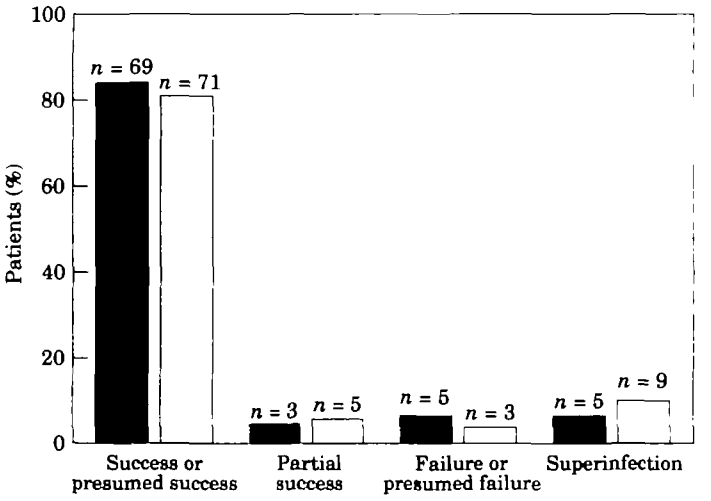

Figure 2. Bacteriological response at the end of treatment: ■, meropenem (n = 82); □, imipenem/cilastatin (n = 88).

Table VI. Satisfactory response rate of individual organisms

	Meropenem		Imipenem/cilastatin	
	n	%	*n*	%
Gram-positive aerobes				
Enterococci	12/18	67	13/13	100
Viridans streptococci	28/29	97	15/16	94
Staphylococcus epidermidis	5/6	83	2/4	50
S. aureus	3/3	100	2/3	67
Staphylococcus spp.	3/3	100	1/1	100
Others	18/20	90	19/21	90
Total	69/79	87	52/58	90
Gram-negative aerobes				
E. coli	44/48	92	48/51	94
Klebsiella spp.	10/13	77	6/6	100
P. mirabilis	3/5	60	3/3	100
P. aeruginosa	2/4	50	6/7	86
Morganella morganii	3/3	100	1/2	50
Others	18/19	95	16/17	94
Total	80/92	87	80/86	93
Anaerobes				
B. fragilis Group.	27/28	96	20/21	95
Bacteroides spp.	3/3	100	1/1	100
Peptostreptococcus spp.	4/5	80	2/2	100
Clostridium perfringens	3/3	100	5/5	100
Others	34/37	92	30/35	86
Total	71/76	93	58/64	91
Overall total	220/247	89	190/208	91

The most frequently reported adverse events in both treatment groups were injection site inflammation, elevated AST and elevated ALT. Injection site inflammation was reported in nine meropenem and 13 imipenem/cilastatin patients. The AST was increased in seven meropenem and six imipenem/cilastatin patients whilst the ALT was increased in six patients in each group.

Table VII. Adverse events considered drug-related occurring in more than one patient

	Meropenem ($n = 116$)	Imipenem/cilastatin ($n = 116$)
Injection site inflammation	9	13
AST increased	7	6
ALT increased	6	6
Prothrombin time increased	4	1
Alkaline phosphatase increased	4	3
Lactic dehydrogenase increased	3	—
Eosinophilia	2	3
Nausea	2	1
Diarrhoea	2	1
Vomiting[a]	1	2

[a]One patient from each group experienced nausea and vomiting.

Five patients (one meropenem and four imipenem/cilastatin) were withdrawn due to adverse events which were considered drug-related: severe nausea (meropenem), severe nausea and vomiting (imipenem/cilastatin), injection site inflammation (two imipenem/cilastatin patients) and severe hypotension (imipenem/cilastatin).

There were nine deaths during the study period, six in the meropenem group and three in the imipenem/cilastatin group. In two cases (meropenem group), the possibility of a relationship to treatment was not excluded by the investigator. Both patients were elderly and died of complications of their underlying disease subsequent to septic shock, one of cardiac failure and one of hepatic failure. The patient who died of hepatic failure had abnormal liver function tests at study entry.

Although a high proportion of renally-impaired patients inadvertently received higher doses than those recommended, there were no safety problems in these patients.

There were no gross differences between treatment groups for haematological variables, with the exception of prothrombin time which was increased in a greater number of meropenem patients. However, none of these changes was considered to be drug-related, and the changes were transient, or clearly related to other factors (e.g. warfarin administration).

Following review of all haematological/biochemical variables, meropenem produced no clinically significant abnormalities in blood elements, clotting systems, renal function or hepatic biochemistry. When elevations in transaminases more than three times greater than baseline values were reviewed, there were no differences between treatments.

Overall, the changes seen in haematology and biochemistry with meropenem compared favourably with those seen with imipenem/cilastatin.

The safety profiles of meropenem and imipenem/cilastatin were similar and none of the differences was considered to be clinically significant.

Discussion

Whilst surgery is usually required for the treatment of intra-abdominal infections, safe and effective broad spectrum antibiotics are needed for immediate empirical treatment of patients presenting with such infections. The results of this large, international study indicate that the clinical and bacteriological efficacy of meropenem and imipenem/cilastatin were equivalent, with high success rates seen in both groups at treatment end and at follow-up.

These results compare well with other studies in intra-abdominal infections. A review of worldwide clinical experience with imipenem/cilastatin has shown an overall clinical efficacy rate of 91% (Clissold, Todd & Campoli-Richards, 1987), whilst individual studies have shown satisfactory clinical response rates of 69% (Eklund *et al.*, 1993), 96% (Eckhauser *et al.*, 1992) and 86% (Norwegian Study Group, 1987), in comparison with piperacillin plus tazobactam (93%), clindamycin plus gentamicin or tobramycin (92%) and cefotaxime plus metronidazole and cloxacillin (92%), respectively.

Imipenem/cilastatin is a recognised standard treatment for intra-abdominal infections and has been shown to be as effective as combination treatment (Geddes & Roylance, 1991). In the present study, meropenem and imipenem/cilastatin showed a broad spectrum of activity against Gram-positive and Gram-negative aerobes, and anaerobes. In particular, both meropenem and imipenem/cilastatin were highly effective against *E. coli* (the commonest causative organism), *B. fragilis* group and *Streptococcus* spp. The small numbers of patients with other causative organisms do not allow for meaningful

comparisons. Meropenem and imipenem/cilastatin produced high clinical response rates irrespective of the pathology of infection, i.e. whether the peritonitis was local or diffuse, or whether an abscess was present.

Although the number of colonisations was similar in both treatment groups, there were fewer superinfections in patients receiving meropenem. Superinfections contribute to treatment failure and their prevention is therefore beneficial. Of the resistant strains of new organisms which were isolated from intra-abdominal cultures, *Enterococcus faecium* and methicillin-resistant staphylococci have documented resistance to carbapenems (Benfield & Chrisp, 1992; Havlik, 1993).

Whilst the tolerability of imipenem/cilastatin is acceptable, this combination product is not without problems; seizures have been reported in patients receiving imipenem/cilastatin (Calandra *et al.*, 1988*a*). In this study, no seizures were reported. However, patients with known CNS abnormalities were excluded. Animal data have shown that meropenem has a lower seizure potential than imipenem/cilastatin; whereas both imipenem and imipenem/cilastatin produced significant potentiation of metrazole-induced seizures in mice, no significant potentiation was seen with meropenem (Patel & Giles, 1989; Hori, Kanemitsu & Shimada, 1992). Clinical support for these results was seen in a meningitis study in which there were no drug-related seizures in patients receiving either meropenem or a cephalosporin (Lopez *et al.*, 1993).

Imipenem/cilastatin has also been associated with nausea and/or vomiting especially when given by rapid infusion; vomiting is particularly hazardous in surgical patients as it can lead to wound breakdown. However, the design of this study removed any possibility of showing between-group differences, since imipenem/cilastatin was administered by slow infusion because of this previous experience with the drug. There is no evidence of a relationship between rate of infusion/dose and incidence of nausea and/or vomiting for meropenem.

The most common adverse reactions reported were injection site inflammation and elevated transaminases, which occurred to a similar extent in both groups. Pain at injection site tends to occur with β-lactam antibacterials, as does phlebitis, thrombophlebitis and venous pain (Buckley *et al.*, 1992). In this study, inflammation at the injection site occurred to a similar extent in both groups. However, it led to withdrawal in two imipenem/cilastatin patients.

Transient increases in AST and ALT levels have been previously reported in imipenem/cilastatin studies, although it is difficult to know whether these are due to the drug or the underlying infection treated, and few were considered to be drug-related (Wang *et al.*, 1985; Wise, 1990; Buckley *et al.*, 1992). When liver function test results from the present study were reviewed for changes or trends, meropenem compared favourably with imipenem/cilastatin. A careful review of renal function tests revealed no evidence of nephrotoxicity with meropenem and there was no identifiable increase in adverse events in renally-impaired patients.

In this study, meropenem was as well tolerated as imipenem/cilastatin. It should also be borne in mind that this was an open study and the likelihood is much higher of minor adverse events being reported for a new treatment (meropenem) as opposed to an established regimen (imipenem/cilastatin). Furthermore, the study was designed to reduce the known intolerance of imipenem/cilastatin which results from rapid infusion.

In conclusion, meropenem (1 g every 8 h) is highly effective in the treatment of intra-abdominal sepsis, producing a high rate of clinical and bacteriological response. It has equivalent efficacy to imipenem/cilastatin and has a particularly high

efficacy against anaerobes. Meropenem and imipenem/cilastatin also showed equivalent tolerability in this study. Meropenem offers greater flexibility of administration than imipenem/cilastatin and can confidently be given as empirical monotherapy by intravenous infusion or bolus injection for the treatment of moderate to severe intra-abdominal infections.

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