MAJOR ARTICLE

Safety and Effectiveness of Meropenem in Infants With Suspected or Complicated Intra-abdominal Infections

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(See the Editorial Commentary by Jacqz-Aigrain, on pages 1503–4.)

Background. Intra-abdominal infections are common in young infants and lead to significant morbidity and mortality. Meropenem is a broad-spectrum antimicrobial with excellent activity against pathogens associated with intra-abdominal infections. The purpose of this study was to determine the safety and effectiveness of meropenem in young infants with suspected or complicated intra-abdominal infections.

Methods. Preterm and term infants <91 days of age with suspected or confirmed intra-abdominal infections hospitalized in 24 neonatal intensive care units were studied in an open-label, multiple-dose study. Adverse events and serious adverse events were collected through 3 and 30 days following the last meropenem dose, respectively. Effectiveness was assessed by 3 criteria: death, bacterial cultures, and presumptive clinical cure score.

Results. Of 200 subjects enrolled in the study, 99 (50%) experienced an adverse event, and 34 (17%) had serious adverse events; no adverse events were probably or definitely related to meropenem. The most commonly reported adverse events were sepsis (6%), seizures (5%), elevated conjugated bilirubin (5%), and hypokalemia (5%). Only 2 of the serious adverse events were determined to be possibly related to meropenem (isolated ileal perforation and an episode of fungal sepsis). Effectiveness was evaluable in 192 (96%) subjects, and overall treatment success was 84%.

Conclusions. Meropenem was well tolerated in this cohort of critically ill infants, and the majority of infants treated with meropenem met the definition of therapeutic success.

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Intra-abdominal infections in young infants (<91 days of age) lead to substantial morbidity and mortality; approximately 20% of infants with necrotizing enterocolitis die, and survivors suffer from severe neurodevelopmental impairment [1–3]. Consequently, most infants with suspected or confirmed intra-abdominal infections are treated with empirical antimicrobial therapy. Broad-spectrum or combination antimicrobial agents are often prescribed for these infections given their polymicrobial nature [4, 5].

Meropenem possesses one of the broadest spectra of antimicrobial activity available [6], due to its stability against most extended-spectrum and AmpC chromosomal β-lactamases. This property increases the drug's activity against many antibiotic-resistant bacteria commonly responsible for life-threatening infections among young infants [6].

Meropenem is currently approved by the Food and Drug Administration (FDA) for use in children ≥3 months of age with bacterial meningitis and/or complicated intra-abdominal infections; however, there is substantial off-label use of meropenem in infants <3 months of age [7] despite the lack of adequate dosing, safety, and efficacy data in this vulnerable group. Owing to this lack of data and under the Best Pharmaceuticals for Children Act, the FDA made a formal written request to obtain needed pediatric information on meropenem. Therefore, a study was conducted to determine the pharmacokinetics (PK), safety, and effectiveness of meropenem in young infants with suspected or confirmed intra-abdominal infections. The PK results of the meropenem study have been published previously [8]. Here the safety and effectiveness data are described.

METHODS

Study Design

This was an open-label, 24-center, prospective, multidose, PK, safety, and effectiveness study of meropenem in infants <91 days of age with suspected or confirmed intra-abdominal infection, possible necrotizing enterocolitis, or otherwise receiving meropenem per local standard of care and likely to survive >48 hours after enrollment. Participants were excluded for renal dysfunction (urine output <0.5 mL/hour/kg or serum creatinine >1.7 mg/dL); history of clinical seizures or electroencephalography (EEG)–confirmed seizures; or concomitant treatment with ertapenem or imipenem. The institutional review board at each participating center approved this study. All study participants were enrolled after obtaining informed consent from a parent or legal guardian. Study procedures were in accordance with the ethical standards of the Helsinki Declaration (1964, amended in 2008) of the World Medical Association.

Administration of Study Drug and Procedures

Subjects were stratified into 4 groups based on gestational age (GA, <32 weeks and ≥32 weeks) and postnatal age (PNA, <2 weeks and ≥2 weeks) to receive intravenous meropenem: group 1 (GA <32 weeks, PNA <2 weeks), 20 mg/kg body weight every 12 hours; group 2 (GA <32 weeks, PNA ≥2 weeks) and group 3 (GA ≥32 weeks, PNA <2 weeks), 20 mg/kg body weight every 8 hours; and group 4 (GA ≥32 weeks, PNA ≥2 weeks), 30 mg/kg body weight every 8 hours [8]. During the study, meropenem was administered to each subject for ≥3 days and ≤21 days. While the protocol recommended that aminoglycoside therapy be administered concomitantly with meropenem, treatment with other antimicrobial agents during the study was determined by the local standard of care. Blood, urine, or cerebrospinal fluid cultures were obtained as part of routine care.

Safety Assessments

The population evaluated for safety included all participants who received ≥1 dose of meropenem as part of the study. Deaths and adverse events (AEs) were assessed in real time by a clinical events safety committee and an independent data and safety monitoring board. Specific safety endpoints included death, seizures, strictures, perforation, wound dehiscence, short-gut syndrome, infection with extended β-lactamase–producing organisms, candidiasis, and antimicrobial therapy failure. Clinical laboratory values (liver function tests, renal function tests, blood counts) and vital signs were monitored weekly if collected as part of the standard of care; laboratory tests were not collected specifically for study purposes.

All AEs (through 3 days following the last study dose of meropenem) and all serious adverse events (SAEs; through 30 days following the last dose) were collected. AE causality was determined by the local investigator as not related, possibly related, probably related, or definitely related to meropenem. Additional data were obtained on AEs of special interest: (1) direct bilirubin >5 mg/dL; (2) indirect bilirubin >15 mg/dL if <36 weeks postmenstrual age (PMA); (3) indirect bilirubin >20 mg/dL if ≥36 weeks PMA; (4) aspartate aminotransferase (AST) increased 10-fold over baseline; (5) alanine aminotransferase (ALT) increased 10-fold over baseline; (6) serum creatinine >2.5 mg/dL; and (7) seizures.

Seizures were recorded and assessed by the local site principal investigator (PI), and EEGs were evaluated by the site PI and clinical events safety committee (including a pediatric neurologist) if they were obtained per local standard of care. If seizures occurred during meropenem therapy, a blood sample was collected and meropenem plasma concentrations were measured. To determine if meropenem concentrations were associated with seizures, maximum meropenem concentrations at steady state ($Cmax_{ss}$) were predicted for subjects with seizures and matched PMA subjects without seizures.

A 1-compartment structural PK model and individual Bayesian PK parameter estimates generated during the population PK analysis were used for these calculations [8].

Effectiveness Assessments

All participants who underwent an effectiveness assessment both pre- and postdose were evaluated for effectiveness. Infants who died during the study period were also considered in the effectiveness population. Initial clinical status was based on the presenting signs of each infant and was recorded by the local PI prior to administration of the first dose of study meropenem. The same clinical signs and physical findings were recorded on a subsequent study visit on study day 28 or ≥7 days after treatment ended. The clinical, laboratory, and radiographic findings used in the presumptive clinical cure score calculation included mean blood pressure, temperature, oxygen saturation, serum pH, presence or absence of seizures, urine output, presence of cardiovascular inotrope support, C-reactive protein, abdominal girth, and findings on abdominal radiograph. The overall presumptive clinical cure score was determined by comparing each criterion in the presumptive clinical cure scale between the baseline and the final assessment visit. One point was awarded for each criterion if the subject was asymptomatic at baseline, and the subject remained asymptomatic, had no change, or improved at the effectiveness visit. One point was also awarded for each criterion if the subject was symptomatic at baseline and then was asymptomatic or improved at the effectiveness visit. The sum of the points assigned to each of the 10 criteria was assigned as the presumptive clinical cure score.

Success at the effectiveness visit was defined as all of the following: (1) alive; (2) negative bacterial cultures from sterile body fluid (except *Staphylococcus* species); and (3) presumptive clinical cure score ≥7. Treatment failure was defined by any of the following: (1) change in antibiotic therapy while on study drug with the exception of addition of gram-positive coverage against culture-confirmed meropenem-resistant organisms (ie, methicillin-resistant *Staphylococcus aureus*); (2) death; or (3) presumptive clinical cure score <7. The antibiotic change was not a trigger for an effectiveness failure if it was started on the same day that study meropenem was started or if the antibiotic was started on the same day that study meropenem ended.

Statistical Analysis

This study was not powered to determine effectiveness, and no inferential statistical tests were performed. The number and the proportion of subjects who were considered as treatment successes and the number of AEs and proportion of subjects who suffered an AE were determined. Logistic regression analysis was used to evaluate baseline effectiveness predictors of SAEs, level II AEs, seizures, and death. This analysis was adjusted for GA, PNA, sex, and birth weight. No inferential statistics were performed on laboratory values collected during the study because laboratory values were recorded only if obtained per standard clinical care, and there was no placebo arm for comparison. Wilcoxon rank sum test was used to compare predicted meropenem $Cmax_{ss}$ between subjects with and without seizures.

RESULTS

Two hundred subjects were enrolled; 142 (71%) were born at <32 weeks GA, and 130 (65%) were ≥2 weeks PNA at the time of enrollment (Table 1). The median PNA for the safety population was 21 days (range 1–92), median GA 27.8 weeks (range 22.5–40.0), median birth weight 1080 g (range 330–4768); 59% of the subjects were male, and 65% were white. All subjects were included in the safety evaluation. Overall, 89% of subjects had respiratory conditions, 90% a gastrointestinal condition, and 73% cardiovascular conditions at baseline. Forty-five percent of subjects had abdominal surgery prior to enrollment. Thirty-eight percent received meropenem per routine medical care prior to enrollment.

Indications for meropenem administration included stage II or higher necrotizing enterocolitis based on Bell's criteria (31%), spontaneous intestinal perforation (11%), perforation/peritonitis (10%), stage I necrotizing enterocolitis (17%), and receipt of meropenem as part of the standard of care (33%). Baseline radiography was performed in 174 (87%) subjects and was normal in 17 (10%) cases. The most commonly administered concomitant medications were vancomycin (53%), gentamicin (51%), furosemide (46%), caffeine citrate (37%), morphine (36%), fentanyl (35%), midazolam (30%), fluconazole (26%), and hydrocortisone (23%). Only 21 (11%) subjects received meropenem monotherapy.

There were 316 AEs reported in 99 (50%) subjects (Table 2). Group 1 (<32 weeks GA and <2 weeks PNA) subjects suffered an AE in 26 of 39 (67%) of cases. Twenty-one (11%) infants had 30 AEs that were determined to be possibly related to meropenem, and no subjects had an AE that was probably or definitely related to meropenem. AEs possibly related to meropenem included coagulopathy (n = 1), spontaneous ileal perforation (n = 1), infusion site extravasation (n = 1), sepsis (n = 3), fungal skin infection (n = 1), elevated AST (n = 1), elevated direct bilirubin (n = 4), elevated triglycerides (n = 1), hypoglycemia (n = 1), elevated creatinine or acute renal failure (n = 2), osteopenia (n = 1), skin breakdown (n = 1), rash (n = 1), acute respiratory failure or pneumothorax (n = 2), hypotension (n = 2), and seizures (n = 7).

AEs of special interest were observed in 19 infants: 9 (4%) infants experienced a laboratory event of special interest, and

Table 1. Subject Demographics

	GA <32 Weeks		GA ≥32 Weeks		
	PNA <2 Weeks	PNA ≥2 Weeks	PNA <2 Weeks	PNA ≥2 Weeks	Total
No.	39	103	31	27	200
Gestational age (weeks), median (range)	26.0 (22.5–31.5)	26.3 (23.0–31.5)	36.0 (32.1–40.0)	34.4 (32.0–40.0)	27.8 (22.5–40.0)
Postnatal age (days), median (range)	9 (1–13)	32 (14–92)	6 (1–14)	26 (14–82)	21 (1–92)
Male sex, No. (%)	24 (62)	56 (54)	22 (71)	16 (59)	118 (59)
Hispanic or Latino ethnicity, No. (%)	5 (13)	16 (16)	4 (13)	3 (11)	28 (14)
Race, No. (%)					
African-American	12 (31)	33 (32)	8 (26)	6 (22)	59 (30)
White	26 (67)	65 (63)	21 (68)	18 (67)	130 (65)
Other	2 (5)	5 (5)	2 (6)	4 (15)	13 (7)

Abbreviations: GA, gestational age; PNA, postnatal age.

seizures were reported in 10 (5%) infants (Table 2). All infants with laboratory AEs of special interest were <32 weeks GA, and these AEs included 5 elevated conjugated bilirubin levels, 3 elevated serum creatinine levels, and 1 elevated AST level. Four (10%) subjects <32 weeks GA and <2 weeks PNA, 3 (3%) subjects <32 weeks GA and ≥2 weeks PNA, 1 (3%) subject ≥32 weeks GA and <2 weeks PNA, and 2 (7%) subjects ≥32 weeks GA and ≥2 weeks PNA had clinically apparent seizures. Six of 10 subjects had EEG performed, but only 1 (10%) of the 10 seizures was confirmed by EEG. Of the 10 subjects who developed seizures, 1 (10%) was not receiving study drug on the day of the seizure, 5 (50%) had history of intraventricular hemorrhage, and 2 (20%) had a plasma sample obtained for quantitation of meropenem within 4 hours of the event (Table 3). On average, predicted meropenem $Cmax_{ss}$ in subjects with seizures did not differ from those subjects without seizures (mean ± SD: 57.18 [±13.50] vs 53.12 [±5.08] mg/L; $P = .24$; Table 3).

Thirty-six SAEs were reported in 34 (17%) infants. SAEs were most commonly reported among infants <32 weeks GA and <2 weeks PNA (9/39 [23%]; Table 2). Only 2 (6%) of the SAEs were determined to be possibly related to study drug

Table 2. Overall Safety Summary

	GA <32 Weeks		GA ≥32 Weeks		
	PNA <2 Weeks, No. (%)	PNA ≥2 Weeks, No. (%)	PNA <2 Weeks, No. (%)	PNA ≥2 Weeks, No. (%)	Total
No.	39	103	31	27	200
No. with at least 1 AE	26 (67)	47 (46)	13 (42)	13 (48)	99 (50)
AE by causality					
Unrelated	19 (49)	37 (36)	12 (39)	10 (37)	78 (39)
Possibly related	7 (18)	10 (10)	1 (3)	3 (11)	21 (11)
Seizure	4 (10)	3 (3)	1 (3)	2 (7)	10 (5)
Level II laboratory AE[a]	2 (5)	7 (7)	0 (0)	0 (0)	9 (5)
AST increased	0 (0)	1 (1)	0 (0)	0 (0)	1 (1)
Direct bilirubin increased	2 (5)	3 (3)	0 (0)	0 (0)	5 (3)
Serum creatinine increased	0 (0)	3 (3)	0 (0)	0 (0)	3 (2)
No. with at least 1 SAE	9 (23)	18 (18)	2 (7)	5 (19)	34 (17)
Death	3 (8)	8 (8)	0 (0)	0 (0)	11 (6)
AE that led to study drug discontinuation	1 (3)	3 (3)	0 (0)	2 (7)	6 (3)

Abbreviations: AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GA, gestational age; PMA, postmenstrual age; PNA, postnatal age; SAE, serious adverse event.

[a] Level II laboratory AE: direct bilirubin >5 mg/dL; indirect bilirubin >15 mg/dL if <36 weeks PMA; indirect bilirubin >20 mg/dL if ≥36 weeks PMA; AST increased 10-fold over baseline; ALT increased 10-fold over baseline; and serum creatinine >2.5 mg/dL.

Table 3. Predicted Meropenem Concentrations in Subjects With Seizures

Subject ID	On Study Drug at Time of Seizure	Days on Therapy Prior to Seizure	Postmenstrual Age (Weeks)	Observed Cp at Time of Seizure	$Cpmax_{ss}$ (mg/L)	$Cpmax_{ss}$ in Matched Controls Without Seizures (mg/L)[a]
1	Yes	2	24	…	60.71	47.42 (11.54)
2	Yes	2	25	…	63.08	57.34 (14.41)
3	Yes	8	26	4.84	52.73	54.66 (17.20)
4	Yes	0	26	…	50.83	54.66 (17.20)
5	Yes	10	27	…	40.85	54.32 (7.26)
6	No	…	30	…	61.90	52.63 (20.50)
7	Yes	2	30	…	69.61	52.63 (20.50)
8	Yes	1	35	14.93	74.07	52.92 (18.90)
9	Yes	14	36	…	67.32	61.64 (22.14)
10	Yes	9	39	…	30.67	42.95 (10.75)

Abbreviations: Cp, meropenem plasma concentration; $Cpmax_{ss}$, predicted meropenem maximum concentration at steady state.

[a] Data are mean (standard deviation).

(isolated ileal perforation and an episode of fungal sepsis). Eleven infants (6%) in the study died. All deaths occurred in infants <32 weeks GA: 3 of 39 (8%) in the PNA <2 weeks group and 8 of 103 (8%) in the PNA ≥2 weeks group. Two of the subjects of PNA <2 weeks died of multiorgan failure, and 1 died from subarachnoid hemorrhage. Of the 8 deaths in the PNA ≥2 weeks group, 2 had multiorgan failure, and 1 each died of pulmonary hemorrhage, intestinal perforation, congenital diaphragmatic hernia, respiratory failure, presumed meningitis, and presumed bacterial sepsis. None of the deaths were considered related to meropenem.

The most commonly reported AEs were sepsis (6%), seizures (5%), elevated conjugated bilirubin (5%), and hypokalemia (5%; Table 4). There were no reports of strictures, development of short-gut syndrome, or extended-spectrum β-lactamase (ESBL) infections during administration of meropenem or in the follow-up period. Eight (4%) infants developed candidiasis, 4 (2%) had perforations, and 4 (2%) had wound dehiscence during the study period. On average, serum creatinine, AST, and ALT obtained per routine medical care remained stable (Table 5). We observed an increasing trend in alkaline phosphatase and direct bilirubin values during the study period.

Table 4. Frequently Occurring (≥5 Participants) Adverse Events

	GA <32 Weeks		GA ≥32 Weeks		
	PNA <2 Weeks, No. (%)	PNA ≥2 Weeks, No. (%)	PNA <2 Weeks, No. (%)	PNA ≥2 Weeks, No (%)	Total
No.	39	103	31	27	200
AST increased[a]	0 (0)	3 (3)	0 (0)	2 (7)	5 (3)
Atelectasis	2 (5)	0 (0)	0 (0)	3 (11)	5 (3)
Conjugated bilirubin increased[a]	5 (13)	3 (3)	0 (0)	1 (4)	9 (5)
Hyperglycemia[a]	2 (5)	2 (2)	1 (3)	0 (0)	5 (3)
Hypoglycemia[a]	3 (8)	2 (2)	0 (0)	0 (0)	5 (3)
Hypokalemia[a]	2 (5)	6 (6)	0 (0)	1 (4)	9 (5)
Hypotension[a]	1 (3)	5 (5)	0 (0)	0 (0)	6 (3)
Patent ductus arteriosus	4 (10)	1 (1)	0 (0)	1 (4)	6 (3)
Retinopathy of prematurity	0 (0)	5 (5)	0 (0)	0 (0)	5 (3)
Sepsis	5 (13)	5 (5)	1 (3)	1 (4)	12 (6)
Seizures	4 (10)	3 (3)	1 (3)	2 (7)	10 (5)
Vomiting	0 (0)	1 (1)	4 (13)	0 (0)	5 (3)

Abbreviations: AST, aspartate aminotransferase; GA, gestational age; PNA, postnatal age.

[a] Defined per the local site.

Table 5. Laboratory Evaluations

	Baseline	Days 1–7	Days 8–14	Days 15–21	Days 22–28
Serum creatinine (No.)	181	173	127	85	53
Median (range), mg/dL	0.5 (0.1–1.9)	0.4 (0.0–3.1)	0.4 (0.0–2.7)	0.3 (0.0–2.9)	0.3 (0.0–2.0)
AST (No.)	60	78	68	55	32
Median (range), U/L	37 (12–3358)	33 (9–419)	33 (11–308)	40 (15–567)	50 (19–788)
ALT (No.)	60	80	69	55	30
Median (range), U/L	25 (4–956)	18 (5–140)	16 (4–131)	20 (5–605)	27 (8–168)
Alkaline phosphatase (No.)	64	86	65	52	28
Median (range), U/L	255 (72–1368)	244 (35–967)	321 (104–1103)	412 (101–1600)	508 (123–1145)
Direct bilirubin (No.)	70	71	52	34	14
Median (range), mg/dL	0.6 (0.0–10.8)	0.8 (0.0–10.3)	1.5 (0.0–10.7)	1.7 (0.1–8.5)	3.7 (0.2–6.0)

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase.

Effectiveness was evaluable in 192 (96%) subjects. Overall success for effectiveness in this population was 84% (162/192; Table 6). Mortality prior to the effectiveness assessment was 8 of 192 (4%). None of the 50 infants with GA ≥32 weeks died prior to the effectiveness visit. Success was lowest among infants <32 weeks GA and <2 weeks PNA (29/39 [74%]) and highest among infants ≥32 weeks GA in both PNA groups (51/55 [93%]). Change in antibiotic therapy was the most common treatment failure surrogate (23/30 [77%]). Of the 23 infants with changes in antibiotic therapy, 2 (10%) had positive peritoneal fluid cultures while receiving meropenem (*Escherichia coli* and organism not specified). One hundred seventeen subjects had 262 cultures (184 blood, 44 urine, 19 cerebrospinal fluid, 14 peritoneal, 1 missing) obtained in the 7 days prior to the first dose of meropenem; 29 had a positive culture. Of 262 cultures obtained, 40 were positive (27 blood, 8 urine, 5 peritoneal): 75% gram-negative rods, 20% gram-positive cocci, and 5% gram-positive rods. No study subjects were blood culture positive for nonstaphylococcal species after initiation of meropenem therapy.

DISCUSSION

Meropenem is commonly used off-label in infants <3 months of age, despite a lack of safety and efficacy data, because of its broad range of antimicrobial activity and its stability against chromosomally encoded and plasmid-mediated ESBL infections [9]. Meropenem's spectrum includes *Enterobacteriaceae*, *Pseudomonas aeruginosa* [6], methicillin-sensitive *S. aureus*, *Enterococcus faecalis* [6], and *Bacteroides fragilis* [10]. Despite the benefits associated with meropenem's extended

Table 6. Effectiveness Results

	GA <32 Weeks		GA ≥32 Weeks		
	PNA <2 Weeks, No. (%)	PNA ≥2 Weeks, No. (%)	PNA <2 Weeks, No. (%)	PNA ≥2 Weeks, No. (%)	Total
Evaluable for effectiveness, No.	39	98	28	27	192
Effectiveness success	29 (74)	82 (84)	26 (93)	25 (93)	162 (84)
Death[a]	3 (8)	5 (5)	0 (0)	0 (0)	8 (4)
Presumptive clinical cure score ≥7	35 (90)	90 (92)	27 (96)	27 (100)	179 (93)
Presumptive clinical cure score <7	0 (0)	1 (1)	0 (0)	0 (0)	1 (1)
Presumptive clinical cure score missing	4 (10)	7 (7)	1 (4)	0 (0)	12 (6)
Change in antibiotic therapy	7 (18)	12 (12)	2 (7)	2 (7)	23 (12)[b]
Cultures negative for bacteria	27 (69)	49 (50)	9 (32)	13 (48)	98 (51)
Cultures not done	12 (31)	49 (50)	19 (68)	14 (52)	94 (49)

Abbreviations: GA, gestational age; PNA, postnatal age.

[a] Death occurring ≤7 days from end of study meropenem.

[b] Of the 23 participants with change in antibiotic therapy, 1 also died and 1 had a presumptive clinical cure score <7.

antimicrobial spectrum, there are safety concerns related to potential central nervous system (CNS) side effects in young infants.

The potential for adverse CNS effects of meropenem, particularly seizures, has been carefully studied in older children [11, 12]. In a randomized trial of meropenem or cefotaxime for bacterial meningitis in children, seizures were reported in 12% (15/129) of the meropenem cohort and 17% (22/129) of the cefotaxime cohort [13]. None of the seizures were thought to be related to antibiotic therapy. In the present trial, clinical seizures were reported in 10 (5%) infants; however, only 1 was confirmed by EEG, and none were thought to be probably or definitely related to meropenem by the site PI. Additionally, 50% of infants with seizures had a CNS condition that could be responsible for the seizures, and we observed no apparent difference in predicted meropenem plasma concentrations in patients with or without seizures. Because a comparator arm was not included in this trial and the number of study participants was relatively small from an epidemiologic standpoint, it is difficult to know if the rate of seizures associated with meropenem is above the background seizure rate for this population. However, among infants admitted to the neonatal intensive care unit, seizure rates of 9% have been previously reported [14], and the cumulative incidence in the most premature infants (<28 weeks GA) is as high as 12%. The majority (>70%) of infants enrolled in this study were <32 weeks GA and critically ill at baseline, which suggests that the seizure rate observed is similar or lower than that reported in prior studies.

The most commonly reported adverse effects of meropenem from previously published pediatric studies are diarrhea (3.3%–4.7%), nausea and vomiting (0.4%–1%), rash (0.8%), glossitis (1%), and oral thrush (1.9%) [11]. In comparison trials, these reactions occurred with similar frequency in the comparison (cephalosporin) group [11, 12]. In our cohort, there were no reports of diarrhea, glossitis, or oral thrush. Only 1 (0.5%) subject was reported to have a rash. Vomiting was reported in 5 (2.5%) infants in this study.

In a review of 6154 patients receiving meropenem in 54 clinical trials (>900 children), meropenem demonstrated a favorable safety profile relative to comparators including cephalosporins, imipenem/cilastatin, and clindamycin/aminoglycoside [15]. Children were given 10–40 mg/kg every 8 hours in the studies reviewed. The incidence of seizures among all subjects was 0.37%, 0.25%, 0.43%, and 0.38% in the meropenem, cephalosporin, imipenem/cilastatin, and clindamycin/aminoglycosides groups, respectively. This finding is not surprising given that meropenem has less affinity than imipenem for γ-aminobutyric acid receptors—the potential target for CNS adverse effects—and has been found to cause less neurotoxicity than imipenem both in animal models and during clinical trials [11, 16]. In addition, among subjects who received meropenem, elevated ALT, AST, alkaline phosphatase, and bilirubin levels were observed in 5.2%, 4.3%, 2.2%, and 0.7%, respectively [15]. In our study, elevation in alkaline phosphatase levels was reported as an AE in 1% of subjects. The trend toward higher alkaline phosphatase and direct bilirubin levels observed in laboratory values collected throughout this trial as standard of care (Table 5) may be explained by selectively obtaining liver function tests only in infants with previously abnormal values or in infants suspected of having abnormal values. Also, many of the infants in this trial were receiving total parenteral nutrition, which may lead to cholestasis [17].

Gastrointestinal complications comprise another potential concern associated with broad-spectrum antimicrobial treatment of neonates. Addition of anaerobic antibiotic coverage has been associated with the development of strictures in a cohort of infants with necrotizing enterocolitis [4]. However, no strictures were reported in this cohort, although our follow-up for strictures was limited to observation through 30 days following the last dose of meropenem.

In conclusion, meropenem was well tolerated in the cohort of critically ill infants with suspected and/or proven intra-abdominal infection. Although our study was not randomized, the overall success rate was 84% (162/192), meeting the definition of therapeutic success. The success rate was highest in more mature infants (≥32 weeks GA; 93% [51/55]). Serious adverse events probably or definitely associated with meropenem were not observed. Collectively, these data support and may inform the development of comparative trials of meropenem in infants with complicated intra-abdominal infections.

Notes

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Potential conflicts of interest. R. Ward has been a paid consultant to Wyeth and has supervised the pediatric studies for Wyeth, TAP, Eisai, and AstraZeneca. J. Sullivan has been an investigator for or received grants from Wyeth Research, TAP Pharmaceuticals, Johnson & Johnson, and AstraZeneca. D. Benjamin has received research grants from Astellas Pharma US, AstraZeneca, and UCB Pharma and has also served as a consultant for Astellas Pharma US, Biosynexus, Cubist Pharmaceuticals, Johnson & Johnson Pharmaceutical Research & Development, Merck & Co, Pfizer, and The Medicines Company. P. Smith has received a research grant from CV Therapeutics, Inc, and has also served as consultant for Astellas Pharma US, CV Therapeutics, Inc, Johnson & Johnson, Pangen, Biostystems, Inc, and Pfizer. All other authors report no potential conflicts.

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