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REVIEW ARTICLE

Doripenem Use in Pediatrics- Learning from Pharmacokinetic Data of Other Carbapenems

Patrick Grove, Tsz-Yin So

Abstract: In 2005, doripenem, the newest carbapenem on the market, was developed by a pharmaceutical company in Japan, and it was recently approved by the United States (US) Federal Drug Administration (FDA) to be used in the adult population. Doripenem is a broad spectrum antimicrobial agent that can be used in many different infections ranging from pneumonia to abdominal infections. Even though doripenem has shown to be safe and efficacious in adults, it lacks pharmacokinetic and safety information in the pediatric population. However, by looking at the pediatric pharmacokinetic data of other carbapenems and a recent multicenter study of doripenem in patients between the age of 3 months and 18 years of age, clinicians can gain a better understanding of how to dose this antimicrobial agent in infants, children, and adolescents.

Key words: doripenem; pediatrics; carbapenems; pharmacokinetic; dosing

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Introduction

Doripenem is the newest carbapenem on the market, and it was recently approved by the US FDA to be used in the adult population. This broad spectrum antibiotic is a potential treatment option for infections such as pneumonia, abdominal infections, and skin and soft tissue infection. A review on carbapenemases was recently published [1]. This article prompts our interest in looking at the effectiveness and appropriate dosing of carbapenems in pediatric patients.

Carbapenems are generally considered as one of the last line antibiotics to be used for infections that are resistant or presumed to be resistant to other more common antibiotics. In pediatrics, carbapenems are not commonly used, and therefore, dosing for pediatric patients tends to lag behind dosing for adults. Currently, doripenem is the only carbapenem that does not have specific pediatric dosing recommendation by the manufacturer, as it is the newest of the carbapenem agents to be released in the U.S. market. In a recent clinical trial, doripenem was

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found to have the lowest minimum inhibitory concentration for 90% (MIC₉₀) of the *Pseudomonas aeruginosa* isolates when compared to other anti-pseudomonal agents including meropenem and imipenem [2]. Doripenem and other carbapenems, however, may not be a good option for multi-drug resistant pseudomonal infections since their MIC₉₀ in such clinical setting is > 64mg/L [3].

Meropenem and imipenem/cilastatin have shown great efficacy in patients with febrile neutropenia and infections in immunocompromised host [4], but data is still limited with doripenem use in these populations, especially in pediatrics. Since doripenem has similar properties as meropenem and that it has better antimicrobial coverage than other carbapenems, doripenem can most likely be used in the populations previously mentioned but further studies need to be performed to assess its efficacy [4]. Nonetheless, there are instances in which doripenem would be a more appropriate choice for an infection in pediatric patients including complicated urinary tract infections or pyelonephritis caused by extended-spectrum beta-lactamase (ESBL) producing bacteria [5,6]. Without specific dosing recommendations, those children may not be treated effectively.

Unfortunately, to date, there are not any published clinical trials that evaluate the efficacy and safety of doripenem in children under the age of 18. Without these trials, it will be impossible to know the true safety of doripenem in children. However, to begin thinking about the appropriate dosing of doripenem in this population, we may look only as far as the other drugs in the carbapenem class. In this way, we could project possible starting doses to test in such trials.

Pediatric Pharmacokinetic Data of Other Carbapenems

Imipenem/cilastatin

Based on published studies, the recommended dose of Primaxin (imipenem/cilastatin) is 15-25mg/kg/dose q6h in patients 3 months to 12 years old. These doses have shown to provide adequate concentrations to treat non-CNS infections in pediatric patients [7-10]. The dosing in patients less than or equal to 3 months of age is based on the patients' weight and age. In infants less than 1 week of age, the dose should be 25mg/kg every 12 hours as compared to those who are 1-4 weeks of age, when the dose should be 25mg/kg every 8 hours. From 4 weeks to 3 months of age, the dose should be 25mg/kg every 6 hours. These patients need to weigh at least 1500 grams for this dosing to be appropriate [11]. Imipenem/cilastatin should not be used in patients (e.g. neonates) with CNS infections because of the

increased risk of seizures with the use of this antibiotic. Since younger pediatric patients (e.g. neonates) may not be developed neurologically, they could be at higher risk of developing seizures when put on this antibiotic [12,13]. It also should not be used in pediatric patients with impaired renal function and weighing less than 30kg as there is not any data in this population.

The pharmacokinetics of imipenem /cilastatin are very similar to that of Merrem (meropenem), and the mean half life is around 1-1.5 hours for patients 2 months to 12 years of age [10]. The volume of distribution of imipenem/cilastatin and meropenem is approximately 0.43L/kg, and the clearance is about 5.63 mL/kg/min. The pharmacodynamics of imipenem/cilastatin were studied in a population of 10-year-olds. The goal was to see the percentage of time the free drug concentration was above the minimum inhibitory concentration (MIC) in gram-negative infections at the predetermined doses. Up to an MIC of 4µg/mL, the percentage of time at the appropriate levels for bacteriostatic or bactericidal activity in gram negative infections was 87.1% and 98.3% at 15mg/kg every 6 hours and 25mg/kg every 6 hours, respectively. The plasma half-life of imipenem/cilastatin is approximately 1 hour, which was also found in a different study [10].

In comparison, imipenem/cilastatin dosing in adults is a little different. The dosing is still based on weight and renal function, but the doses are fixed. The dosing is anywhere between 125-500mg, to be dosed between every 6-12 hours. These doses are dependent on the severity of infection, susceptibility of the organism, weight, and renal function of the patient. Using the comparison of dosing between adult and pediatric patients as young as 3 months old, if the pediatric patient is 20 kg with normal renal function, the dose (25mg/kg/dose) will be the same as the adult dose (500mg) [11,14].

Meropenem

Since imipenem/cilastatin poses a safety concern in younger pediatric patients, meropenem was tested in pediatric patients as an alternative carbapenem with efficacy against highly resistant bacteria and without the dangers associated with imipenem/cilastatin. The safety and efficacy of meropenem in pediatric patients have been studied

in those greater than or equal to 3 months of age. Meropenem dosing for meningitis and intra-abdominal infections has been established in well-controlled pediatric studies. In pediatric patients weighing over 50kg, the dose for intra-abdominal infections is 1 g every 8 hours, and for bacterial meningitis, it is 2 g every 8 hours. In patients greater than or equal to 3 months old and less than 50kg, the dosing for intra abdominal infections is 20mg/kg/dose every 8 hours and for bacterial meningitis is 40mg/kg/dose every 8 hours [7-10]. Doses for neonates were determined in a study of the pharmacokinetics and pharmacodynamics of meropenem in 37 term or preterm neonates. In this study, the goal was to attain levels above the MIC of the infecting organisms greater than 60% of the time. For neonates, 20mg/kg/dose every 12 hours is used for septic infections and 40mg/kg/dose every 8 hours is used for meningitis. At the 20mg/kg/dose, in preterm neonates, this goal was achieved in 95% of cases; and in term neonates, the goal was achieved in 92% of neonates. The population's average volume of distribution, half-life, and clearance were 0.4 L/kg, 2.9 hours, and 0.104L/kg/h, respectively [10,15].

Adult dosing for meropenem is equal to that of pediatric doses in patients that weigh at least 50kg [16,17]. This means that the dosing of meropenem per weight in kg is the same between adults and children up to the maximum dose of 2g every 8 hours or 1g every 8 hours depending on the infection type [12].

Ertapenem

Similarly, there are dosing guidelines for pediatrics based on published studies of Invanz (ertapenem) in patients between 3 months and 17 years of age in two randomized, multicenter trials [18,19]. The first study of 404 patients compared ertapenem 15mg/kg/dose every 12 hours (not to exceed 1 g daily) in patients between 3 months and 12 years of age and ertapenem 1gm daily to those between 13-17 years of age with ceftriaxone 50mg/kg/day. These doses were tested in patients with complicated urinary tract infections, skin and soft tissue infections, and community-acquired pneumonia. The success rates for treatment in the groups were similar meaning the studied doses in pediatrics were appropriate.

In the second study of 112 patients with either intra-abdominal infections or acute pelvic infections, the same doses of ertapenem were compared to ticarcillin/ clavulanate (50mg/kg for children less than 60kg and 3g for those greater than 60kg either 4 or 6 times daily). The efficacy of ertapenem was found to be higher than that of ticarcillin/clavulanate for intra-abdominal infections and equal for acute pelvic infections [20]. This study gives us more evidence showing the appropriate dosing for ertapenem in pediatric patients.

According to a pharmacokinetic study of ertapenem by Mistry et al., "The ertapenem dose of 1 g every day in 13-17 year-old patients and 15mg/kg twice daily in patients 3 months to 12 years of age result in levels $>2\mu\text{g/mL}$ at the midpoint of the dosing interval and pharmacokinetic data is comparable to the standard dose used in adults." Considering that in patients <12 years of age, the half-life of the drug is lower and the clearance of the drug is double that of the clearance in adults, these pediatric dosing recommendations seem appropriate [21].

The adult dosing for ertapenem is very simple at a fixed dose of 1 gm daily for different kinds of infections with different treatment durations. From this information, if the average adult weighs about 70kg, the dose in mg/kg for the average adult is 15mg/kg/day. The dose in pediatrics as young as 3 months is the same at 15mg/kg/dose, although they get 2 doses per day as long as the total dose does not exceed 1 g daily. Ertapenem exhibits nonlinear kinetics and has a terminal half-life of 4 hours [21,22].

Potential Dosing Scheme of Doripenem in Pediatrics

Currently, Doribax (doripenem) only has dosing for adults and only in two types of infections. The indications for doripenem's use include complicated urinary tract infection with pyelonephritis and complicated intra-abdominal infection, and the dosing for both of these types of infections is 500mg every 8 hours. The only difference between the treatments of these two infections is the duration of treatment [23].

In certain instances, in order to estimate a pediatric dose of a medication that has recommendations in an adult, we can divide the

Table 1: Dosing, pharmacokinetic data, and antimicrobial spectra of carbapenems [4-8, 10, 12, 15, 16, 23, 29-32]

Medications	Dose	t _{1/2} (hr)	V _d (L/kg)	Clearance (mL/kg/min)	Specific Antimicrobial Spectra ^a
Imipenem/cilastatin		1-3	0.36-0.67	2.3-6	Enterococcus faecalis, L. monocytogenes, Ps. aeruginosa, P. multocida, Actinomyces
< 1 wk	25mg/kg q12h				
1-4 wk	25mg/kg q8h				
1 – 3 mo	25mg/kg q6h				
≥ 3 mo	15-25mg/kg q6h				
Meropenem		1-3	0.43-0.48	1.8-5.63	L. monocytogenes, Ps. aeruginosa, B. cepacia
Neonates	20mg/kg q12h (40mg/kg q8h for meningitis)				
3 mo and <50 kg	20mg/kg q8h (40mg/kg for meningitis)				
≥50 kg	1g q8h (2g/dose for meningitis)				
Ertapenem		2.5-4	0.2	2.1-3.3	P. multocida, Actinomyces, no pseudomonal coverage
3 mo – 12yr	15mg/kg q12h				
≥ 12yr	1g qday				
Doripenem		0.9-1.1	0.22-0.46	3.1-6.5	Ps. aeruginosa (best MIC ₉₀ compared to other carbapenems)
3 mo - <2yr	10mg/kg q8h ^b				
≥ 2yr	15mg/kg (max 500mg/dose) q8h ^b				

V_d = Volume of distribution; t_{1/2} = half life

^a These are antimicrobial spectra that are different from other carbapenems.

^b Proposed dosing interval based on comparisons of pediatric and adult pharmacokinetic data on doripenem. Further studies need to be performed to validate these dosing schemes.

adult dose by 70kg to find the dose in mg/kg. For example, amlodipine is dosed 5-10mg in adults and the recommended dose for children under 6 years old is 0.05-0.13mg/kg/day, which is almost exactly the adult dose divided by 70kg. Following that logic, for an average adult patient, the doripenem dose is about 7mg/kg. This interpretation is based on the assumption that the maximum dose is not 1500mg/day. If the maximum dose is 1500mg/day, then the actual dose in mg/kg of doripenem may need to be much

higher than 7mg/kg/dose in the pediatric population.

The pharmacokinetic and pharmacodynamic properties of doripenem were studied in 56 adult patients [24]. In this study, the mean half-life for doripenem was about 1-1.2 hours and did not vary based on infusion time. The mean clearance for the 56 subjects was approximately 10L/hr and based on an average weight of 70kg, the mean clearance was 0.143 L/kg/h. The mean volume of distribution at steady state for doripenem was

measured at 14-18 L or 0.2 to 0.26 L/kg, based on the same average weight. These values were consistent with all doses and all infusion times. The pharmacokinetics of doripenem in this study are described as linear at all doses studied. The percentage of time greater than the MIC was higher in the doses of doripenem administered over 4 hours than those administered over 0.5 or 1 hour, which supports the use of extended infusion of doripenem in adult patients [25]. Extended infusion of doripenem has also been shown to exert improved efficacy against certain strain of *Pseudomonas* isolates when the MIC₉₀ is > 4mg/L [26], and it is non-inferior to regular infusion of imipenem/cilastatin in terms of clinical cure rate (68.3% vs. 64.2%) but superior in terms of microbiological cure rate (65% vs. 37.5%) [27].

There was one multicenter, open-label, parallel group, single-dose study in pediatric patients between the age of 3 months and 18 years of age that was designed to assess the pharmacokinetics of doripenem [28]. In this study, fifty children were enrolled and stratified into 4 age groups from 3 months to <2 years of age (12), from 2 years to <6 years of age (13), from 6 years to <12 years of age (13), and from 12 years to <18 years of age (12). Of this population, 46 children were included in the pharmacokinetic analysis. The first age group received 10mg/kg and the other three age groups received a 15mg/kg dose. The measured peak plasma concentrations in the four groups plus a group of healthy adult subjects were 16.7, 26.1, 29.1, 18.9, and 23.5µg/mL, respectively. The times to peak concentration were 1.00, 1.00, 1.00, 0.98, and 1.00 h in the five groups respectively. Calculated areas under the curve (AUCs) for the five groups were 29.8, 40.6, 44.8, 31.1, and 36.0µg·hr/mL, respectively. The five groups had half-lives of 1.01, 0.937, 0.919, 0.944, and 1.14 h, respectively. The volumes of distribution at steady state in the five groups were 0.462, 0.393, 0.350, 0.326, and 0.219 L/kg, respectively. Finally, the clearances in the five groups were as expected increasing minimally from the first to second age group and then decreasing with age. The values for clearance were 6.09, 6.46, 6.14, 5.15, and 3.07mL/kg/min, respectively.

Another important factor that was analyzed in the study was the percentage of doses that achieved

35% of time above the MIC. For the MIC of 2µg/mL, the only group that did not achieve 100% of the time above the MIC was the 6 to less than 12-year-old, group who reached 90.9% of the time above the MIC. However, for the MIC 4µg/mL, in the groups from 3 months to < 2 years, 2 years to < 6 years, 6 years to < 12 years, and 12 years to < 18 years, the percentage of doses that achieved 35% of the time above the MIC were 16.7%, 53.8%, 81.8%, and 10.0%, respectively.

If we look at the peak and AUC of the patients between 3 months and 2 years of age, who were receiving 10mg/kg, we see some disparities that may warrant discussion on higher doses in these patients. The differences between the peaks and AUCs seen in the group consisting of patients 3 months and < 2 years of age and the group between the ages of 2 and < 6 years old were quite distinct. The peak in the younger group was about two-thirds of that in the older group and the AUC was about three-fourths of that in the older group. As the dose in the younger group was two-thirds less than that in the older group, it begs the question of why the higher dose of 15mg/kg could not be used in the younger children. With a half-life, clearance, and volume of distribution that was essentially the same in the two groups, it seems like a higher dose would not necessarily be more dangerous in these younger patients. Furthermore, the higher dose may help achieve a better percentage of doses with 35% of the time above the MIC and therefore, confer better efficacy. Table 1 gives a comparison among the different carbapenems (e.g. half-life, volume of distribution, etc).

Conclusion

At this point, there is at least one study that shows safety and efficacy of doripenem in pediatric patients as young as 3 months of age. Given the measured values and the close proximity to the values seen in healthy adult patients, the 10mg/kg/dose of doripenem for those 3 months to 2 years and 15mg/kg/dose for those 2 to 18 years old used in this study seem to be appropriate. More Phase III clinical trials need to be conducted before doripenem can be used safely in the pediatric population.

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