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PHARMACOKINETICS OF POLYMYXIN B IN AN INFANT WITH MULTIDRUG-RESISTANT *KLEBSIELLA PNEUMONIAE* BACTEREMIA

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Abstract

We report our experience with a 9-month-old infant treated with intravenous polymyxin B for multidrug-resistant *Klebsiella pneumoniae* bacteremia. Serial blood samples were obtained at steady state and serum drug concentrations were determined using a validated liquid chromatography-mass spectrometry method. The elimination half-lives of polymyxin B1 and isoleucine-polymyxin B1 were found to be 3.1 and 4.7 hours, respectively.

Keywords

pediatric dosing; *Klebsiella pneumoniae* bacteremia; multidrug resistance; polymyxin B

An emerging mechanism of multidrug resistance in *Enterobacteriacae* spp. is the serine-based carbapenemases (eg, KPC). It is of great concern as viable therapeutic options are severely limited.[1] Polymyxin B is increasingly used in this clinical situation, despite a limited understanding of its pharmacologic properties.[2] There is a paucity of polymyxin B pharmacokinetic data in both adults and children, and optimal dosing of polymyxin B in pediatric patients is unknown. We report our pharmacokinetic observations in a 9-month-old infant treated with intravenous polymyxin B.

CASE REPORT

A 9-month-old girl, born at 24 weeks of gestational age was admitted to the pediatric intensive care unit for treatment of acute hypoxemic respiratory failure. She was a

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resident of a long-term care facility due to multiple complications of prematurity, including grade I intraventricular hemorrhage, chronic lung disease, gastroesophageal reflux, tracheolaryngomalacia requiring tracheostomy, and volvulus with small bowel obstruction requiring bowel resection and ileostomy.

On admission, she had fever (39.2°C), hemodynamic instability, and significant oxygen requirements with 100% FiO_2 to maintain oxygen saturation above 88%, necessitating therapy with high frequency oscillatory ventilation. A chest radiograph showed bilateral hazy opacities that could have represented bronchial aspiration. Laboratory results included white blood cell count ($12.8 \times 10^3/mm^3$ with 59% neutrophils and 24% bands), elevated C-reactive protein (16.8 mg/dL), normal creatinine, and hypoalbuminemia (2.4 g/dL). Blood and urine cultures were negative. On day 2 of hospitalization, a bronchoalveolar lavage was performed and cultures were negative for bacteria and fungi. However, a culture from an endotracheal aspirate yielded *Acinetobacter baumannii* susceptible to piperacillin/tazobactam (minimal inhibitory concentration [MIC] = <4 μg/mL). She completed a 10-day course of piperacillin/tazobactam therapy with significant improvement in respiratory status.

On day 14 of hospitalization, she had recurrence of fever (39°C) with elevated white blood cell count and C-reactive protein value. No increase in the respiratory requirements or hemodynamic instability was noted. An endotracheal culture yielded *Stenotrophomonas maltophilia* and *Pseudomonas aeruginosa*. Urine culture was negative. The blood culture grew multidrug resistant *Klebsiella pneumoniae*. Initial empiric treatment consisted of intravenous meropenem. The *Klebsiella* was resistant to piperacillin/tazobactam (MIC = >128 μg/mL, resistant-R), ampicillin/sulbactam (MIC = >32 μg/mL, R), aztreonam (MIC = >64 μg/mL, R), ceftazidime and ceftriaxone (MIC = 16 μg/mL, R), meropenem (MIC = 32 μg/mL by E-test, R), and susceptible to polymyxin B (MIC = 1.5 μg/mL by E-test, sensitive-S) and amikacin (MIC = <2 μg/mL, S). On the basis of these studies, meropenem was discontinued and intravenous polymyxin B at 1.5 mg/kg/dose every 12 hours (weight of 4 kg) in combination with amikacin once daily was started. She remained persistently febrile and the blood cultures were persistently positive for 3 days (total days of bacteremia were 6). As a result, the dose of polymyxin B was increased to 2 mg/kg/dose every 12 hours. An echocardiogram was negative for vegetations. Cerebrospinal fluid values were normal and the culture was sterile. She defervesced within 24 hours and completed a 2-week course of polymyxin B. Subsequent blood cultures were sterile. Her inflammatory indices normalized within 10 days and her renal function remained normal.

METHODS AND RESULTS

Polymyxin B sulfate (lot number 204475; APP Pharmaceuticals, Schaumburg, IL) was given as an intermittent intravenous infusion initially at 1.5 mg/kg every 12 hours infused during 90 minutes, and subsequently 2 mg/kg every 12 hours in 60 minutes. Serial blood samples were obtained at steady states (after 3 doses). The serum samples were assayed in duplicate for polymyxin B concentrations using a validated liquid chromatography-tandem mass spectroscopy method[3]; which was modified to detect various major polymyxin B components concurrently.[4] The proportions of polymyxin B1 and isoleucine polymyxin B1 in polymyxin B (polymyxin B sulfate) were assumed to be 73.5% and 8.6%, respectively,

as previously reported.[5] A one-compartment linear model was fit to the concentration-time profiles to derive the best-fit pharmacokinetic indices. All model fittings were performed with the ADAPT II program.[6] Using the best-fit parameter estimates, elimination half-life was derived by Ln 2 divided by eliminating rate constant, clearance was derived by elimination rate constant times volume of distribution, and area under the concentration-time curve over 24 hours was derived by daily dose divided by clearance. Serum protein binding of polymyxin B was not determined.

Both polymyxin B1 and isoleucine polymyxin B1 (>80% of total polymyxin B content) were satisfactorily detected in the serum samples. The overall model fits to the data were reasonable (r^2 ≥0.92, Fig., Supplemental Digital Content 1, http://links.lww.com/INF/A710), and the best-fit pharmacokinetic indices are as shown in Table 1.

DISCUSSION

Polymyxin B is increasingly used for the management of difficult-to-treat infections. However, dosing of polymyxin B is mostly based on convention or anecdotal experience, rather than the results of well-designed pharmacokinetic studies. The conventional weight-based dosing strategy in adults may not be directly applicable in infants, as infants often have a higher percentage of total body water. For a hydrophilic drug, lower drug concentrations would thus be expected if the same mg/kg dose is used. With increasing use of polymyxin B, an optimal treatment and dosing strategy is needed to provide a balance between efficacy and safety in the setting of increasing multidrug-resistant pathogens.[7,8]

For optimal therapy, the pharmacokinetic data should be considered in light of pharmacodynamics. Most pharmacodynamic data available for polymyxin B apply to *P. aeruginosa*; the agent was shown to demonstrate concentration-dependent killing and area under the concentration-time curve/MIC appeared to be most closely linked to bactericidal activity.[9] It is unknown whether these data can be extrapolated to *Klebsiella* spp. On the basis of this knowledge the dose in our patient was increased.

To the best of our knowledge, this is the first case reporting the pharmacokinetics of polymyxin B in an infant. Our limited data did not allow us to adequately explore complex pharmacokinetic profiles. Based on our simple analysis, the elimination half-life of polymyxin B1 was found to be 3.1 hours, which was shorter than those previously observed in adults.[3] In addition, the pharmacokinetics of isoleucine polymyxin B1 appeared to be slightly different, but such a conclusion would be premature with only limited observations in 1 patient. More studies are warranted to define the disposition of this agent in pediatric patients.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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TABLE 1.

Pharmacokinetic Indices of Polymyxin B1 and Isoleucine Polymyxin B1

	Polymyxin B1	Isoleucine Polymyxin B1
Ke (h^{-1})	0.2258	0.1462
$T_{1/2}$ (h)	3.07	4.74
V (L)	1.345	1.645
V (L/kg)	0.336	0.411
Cl (L/h)	0.304	0.241
AUC_{24} (mg.h/L) (1.5 mg/kg q12 h)	29.042	4.291
AUC_{24} (mg.h/L) (2 mg/kg q12 h)	38.722	5.721
Model fit (r^2)	0.98	0.92

The proportions of polymyxin B1 and isoleucine polymyxin B1 in polymyxin B (USP) were assumed to be 73.5% and 8.6%, respectively.

Ke indicates eliminating rate constant; $T_{1/2}$, elimination half-life; V, volume of distribution; Cl, clearance; AUC_{24}, area under the concentration-time curve over 24 hours.