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Steady-state Pharmacokinetics of Polymyxin B in Overweight and Obese Individuals

Study Purpose and Rationale

Polymyxin B (PMB) is a lipoprotein antibiotic with bactericidal activity against Gram-negative organisms that was developed for clinical use in the 1950s and 60s. However, its clinical utility declined with the subsequent development of the less toxic aminoglycosides and ß-lactams (Evans, Feola et al. 1999). With the recent emergence of multidrug resistant (MDR) gram-negative bacteria, such as *Pseudomonas aeruginosa* and *Acinetobacter baumannii*, and no new antibiotics to combat these resistant strains, there has been renewed interest in parenteral PMB as a last therapeutic option for MDR gram-negative bacterial infections (Evans, Feola et al. 1999; Livermore 2004; Zavascki, Goldani et al. 2007). Although its use is increasing, knowledge of PMB's pharmacokinetics and pharmacodynamics remains limited, both because the drug has not been widely used for the past 50 years and because it never underwent the rigors of contemporary drug testing. Indeed, the data on the pharmacokinetics of PMB is derived largely from studies of intramuscular rather than intravenous administration, which were conducted prior to 1980, and two modern studies, with variable and inconsistent results that require further clarification. Thus, the information on which current dosage regimens are based is tenuous, at best (Evans, Feola et al. 1999; Tam, Schilling et al. 2005; Zavascki, Goldani et al. 2007).

In addition, there is growing evidence that these regimens may be inadequate. The antibacterial activity of PMB is concentration-dependent, with its efficacy correlating with a high ratio of Area Under the Curve (AUC) to the Minimum Inhibitory Concentration (MIC); therefore it is important to administer adequate concentrations of the drug to ensure sufficient bactericidal activity. At the same time, the nephrotoxicity and neurotoxicity of PMB, its two primary toxicities, are also believed to be dose-dependent, although this relationship has not been clearly quantified (Evans, Feola et al. 1999). Thus, an optimal dosage regimen for PMB must balance both of these considerations. While acquired resistance to PMB is currently rare in MDR-resistant gram-negative bacteria, reported cases of resistant strains, as well as the MICs of PMB for MDR gram-negative bacteria, have increased in the past ten years, suggesting that existing dosing regimens may be inappropriate (Urban, Mariano et al. 2001; Reis, Luz et al. 2003; Antoniadou, Kontopidou et al. 2007; Falagas and Bliziotis 2007; Zavascki, Goldani et al. 2007). As there are no new antibiotics for these MDR gram-negative bacteria in the drug discovery and development pipeline, it is essential to design dosage regimens based on the specific pharmacokinetics of PMB in order to maximize its clinical efficacy and minimize the development of resistance to it (Livermore 2004; Tam, Schilling et al. 2005). Improved understanding of the pharmacology of PMB may facilitate the design of dosage regimens that improve patient outcomes while minimizing resistance.

In an effort to maximize the clinical efficacy of this increasingly relevant antibiotic, there have been several steps taken here at CUMC to address our poor understanding of PMB pharmacokinetics. First, although several methods have been developed to analyze the composition and activity of PMB, few of these are suited for the efficient analysis of clinical samples [(Howlett and Selzer 1967; Stretton, Carr et al. 1969; Haemers and De Moerloose 1970; Jacobson, Koch et al. 1972; Kotula, Piekut et al. 1974; Kang, Van Schepdael et al. 2000; Orwa, Van Gerven et al. 2000; Lemus Gallego and Perez Arroyo 2001; Srisom, Liawruangrath et al. 2007; Cao, Ali et al. 2008; Kwa, Lim et al. 2008; Cheng, Liu et al. 2010; Gobin, Lemaitre et al.

2010)]. To enable the clinical studies needed to further characterize the pharmacokinetics of PMB, a rapid high performance liquid chromatography-mass spectrometry (LC/MS) assay that quantifies PMB1 and B2, the two primary components of PMB, in human plasma was developed and validated (unpublished data). In parallel with these efforts, a retrospective study of the incidence and predictors of nephrotoxicity among patients who received intravenous PMB for at least 3 days during 2010 at Columbia University and Weill Cornell Medical Centers was undertaken. It was found that a higher body mass index (BMI) was associated with an increased risk of acute kidney injury (AKI) during PMB treatment. Specifically, the group of individuals who developed AKI during their treatment course had a significantly higher BMI than those who did not develop AKI. Further statistical analysis revealed that the percent those patients with a BMI $\geq$25 kg/m^2 who developed AKI was 73 percent, compared to 47 percent of those patients with a BMI <25 kg/m^2 ($p = 0.045$, Ellman 2011). The increased incidence of nephrotoxicity among individuals with higher BMIs suggests that the pharmacokinetic parameters of PMB may be different in the overweight, obese, and volume-overloaded, predisposing these individuals to toxicity within current dosing regimens. Many drugs have specific dispositions in obese individuals that require dosage adjustments to either maintain therapeutic levels or avoid toxicity (Hanley, Abernethy et al. 2010).

In order to clarify the increased rates of toxicity observed among overweight and obese individuals receiving PMB, we propose a study comparing the pharmacokinetics of intravenous PMB in normal weight individuals to those in overweight and obese individuals. Currently, PMB is dosed according to total body weight (TBW). As the nephrotoxicty associated with PMB has been characterized as dose-dependent, we hypothesize that there is overall greater drug exposure in overweight and obese individuals, manifested quantitatively by a higher AUC. This may be due either to limited distribution of the drug into adipose tissue, resulting in higher drug levels as a result of the current per-kilogram dosing, or due to an increased volume of distribution (V_d) but decreased clearance (Cl) of PMB in these individuals, resulting in drug accumulation and higher serum levels, particularly later in the treatment course. Of note, the latter pattern was observed in a recently published pharmacokinetic study of colistin (Garonzik S.M., J. Li, et al 2011). Through the proposed study, we hope to determine whether dosing by lean body weight (LBW) or ideal body weight (IBW) rather than TBW may be more appropriate. Moreover, we believe that characterizing the pharmacokinetics of PMB in these two populations will further clarify the pharmacologic understanding of this drug and the particular rationale behind its dosing in all populations.

Study Design and Statistical Procedures

Power calculations: If we suppose that obese individuals have greater drug exposure than non-obese individuals, then we can also hypothesize that obese individuals have a larger AUC than non-obese individuals, as this is the pharmacokinetic parameter most often used to estimate total drug exposure. There is no data in the literature that describes a therapeutic range for PMB AUC. Therefore, we were unable to use PMB AUC data to calculate the sample size needed to detect a clinically relevant increase in this parameter. Like PMB, daptomycin is a lipoprotein antibiotic that has been found to have increasing serum levels with increasing BMI. In a recent study, the daptomycin AUC for obese individuals was calculated to be 375.1 $\pm$ 61.32 μg•h/ml compared to 268.91 $\pm$ 34.88 μg•h/ml in non-obese individuals (Dvorchik and Damphousse

2005). This data was used to calculate sample size for this study. Thus, with a sample size of 12 individuals, and assuming a standard deviation of approximately 50, we will have 80% power to detect a change in AUC of 106 μg•h/ml. In other words, our study will be powered to detect a difference between the two groups equivalent to approximately two standard deviations. To ensure proper matching between the groups, our target enrollment will be 16 patients.

Design: This will be a prospective observational, open-labeled pharmacokinetic study conducted in 12-16 individuals receiving intravenous PMB alone or in combination with other antibiotics. We will recruit 6-8 individuals who have a BMI of at least 25kg/m^2, which classifies them as either overweight or obese according to the International Classification of BMI, and 6-8 normal-weight individuals with a BMI between 18 and 24.99kg/m^2, matched for age, sex, baseline serum creatinine, and duration of PMB therapy prior to enrollment.

Pharmacokinetic and statistical analysis: We will use the compartmental model for polymyxin B1 and B2 previously developed using MW\Pharm (Mediware, Groningen, The Netherlands) on n=6 patients, limited sampling and a maximum a posteriori Bayesian fitting method embedded within MW\Pharm to estimate the compartmental pharmacokinetic parameters for each patient (V_d, k_{elm}, unpublished data). From these parameters, clearance (Cl), AUC, and biological half-life ($t_{1/2}$) will be determined. Descriptive statistics will be used where appropriate. Student's t-test (unpaired) or the Mann-Whitney U test will be used to compare continuous data, with a P value of <0.05 defined as statistically significant. Fisher's exact test will be used to compare demographic variables of the two groups. Regression analysis will be used to compare calculated pharmacokinetic parameters with TBW, IBW [calculated as 45.4kg+0.89(height in cm - 152.4) for men, and 49.9kg+0.89(height in cm - 152.4) for women], and LBW [calculated as (9270xTBW)/(6680 + 216 x BMI) for men, and (9270xTBW)/(8780 + 224 x BMI) for women].

Study Procedures

A complete medical history, examination, serum chemistry, and hepatic function panel will be obtained for each patient at baseline, if not already done so as a part of their medical care. Venous blood samples will be taken on or after Day 3 of PMB therapy at the following intervals: -0.5 hours prior to infusion; 1h (end of infusion), 0.5, and 1h after start of infusion in case of a 1h infusion; 2h (end of infusion), 2.5, and 3h after start of infusion in case of a 2h infusion; 3h (end of infusion), 3.5, and 4h after start of infusion in case of a 3h infusion. At each time point, 3ml will be collected in a 6ml pink-top (EDTA containing) blood collection tube. Samples will be centrifuged, and plasma will be frozen at -70°C until sample processing. Concentrations of PMB1 and B2 in plasma will be measured using the LC-MS assay developed and validated here at CUMC (unpublished data). Additional venous blood samples will be obtained at -0.5h prior to infusion and 0.5h time points to determine the protein binding of PMB using a centrifree device (Amicon Inc, Beverly, MA).

Study Drugs or Devices

Intravenous PMB will be administered for its approved indications to patients at the discretion of their treating physicians, in accordance with the NYPH-CUMC drug dosing guidelines (Clinical References: Antibiotic Dosing Guide 2010).

Study Questionnaires

Not applicable

Study Subjects

Inclusion criteria:
Age 18 years and older
Receiving intravenous PMB
BMI $\geq$18kg/m^2

Exclusion criteria:
Age less than 18 years
CrCl < 30ml/min at PMB initiation (calculated by Cockcroft-Gault equation)
Life expectancy less than 96 hours
Pregnancy
Inability to consent or lack of a legally authorized court appointed representative for consent
Concurrent use of aerosolized colistin or PMB
Participation in another study

Recruitment

All patients at NYPH-CUMC who are prescribed intravenous PMB will be evaluated according to the study inclusion/exclusion criteria. Eligible individuals will be identified through pharmacy records and active PMB medication orders in the electronic medical record, and their physician will be contacted to obtain permission from the patient to discuss study participation. Informed consent will be obtained from participants or from their legally authorized representatives.

Confidentiality of Study Data

All patients included in the study will be identified by a unique code unrelated to their personal identifiers. Research data and subject identifiers will be either password-protected on a secure computer or stored in a locked file cabinet in a non-public area. Only authorized study personnel will have access to these records.

Potential Risks

Administration of PMB is associated with both adverse renal and neurological effects. Reported rates of nephrotoxicity, which typically involves rising blood urea nitrogen and serum creatinine levels, albuminuria, and anuria, range from 0 to 36 percent. Neurotoxicity is less common than nephrotoxicity, with rates between 7 and 30 percent reported in the literature. It generally manifests as paresthesias, dizziness, vertigo, visual disturbances, hallucinations, or seizure. In rare cases, PMB has been associated with neuromuscular blockade that resulted in respiratory paralysis, although a case has not been reported in the past 15years. Both nephrotoxicity and neurotoxicity are usually reversible following discontinuation of the drug. Patients may also experience fever, rash, and pain at the IV site following drug infusion (Falagas ME and Kasiakou SK 2006). As we will be recruiting patients for this study who have been prescribed PMB by their physician, the only added risk associated with involvement in our study is that associated with venipuncture.

Potential Benefits

Study subjects will likely experience no direct benefit from this study. The information provided by their participation will contribute to a more complete understanding of the pharmacokinetics of intravenous PMB and thereby assist in the design of more rational dosing regimens for this drug.

Alternatives

Patients will be treated according to the standard of care as determined by their treating physician. No treatment alternatives will be offered as a part of this study. The alternative to consenting to study participation is refusal to participate.

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