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Antimicrobial Pharmacokinetics and Pharmacodynamics in the Treatment of Nosocomial Gram-negative Infections

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Abstract

While infections due to multidrug-resistant Gram-negative organisms overwhelm hospitals worldwide, preservation of current antimicrobial treatment options becomes paramount in the face of dwindling development of novel antibiotics. There is extensive data demonstrating that application of pharmacokinetic/pharmacodynamic principles improves the possibility of enhancing clinical and microbiological outcome. There is expanding evidence demonstrating that unfavorable clinical outcomes and antimicrobial resistance may be suppressed when specific pharmacokinetic/pharmacodynamic targets are attained for beta-lactam and carbapenem antibiotics. This paper highlights pertinent studies that contribute to the principles and application of these principles.

Keywords: Pharmacokinetics; Pharmacodynamics; Gram-negative; Resistance; Beta-lactam; Carbapenem; Continuous, Extended

Introduction

Multiple surveillance studies from across the globe report widespread multi-drug resistant Gram-negative pathogens [1-5]. Multi-drug resistance in *Pseudomonas aeruginosa*, *Acinetobacter* species, *Escherichia coli*, and *Klebsiella* species limits the availability of antimicrobial options in the treatment of these infections [6,7]. Regardless of antimicrobial selection and intervention strategies, clinical outcome of these infections remain undesirable in the form of potential extended length of stay, extended drug exposures leading to adverse effects, or mortality [8-11]. The challenges of this clinical scenario are not only in management of individual infections at the patient level but also in wide-spread antimicrobial use and application at institution and geographical levels to curtail resistance. Antimicrobial stewardship programs are focused to address the need for prudent and optimal use of antibiotics at institution levels [12-14]. These programs have demonstrable impact on selective use of antimicrobials, however, little progress on ameliorating resistance rates are currently observed [15]. During an era where there is a lack of new antimicrobials and antimicrobials with novel mechanisms of action, there is an obvious need for heightened attention to dosing current antibiotics to optimize their efficacy and to curtail resistance development. There has been an increase in pharmacokinetic/pharmacodynamic (PK/PD) investigations of current and old antimicrobials in the past two decades; however, the translation of this knowledge to the bedside is limited by sparse prospective clinical data and the need for more research in specific antimicrobial applications. Clinicians must resort to the collective interpretation of pharmacokinetic properties, in-vitro data, experimental simulations, animal studies, and retrospective evaluations to implement dosing strategies for a variety of infections. It is critical that clinicians optimize therapy both to maximize clinical outcomes and to minimize the risk of resistance. This review will primarily focus on the application of PK/PD principles in the treatment and prevention of gram-negative resistance with commonly used antimicrobials.

PK/PD Principles

The pharmacokinetics/pharmacodynamics of an antimicrobial can be described as the complex relationship between the pharmacokinetic exposure characteristics of an antimicrobial in a human to the effect of that antimicrobial [16,17]. The pharmacokinetic exposure has been typically characterized by steady-state parameters such as peak concentration, the duration that concentrations remain at specific levels, and the area under-the-curve while the antimicrobial effect has been typically characterized by reduction of bacterial colonies in attempts to quantify magnitudes of this relationship. This relationship can be possible when there is an association between drug exposure characteristics to antimicrobial potency such as the minimum inhibitory concentration (MIC). Therefore, antimicrobial dosing and regimens may be designed to achieve exposure targets that are associated with a higher probability of desirable microbiological and clinical outcomes [17].

The three practical PK/PD parameters that have been mainly investigated are the ratio of peak concentration to the MIC (Cmax/MIC), the time during which the concentration exceeds the MIC as a percentage of the dosing interval (%T>MIC), and the ratio of the 24-hour area under the concentration-time curve to the MIC (AUC/MIC or AUIC). AUC is the most measured parameter for many antimicrobials as it can be regarded as the entire exposure of a drug over a given time period. Furthermore, most antimicrobials exhibit linear pharmacokinetics where the AUC is directly proportionate to dose, the most easily manipulated component of an antimicrobial regimen. The peak concentration and the concentration over time can independently affect the AUC. Consider the example of a concentration-time profile of a drug where all PK parameters (peak concentration, absorption rate, time) remain constant with the exception of clearance. Decreasing the rate of clearance of a drug over the same time period increases concentrations throughout the period, thereby, increasing the AUC

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(and AUC/MIC) and potentially durations that concentrations remain above a threshold (as in the %T>MIC). Thus certain antimicrobials may be linked with both AUC/MIC and another parameter, but one parameter typically prevails with a relatively higher association. Animal and *in vitro* experimental models have demonstrated that this interdependence can be addressed with dose-fractionated approaches [16,18].

The application of each of these PK/PD parameters varies according to the microbial killing characteristics of different antimicrobial drug classes. Antimicrobials that exhibit increased bacterial kill with increasing concentrations are categorized as concentration-dependent drugs. Antimicrobials such as aminoglycosides, fluoroquinolones, and daptomycin exhibit increasing bactericidal activity as concentrations increase with relatively little dependence on duration of exposure. The PK/PD parameters, Cmax/MIC or AUC/MIC ratio, logically correlates with their activity [19-21]. Conversely, antimicrobials that reach maximal killing early in the presence of low concentrations within clinically achievable ranges and with higher dependence on duration of exposure, are categorized as concentration-independent or time-dependent antimicrobials. Antimicrobials such as beta-lactams, carbapenems, linezolid and tigecycline are considered time-dependent drugs whose activity is maximized as the duration that their concentrations remain above a multi-fold of the MIC (T>MIC) is extended [22-24].

Negri et al. was one of the first investigators to demonstrate that the selection of resistant bacteria is associated with antimicrobial concentrations [25]. These investigators hypothesized that there is a selection window of concentrations in which there is a higher potential for selection of strains with increased levels of resistance. This concept soon translated to the 'mutant prevention concentration' (MPC), which describes the lowest antimicrobial concentration that is able to prevent the growth of the least susceptible single-step mutant. Therefore, the mutant selection window describes the concentration range between the MPC and the MIC of the more susceptible sub-population of a given organism [26]. At this point, several experimental models have utilized this pharmacodynamic endpoint and there is a need for further determination of the application of this resistance measure in experimental and clinical evaluations.

Antimicrobial Resistance

The prevalence of antimicrobial resistance is threatening the human race on a global level. The World Health Organization has labeled this critical issue as one of the three greatest threats to human health [27-29]. There is justified concern over the increased morbidity and mortality in patients with infections due to antimicrobial-resistant gram-positive, gram–negative, fungal, and viral pathogens. The overwhelming prevalence of resistant gram-positive organisms has resulted in the development of several potent and efficacious antimicrobials in the forms of linezolid, daptomycin, tigecycline and ceftaroline to battle infections caused by methicillin-resistant *Staphylococcus aureus* (MRSA) or vancomycin-resistant *Enterococci* (VRE) [30-32]. Tigecycline and ceftaroline are broad-spectrum antimicrobials that exhibit activity against gram-negative pathogens as well. However, there is an absence of new antimicrobials with novel mechanisms of action and narrow spectrum of activity against resistant-gram-negative pathogens. This deficiency necessitates heightened assessment of PK/PD characteristics of ubiquitous antimicrobials that are used both broadly and specifically for nosocomial gram-negative infections: beta-lactams (i.e. piperacillin/tazobactam, cefepime) carbapenems (i.e. meropenem, doripenem) [33].

Beta-lactams

Beta-lactam-resistant organisms have been reported in the literature as far back as the 1950s following the development of penicillin, as well as prior to its introduction into clinical use [34]. Predictably, the introduction of cephalosporins and other broad-spectrum beta-lactams was followed by the same timeline of events [35-37]. Of greater concern is the increasing prevalence of extended-spectrum beta-lactamases (ESBL) in *Pseudomonas* species, *Acinetobacter* species, and *Enterobacteriaceae* that render current beta-lactam antimicrobials useless. A worldwide survey in 2004 collected 6156 gram-negative isolates from patients with intra-abdominal infections in 28 different countries. The overall rate of ESBL production was 17% among *K pneumoniae* and 10% among *E coli* isolates [38]. Similar results were reported by the Tigecycline Evaluation and Surveillance Trial global surveillance study in 2007 [39].

Numerous *in vitro* and *in vivo* investigations confirm that T>MIC is widely regarded as the main parameter that describes the pharmacodynamic killing activity of beta-lactam antibiotics. The %T>MIC required for bacteriostasis and bactericidal activity for penicillins and cephalosporins is 30% and 50% and 35-40% and 60-70%, respectively [16,22,40,41]. Evidence for %T>MIC endpoints for beta-lactams that prevent the development of resistance in Gram-negative organisms is currently sparse. For example, one *in vivo* experimental study reported that resistant strains of *Pseudomonas aeruginosa* were only detected in those animals receiving cephalosporins in which the %T>MIC was less than half of the dosing interval [42]. Until further evidence becomes available, it would be prudent to employ dosing regimens designed at achieving concentrations greater than 4 times the MIC for extended intervals to maximize the likelihood of eradicating entire bacterial populations that may include resistant sub-populations [43,44].

It has been suggested that bacteriostasis and bactericidal-based endpoints may not be adequate to treat serious infections [45,46]. Recent retrospective clinical data for critically ill patients suggest higher and longer antimicrobial exposures than those reported in experimental studies [47,48]. McKinnon et al. demonstrated that patients receiving a cephalosporin for serious infections with %*T*>MIC of 100% had significantly better clinical and bacteriological outcomes than patients with %*T*>MIC of <100%. Consequently, maintaining concentrations above the MIC for 90-100% of the dosing interval with continuous infusion (CI) or extended-infusion (EI) of antimicrobials has been suggested to ensure that minimum PK/PD targets are achieved [47,49,50]. Alternatively, time-dependent antimicrobials could be dosed more frequently to achieve higher %T>MIC but with obvious practical and convenience issues. Targeting a multi-fold of the MIC for extended durations can become difficult to achieve with intermittent dosing of rapidly clearing beta-lactams. This may be especially true when treating critically-ill patients with variable pharmacokinetics and infections due to potential pathogens with higher baseline MIC's or greater resistant sub-populations. Two clinical studies provide evidence for unfavorable outcomes when PK/PD target attainment is not achieved in infections due to pathogens with elevated MIC's. Bhat et al. demonstrated significantly worse 28-day mortality in subjects who had Gram-negative bacteremia with cefepime MICs of ≥ 8 μg/mL vs. those with MICs of <8 μg/mL (54.8% vs. 24.1%) [51]. In investigations of piperacillin-tazobactam for *Pseudomonas aeruginosa* bacteremia, Tam et al. demonstrated higher 30-day mortality in subjects with elevated MICs of 32 μg/mL or 64 μg/mL [52].

While CI dosing has been shown to be superior to intermittent dosing

in *in vitro* and *in vivo* experimental studies, numerous comparative clinical studies have demonstrated no significant differences in patient outcome [53-55]. This investigational group of studies is characterized by variety of study design archetypes, heterogeneous subjects, mixed infections, an array of outcome measures, and limited power [50]. An example of a reasonably designed larger comparative clinical study was performed by Lau et al. who investigated CI versus traditional intermittent dosing of piperacillin-tazobactam in 167 patients [56]. They reported cure rates of 86.4% and 88.4% for continuous infusion and the intermittent infusion, respectively. Similar microbiological results with no statistical difference was noted in a large variety of clinical trials [57-60]. Recent meta-analyses also echo similar outcomes between CI and intermittent dosing of beta lactams across heterogeneous hospitalized patient populations [61-63]. Alternatively, prolonging the infusion time of intermittent dosing regimens has been suggested to enhance the %T>MIC without some of the CI-associated disadvantages such as drug stability, waste, and toxicity [48,50]. Recently, two retrospective clinical trials demonstrated advantages with piperacillin-tazobactam given as extended-infusion (4-hour infusion period) compared to traditional intermittent (30-minute infusion period) dosing regimens in collectively, 288 subjects. Both studies exhibited a statistically significant lower mortality in the EI groups (9.2% and 12.2%) versus intermittent dosing groups (17.9% and 31.6%) [48,64]. Additionally, a significantly lower length of stay was noted in the single-center cohort study with critically ill patients [48]. In another retrospective investigation, no difference was observed in 30-day mortality rates between patients who received EI piperacillin-tazobactam compared to historical controls who received intermittent infusions [65]. In addition, several publications report successful implementation of hospital wide dosing of extended infusion of piperacillin-tazobactam [66,67].

Carbapenems

The development of carbapenemases in gram-negative organisms with the ability to hydrolyze carbapenems was foreseeable. Since their introduction to clinical use in the 1980's, carbapenems have widely been considered as the antimicrobials of choice for the treatment of infections due to resistant-Gram-negative organisms [68-70]. Following historical resistance trends, we now witness an alarming increase of pathogens resistant to carbapenems including outbreaks resulting in overwhelming morbidity and mortality [71-74]. Carbapenem resistance was reported in up to 4.0% and 10.8% in *Escherichia coli* and *Klebsiella pneumoniae*, respectively, in the National Healthcare Safety Network (NHSN) from isolates collected in 2006-2007 [75]. Surveillance of meropenem susceptibility in the Meropenem Yearly Susceptibility Test Information Collection Program report significant increase in non-susceptible clinical isolates of *Klebsiella pneumoniae* from 0.6% in 2004 to 5.6% in 2008 [76].

The pharmacodynamic activity of carbapenems, possessing the beta-lactam ring in their chemical structure, is best described by time-dependent bactericidal activity. Therefore, the PK/PD parameter that is linked with carbapenems is the percent time that the unbound concentration exceeds the MIC (%T>MIC). Previous experimental *in vivo* studies have established that carbapenems achieve bacteriostasis and bactericidal maximal activities when %T>MIC of 20% and 40% are achieved, respectively [16,77,78]. Relative to beta-lactams, %T>MIC requirements are lower and may be due to their inherent potency and post-antibiotic effect. As discussed earlier for other beta-lactam antibiotics, the same general principles of maximizing the %T>Max continues to hold true for carbapenems for the same reasons. Thus, conventional dosing schemes may be modified to achieve a target %T>MIC through extended- or continuous-infusion dosing regimens. A few studies have demonstrated the potential application of CI of carbapenems with comparable outcomes to intermittent dosing in both experimental modeling and human investigations [58,79-82]. For example, a PK/PD study evaluated CI versus intermittent dosing of meropenem at low and high doses [82]. Utilizing Monte Carlo simulation, a population pharmacokinetic modeling technique, it was determined that the probability of target attainment against *Pseudomonas aeruginosa* was higher with CI and high dose regimens while no differences were noted between dosing regimens against *Klebsiella pneumonia* and *Enterobacter cloacae*. However, the potential utility of the CI dosing strategy is diminished by sparse data and the requirement of frequent intravenous bag exchanges or the use of cold pouches to prevent the rapid drug instability [83].

Given this latter limitation for CI dosing, alternative small and frequent dosing (i.e. 500 mg every 6 hours) of meropenem has been proposed. Several population pharmacokinetic studies utilized the Monte Carlo method to determine the target attainment probability of meropenem given as 500 mg every 6 hours and 1 gm every 8 hours against a variety of Gram-negative pathogens. Pharmacokinetic variables were obtained from healthy volunteers as well as simulated for varying renal function. The probabilities of the two dosing schemes were similar across the simulations [84,85]. Several clinical studies evaluating the same meropenem dosing schemes report similar findings with no statistical difference in in-hospital mortality, clinical success, length of stay, or treatment duration [86-88]. Interestingly, secondary pharmacoeconomic evaluations suggests some cost advantages with this alternate dosing. Despite these theoretical advantages, there is concern over the ability to attain adequate %T>MIC in critically-ill patients with variable pharmacokinetics or who are also infected by pathogens with potentially elevated MICs.

With the beneficial characteristics of slightly longer half-lives and a relatively higher toxicity threshold, carbapenem PK/PD investigations have included the application of EI as well as increasing the dose. Extended-infusions of 3 and 4 hours (as opposed to 30 minute infusions) for meropenem and doripenem, respectively, have been evaluated in multiple experimental model simulations. Li et al. developed a meropenem population pharmacokinetic model using patient data with intra-abdominal infections, community-acquired pneumonia, or ventilator-associated pneumonia [89]. Meropenem dosing regimens of 0.5, 1, and 2 grams over 30 minutes and 3 hours every 8 hours were simulated for a fixed susceptibility concentration of 4 μg/mL to represent the standard susceptibility breakpoints for Enterobacteriaceae, *Acinetobacter* species, and *P. aeruginosa*. Results indicated that the probability of attaining %T>MIC of 40% (minimum bactericidal threshold) was increased from 64% to 90% when the infusion was extended from 30 minutes to 3 hours for the 1 gram dosing level. The highest attainment probability were observed for simulations of meropenem dosing regimens of 2 g every 8 hours administered as a 3 hour infusion for *Acinetobacter* species and *P. aeruginosa. In a comparative population pharmacokinetic study, Lomaestro and Drusano* demonstrated that 1 g of meropenem given every 8 hours as a 3 hour infusion achieved a higher target attainment rate against *Pseudomonas aeruginosa* than either meropenem at 0.5 g or imipenem-cilastatin given as 0.5 g every 6 hours as a 1 hour infusion [90]. Similarly, Jaruratanasirikul et al. evaluated the %T>MIC attainment in 9 patients with ventilator-associated pneumonia (VAP) and in 8 patients with febrile neutropenia with bacteremia (FNB) who received meropenem consecutively as 1 g infused over 10 minutes, 1 g

infused over 3 hours and 2 g infused over 3 hours. At an MIC threshold of 4 μg/mL, the statistically different mean probabilities of %T>MIC of 40% were 57%, 73%, and 86% in VAP and 75.7%, 99.24% and 99.96% in (FNB), respectively, for the consecutive dosing schemes [91].

Doripenem is a newer carbapenem that shares similar pharmacodynamic and pharmacologic properties as meropenem with the important distinctions that it has an approximately 2 fold lower MIC susceptibility profile, a lower propensity to be hydrolyzed by carbapenemases, and is more stable in intravenous solutions at room temperature [92-94]. In 0.9% sodium chloride and 5% dextrose solutions, meropenem is stable for 1 and 4 hours while doripenem is stable for 12 and 4 hours, respectively [95,96]. This increased stability potentiates the possibility of administering extended and continuous infusion dosing strategies for doripenem. A population pharmacokinetic study was performed during the early development of doripenem to discern optimal dosing strategies. Monte Carlo simulation revealed that dosing regimens simulated at 4-6 hour infusions produced higher probabilities of target attainment of %T>MIC of 35% for organisms with higher MICs [97]. A few population PK/PD studies report similar findings with increased probability of target attainment with prolonged infusion when targeting pathogens with elevated MICs [98-100]. These findings lead to a well-designed large clinical trial evaluating EI dosing of doripenem administered as 500 mg every 8 hours over 4 hours vs. intermittent dosing of imipenem [101]. This was a prospective, randomized trial in 531 subjects with ventilator-associated pneumonia across multiple institutions. Doripenem was found to be noninferior to imipenem in the primary efficacy measures of clinical success in both the clinical modified intent-to-treat analysis (59.0% vs. 57.8%, respectively) as well as in clinically evaluable subjects (68.3% vs. 64.2%). Additionally, higher cure rates were observed for doripenem in subjects with higher Acute Physiology and Chronic Health Evaluation II scores and older ages.

Overall

Despite established relation between the pharmacodynamic activity and the clinically-relevant exposures of these antimicrobials, CI or EI dosing of beta-lactam and carbapenem antibiotics remains uncommon. The disparity between the evidence in preclinical experiments and clinical reports, the heterogeneity of study designs, the paucity of data from prospective clinical evaluations, and practical dosing design considerations contributes to the hesitancy of the clinician to shift treatment paradigms away from half a century of traditional dosing of time-dependent antimicrobials.

PK/PD challenges

Since the first description of the influence of pharmacokinetic exposure to the bactericidal activity of penicillin in the 1950, significant progress has been made to elucidate the role of PK/PD principles in the design and application of antimicrobial therapy for optimizing bacterial eradication [102]. There is also a growing body of literature with compelling evidence for the prevention of resistance emergence with PK/PD target attainment. However, a significant portion of this data comes from investigations in gram-positive organisms and with other antimicrobials such as fluoroquinolones [103]. Little progress has been made to elucidate the application of PK/PD principles in the prevention of resistance specifically for beta-lactams and carbapenems, widely accepted antimicrobials of choice for Gram-negative infections [104]. Thus, there is a potential that the PK/PD parameter that reflects resistance suppression may not be the same parameter that is associated with bacterial eradication [105]. In one of these investigations, Tam et al. demonstrated that meropenem dosing that resulted in Cmin (trough concentrations)/MIC ratios of less than 6.2 resulted in selection of resistant mutations in *P. aeruginosa* when tested in an *in vitro* hollow fibre model [106]. Evidence of negative clinical consequences from falling short of PK/PD targets and the difficulty in achieving parameter thresholds in infections due to resistant pathogens, emphasizes the need for research with the pharmacodynamic endpoint of preventing selection of resistance that confer MIC elevations [47,51,52]. This becomes a very challenging task given the necessity to account for a variety of factors. Examples of some of these factors include pharmacokinetic inter- and intra-individual variability, selection of genotypic or phenotypic measures of resistance, selection of the PK/PD parameter that correlates to the desired PD outcome, and application of alternate therapeutic options. Until more progress has been made for resistance prevention strategies in experimental and clinical studies, clinicians are challenged with translating experimental evidence of bacterial eradication to the bedside.

There is a lack of prospective clinical trials that incorporate endpoint measures for the prevention of resistance in general, and specifically for Gram-negative organisms. One exception is a recent prospective clinical trial (mentioned above) that included resistance as a secondary endpoint in the comparative evaluation of the safety and efficacy of extended infusion of doripenem vs. traditional imipenem in patients with ventilator-associated pneumonia. This secondary subgroup analysis reported that 18% (5 of 28) of *P. aeruginosa* isolates had minimum inhibitory concentration ≥ or = 8 μg/mL at baseline or following therapy in the doripenem arm compared with 64% (16 of 25) in the imipenem treatment group. The authors concluded that one of the possibilities for this finding could be improved PK/PD target attainment with the doripenem extended infusion group [101]. There is a great need for more prospective clinical trials across different populations and for a variety of infections that utilize established PK/PD parameters that are associated with the development of resistance. Furthermore, increased clinical evidence of the influence of collective PK/PD targets in combination therapies as well as duration of therapies on the prevention of resistance would contribute to the application of antimicrobial treatment strategies.

Inter- and intra-patient pharmacokinetic variability renders the design of dosing regimens difficult when treating patients. The influence of volume of distribution and renal clearance can drastically change the ability of specific dosing regimens to achieve desirable PK/PD targets. For instance, the rapid volume expansion that occurs early in septic patients can decrease the peak concentration that's achieved with traditional dosing regimens resulting in overall reduced drug exposures and an abbreviated time for concentrations to fall below MICs [107-109]. As these patients develop acute renal dysfunction, the concentration-time profile may shift in favor of time-dependent drugs that have a component of renal clearance. However, these intricate clinical scenarios require a balanced approach of optimizing PK/PD target attainment with avoidance of toxicities. Several Monte Carlo simulations have incorporated varying degrees of renal function to populate their pharmacokinetic variances [110,111]. Volume of distribution becomes more complex when considering the clinical significance of reaching sites of infection with active drug. Pharmacokinetic assessments derived from serum concentrations may not necessarily reflect the concentration-time profile of antimicrobials at the site of infection (i.e. lung, bone, cns, skin, etc.). Cmax, absorption into the tissue, and clearance from the tissue can be dramatically different than serum concentration-time parameters [112,113]. Certainly indirect PK/PD associations can be made, but this pharmacokinetic

consideration is important in assessments of variability. Additional assessments must be made for the influence of protein binding in the utilization of pharmacokinetic parameters and their variability. It has been suggested that the unbound, free fraction of the drug primarily contributes to its pharmacodynamics activity [114]. Consequently, majority of recent experimental investigations account for this protein binding in their PK/PD simulations. Successful clinical experience with highly-bound drugs (>90%), however, suggests that this factor may be more complex than utilizing a free fraction percentage in modeling and necessitates further elucidation *in vivo*.

Total of resolution of infection requires both the rapid attainment of PK/PD targets for sufficient duration in order to optimize bacterial eradication and the host's immune defenses. Early PK/PD target attainment not only reduces time to clinical resolution but may also reduce the likelihood of concentrations that may linger at levels that may promote the selection of resistant mutants [115]. Duration of antimicrobials has been demonstrated to have an impact on the selection of resistance in gram-negative organisms. Logically, shortening the course of therapy to the minimum duration required for bacterial eradication may decrease selective pressure. This understanding holds true for the changes that have been observed in overall reduction of utilization of antimicrobials and the subsequent change in antibiogram, as well as in prolonged use of antimicrobials and resistance development [116,117]. The need for additional determination of optimal durations with the balancing act between adequate exposure for clinical resolution and minimum exposure for selective pressure can be highlighted in two investigations. One of the earliest studies investigating this relationship was a prospective clinical trial that discovered the emergence of multidrug resistance in *P. aeruginosa* after 6 days of therapy in subjects with ventilator-associated pneumonia [118]. More recently, The US Food and Drug Administration notified the public about the early termination of a ventilator-associated pneumonia trial due to safety concerns [119]. In comparison with imipenem/cilastatin, subjects on doripenem 1 gm every 8 hours as extended-infusion (over 4 hours) experienced excess 28-day all-cause mortality (21.5 vs. 14.8%) and lower clinical cure rates (45.6 vs. 56.8%) in the microbiological intent-to-treat analysis. Duration of therapy was fixed at 7 days for the doripenem treatment group and 10 days for the imipenem/cilastatin treatment group. Certainly, there are several other factors beyond duration that could have influenced doripenem's inferiority such as inter- and intra-individual serum pharmacokinetic variability, pharmacokinetics of doripenem in the lung, and clinical factors influencing severity of infection. In attempts to accommodate some of these variables, there has been recent growth of investigations into the utilization of high-dose regimens [120-123].

Summary

Novel dosing strategies for beta-lactams that optimize pharmacokinetic/pharmacodynamic properties exhibit potential for improved clinical outcomes. Carbapenems exhibit a high probability of attaining its bactericidal and bacteriostatic pharmacodynamic targets with both standard and novel dosing regimens. Pharmacokinetic/pharmacodynamic profiling is valuable in the design and application of antimicrobial dosing strategies to optimize clinical outcomes. Moreover, the need for expanded experimental and prospective clinical studies that incorporate resistance endpoints is magnified in the face of increasing resistance and decreasing development of novel antibiotics.

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