Pharmacokinetics of Beta-Lactam Antibiotics in Patients with Intra-Abdominal Disease: A Structured Review

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Abstract

Background and Purpose: The objective of this structured review was to analyze critically the findings of pharmacokinetic studies of beta-lactam antibiotics in patients with intra-abdominal disease; i.e., intra-abdominal infection (IAI) or previous abdominal surgery and determine the requirements for dosage modification in this population.

Methods: Data were identified by structured review of PUBMED from February 1983 to February 2011. All 14 articles reviewed described the pharmacokinetics of beta-lactam antibiotics in patients with intra-abdominal disease.

Results: Antibiotic classes included carbapenems, penicillins, cephalosporins, and monobactams. Possible physiological changes in these patients include development of abscesses, perforation, or ischemia of the bowel as well as intra-abdominal hypertension. These disorders may cause changes in antibiotic pharmacokinetics, including increased volume of distribution and faster drug clearance, both resulting in lower antibiotic concentrations. High inter-individual pharmacokinetic variability was common to each of the studies.

Conclusion: Most of the available data demonstrate that drug volume of distribution can be increased significantly in the presence of intra-abdominal disease. Drug clearance is likely to vary in line with renal or hepatic function. Thus, dose optimization is important to prevent development of antibiotic resistance or therapeutic failure. However, further research is necessary to determine the clinical outcome of individualized dosing on the basis of pharmacokinetic/pharmacodynamic studies.

Managing sepsis in critically ill patients remains a great challenge for clinicians. The incidence of sepsis in such patients has been reported to be approximately 10%, with a population incidence of 1 case/1,000 [1]. Complicated intra-abdominal infection (IAI) is a frequent cause of sepsis and is the second most frequent cause of infectious death in the intensive care unit (ICU)[2]. The treatment of complicated IAI consists of both source control and antibiotic therapy, as outlined by both the Surgical Infection Society and the Infectious Diseases Society of America [3]. This guideline recommends the use of antibiotics at optimal doses to maximize efficacy, minimize toxicity, and reduce antibiotic resistance. Patients with complicated IAI also are at risk of infections caused by resistant pathogens [4], and therefore, the importance of appropriate selection, timing of administration, and dose adjustment of the antibiotic is paramount [5,6]. Multiple factors may contribute to the selection of a resistant pathogen, but achieving optimal drug exposure is likely to be a key factor for minimizing its occurrence [7].

Determination of optimal antibiotic doses on the basis of pharmacokinetic/pharmacodynamic (PK/PD) principles correlates the antibiotic concentration in the body (i.e., PK) with its ability to kill, or inhibit growth, of the pathogen (i.e., PD)[8]. Optimal antibiotic doses will result in therapeutic
concentrations at the focus of infection to ensure organism eradication. This approach is likely to improve clinical outcomes, especially in critically ill patients, who are at high risk of developing severe infections and dying [9–11]. However, penetration of the antibiotic to the site of infection can be hindered by various factors, including the patient’s comorbidities, immune function status, renal and liver function, and concomitant drug use [12]. These factors can be more profound in critically ill patients because of pathophysiological changes, as described in detail in a review article by Roberts and Lipman [13]. Numerous studies have been conducted of the pharmacokinetics of antibiotics in IAI, although we are unaware of any structured reviews of this topic.

The aim of this structured review was to analyze critically the PK studies on beta-lactam antibiotics used in patients with intra-abdominal disease, including IAI and after abdominal surgery.

Search Strategy and Selection Criteria
Data for this review were identified by structured review of PUBMED (February 1983–February 2011). The keywords were “pharmacokinetic,” “pharmacodynamic,” “beta-lactam antibiotics,” “critically ill,” “intra-abdominal,” and “infection.” Twenty-four papers were identified, but ten were reviews and were excluded because they were guideline documents only, discussing antibiotic choice and general management of IAI. Articles discussing PK studies of patients undergoing peritoneal dialysis also were excluded, as this group is likely to have significantly different values. All papers reviewed were written in the English language and described beta-lactam antibiotic pharmacokinetics in patients with intra-abdominal disease. The studies used for this systematic review are summarized in Table 1 and are listed according to antibiotic class. This review also includes a paper by Wittman and Schassan [14], who studied eight beta-lactam antibiotics in patients who had undergone abdominal surgery, although this paper is not listed in Table 1 because it reports only matching serum and peritoneal fluid concentrations and does not describe relevant PK parameters. The PK data available from healthy volunteers were included for each antibiotic for comparison.

General Concepts
Antibiotics can be divided into three major classes on the basis of their bacterial killing properties [34]. Concentration-dependent antibiotics (e.g., aminoglycosides) exhibit bacterial killing that correlates with the peak concentration during a dosing interval (C_{max}). Achieving a higher ratio of C_{max} to the minimum inhibitory concentration (MIC) of the infecting pathogen (C_{max}/MIC ratio) has been advocated to maximize killing. Administration of higher doses should result in a higher ratio. This may be useful clinically when a higher MIC is present [35]. On the contrary, the killing of bacteria by time-dependent antibiotics (e.g., beta-lactams) will depend largely on the time the antibiotic concentration is maintained above the MIC, preferably at least 40%–60% of the dosing interval. Some data on the killing of Pseudomonas spp. suggest greater activity when concentrations are maintained at 4-5× the MIC during continuous infusion [36]. The third group of antibiotics has PK/PD properties consistent with both concentration- and time-dependent antibiotics, and bacterial killing is associated with the ratio of the area under the concentration time curve (AUC) to the MIC (AUC/MIC; e.g., fluoroquinolones and glycopeptides).

The strong relation between PK and PK/PD means that a change in PK may affect the treatment outcome. It follows that an understanding of the pathophysiology of IAI and its effect on PK is necessary to determine the need for altered dosing.

Relation between Physiological Alterations in Patients with Intra-Abdominal Disease and Pharmacokinetics
Intra-abdominal infections are categorized as either complicated or uncomplicated, depending on the extent of the infection [37]. From a clinical point of view, the infectious process involved in complicated IAI extends beyond the organ that is the source of infection and causes localized or diffuse peritonitis, depending on the ability of the host to contain the process within a part of the abdominal cavity [37]. Pathologic changes that could occur during IAI include the development of abscesses, perforation, and ischemia of the bowel. These may lead to intra-abdominal hypertension, as well as significant physiologic changes such as hypotension and tachycardia. Intra-abdominal infections also can develop as a complication of an invasive procedure (i.e., abdominal surgery). Various IAI rates have been reported, but in the presence of intra-abdominal surgical packing, infection rates can be as high as 70% [38]. Similar physiologic changes also can occur in these patients secondary to a higher concentration of anti-diuretic hormone (ADH) in response to the trauma of surgery. Higher concentrations of ADH eventually lead to fluid retention in the abdominal cavity [39].

Pharmacokinetics: Changes in distribution
Fluid expansion. Antibiotic transfer from the intravascular to the interstitial space is diffusion driven, either through pores or transcellularly, depending on the chemical properties of the drug. Small polar hydrophilic molecules move through fenestrated capillary pores, and more lipophilic substances pass directly through the endothelial wall [40]. For hydrophilic antibiotics (e.g., aminoglycosides, glycopeptides, and beta-lactams), distribution typically is limited to the plasma and the interstitial fluid because of the limited extravascular permeability, and the concentrations are in equilibrium during the steady state. Thus, any changes in interstitial fluid will alter the distribution of hydrophilic antibiotics. This is commonly seen when systemic disorders such as the systemic inflammatory response syndrome (SIRS) or sepsis (defined as SIRS in the presence of infection) are present. In IAI, local increases in fluid volumes within the peritoneal cavity will occur secondary to fluid shifts from the intravascular space to the interstitial space as a result of capillary leak associated with sepsis [41]; fluid therapy for restoration of intravascular volume [3] and inflammatory fluid collections can increase fluid volumes within the peritoneal cavity. Furthermore, gut pathology such as ileus can develop from the increased intraluminal pressure, which impairs fluid movement into the gut. This potentiates systemic “third spacing” effects by reducing secretion of fluids into the gut, thereby increasing the volume of fluid present in the gut lumen. Each of these factors will increase the volume of distribution (V_d) of a hydrophilic antibiotic, leading to a dilutional effect, as illustrated schematically.
Table 1. Studies Describing Pharmacokinetics of Beta-Lactam Antibiotics in Patients with Intra-Abdominal Disease

<table>
<thead>
<tr>
<th>Antibiotic class</th>
<th>Reference</th>
<th>Patient population (n)</th>
<th>Samples</th>
<th>CL (L/hour)</th>
<th>V_d (L)</th>
<th>AUC plasma (mg·h/L)</th>
<th>AUC PF (mg·h/L)</th>
<th>AUC ratio</th>
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<tr>
<td><strong>Carbapenem</strong></td>
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<tr>
<td>Meropenem</td>
<td>Bedikian et al. (1994) [15]</td>
<td>Intra-abdominal infection (12)</td>
<td>Plasma at steady state</td>
<td>18.9±4.3</td>
<td>V ss 26.7±6.9</td>
<td>57.5±20.1</td>
<td>NA</td>
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<td>Karjagin et al. (2008) [16]</td>
<td>Severe peritonitis and septic shock (6)</td>
<td>Plasma and PF, AUC from simulated profile of 3 g/day</td>
<td>6.7±4.2</td>
<td>V ss 23.8±4.9</td>
<td>625</td>
<td>491</td>
<td>0.78</td>
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<td>Nilsson-Ehle et al. (1991) [17]</td>
<td>Healthy volunteers (8)</td>
<td>Plasma after one dose</td>
<td>11.3±1.7</td>
<td>V ss 12.5±1.5</td>
<td>77.5±11.5</td>
<td>NA</td>
<td>NA</td>
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</table>

| **Imipenem**     | Ikawa et al. (2008) [18] | Patients after laparotomy (10) | Plasma and PF after one dose | Total 46.8 | Total 14.3 | 59.0±15.7 | 41.0±6.13 | 0.82±0.06 |
|                  | Nilsson-Ehle et al. (1991) [17] | Healthy volunteers (8) | Plasma after one dose | 11.0±1.5 | V ss 14.4±1.2 | 94.4±12.0 | NA | NA |

| **Doripenem**    | Ikawa et al. (2007) [19] | Patients after abdominal surgery (10) | Plasma after one dose | 8.6±1.1 | V ss 8.56±1.14 | 59.3±7.2 | 49.3±6.5 | 0.4±0.3 |

| **Biapenem**     | Cirillo et al. (2009) [20] | Healthy volunteers (48) | Plasma after one dose | 13.0–14.6 | V ss 14.4–18.0 | 35.6–78.8 | NA | NA |
|                  | Ikawa et al. (2008) [21] | Patients after abdominal surgery (10) | Plasma and PF after one dose | 8.11±5.7a | Total 16.4 | NA | NA | NA |

| **Ertapenem**    | Arrigucci et al. (2009) [22] | Patients after abdominal surgery (21) | Plasma and PF taken at different times from three groups | NA | NA | NA | NA | NA |
|                  | Majumdar et al. (2002) [23] | Healthy volunteers (16) | Plasma after one dose of 1 g | 1.7±0.2 | V ss 8.2±1.5 | 572.1±68.6 | NA | NA |

| **Amino-penicillin** | Li et al. (2005) [24] | Patients with complicated intra-abdominal infection (56) | Plasma at steady state | 26 having CI 15.9±5.7 | V ss 22.2±4.5 | NA | NA | NA |
|                     | 30 having IT 13.7±4.3 | IT 22.4±6.2 | NA | NA | NA |

(continued)
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<tr>
<th>Antibiotic class</th>
<th>Reference</th>
<th>Patient population (n)</th>
<th>Samples</th>
<th>CL (L/hour)</th>
<th>Vd (L)</th>
<th>AUC plasma (mg·h/L)</th>
<th>AUC PF (mg·h/L)</th>
<th>AUC ratio</th>
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<tr>
<td>Cefalosporins</td>
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<td>Cefazidine</td>
<td>Bujik et al. (2002) [26]</td>
<td>Patients with severe intra-abdominal infections (13), 9 received CI, and 4 received IB</td>
<td>Plasma and peritoneal exudate</td>
<td>CI 4.1 (Day 2);</td>
<td>4.2 (Day 4);</td>
<td>5.1 (Day 2);</td>
<td>4.0 (Day 4)</td>
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<td>21 (Day 4);</td>
<td>14 (Day 4);</td>
<td>IB 1064 (Day 2);</td>
<td>1166 (Day 4)</td>
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<td>CI 0.56 (Day 2);</td>
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<tr>
<td>Cefepoxide</td>
<td>Heim-Duthoy et al. (1988)</td>
<td>Patients after abdominal surgery (11)</td>
<td>Plasma on day 2</td>
<td>7.0±2.8</td>
<td>21.0±7.0</td>
<td>340.4±277.0</td>
<td>NA</td>
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<td>Cefepoxide</td>
<td>Sommers et al. (1983) [27]</td>
<td>Patients with abdominal infections (11)</td>
<td>Plasma after one dose</td>
<td>5.8–6.9</td>
<td>11.0–13.3</td>
<td>153–178</td>
<td>NA</td>
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<tr>
<td>Cefepoxide</td>
<td>Jules et al. (1988) [29]</td>
<td>Healthy volunteers (24)</td>
<td>Plasma obtained on Day 1 and Day 5</td>
<td>1.7 (Day 1)</td>
<td>13.1 (Day 1)</td>
<td>1,247</td>
<td>NA</td>
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<tr>
<td>Cefepoxide</td>
<td>Meyers et al. (1987) [30]</td>
<td>Healthy subjects (10)</td>
<td>Plasma after one dose</td>
<td>5.1–5.8</td>
<td>10.5–11.2</td>
<td>211.6–423.6</td>
<td>NA</td>
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<td>Cefepoxide</td>
<td>Higuchi et al. (2008) [31]</td>
<td>Patients after laparotomy (8)</td>
<td>Plasma and PF after first dose</td>
<td>Total 23.7</td>
<td>Total 17.2</td>
<td>158.1±36.7</td>
<td>141.6±30.9</td>
<td>0.9±0.1</td>
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<td>Cefepoxide</td>
<td>Ikawa et al. (2008) [32]</td>
<td>Patients after abdominal surgery (8)</td>
<td>Plasma and PF after one dose</td>
<td>Total 16.5</td>
<td>Total 11.6</td>
<td>101.1±26.7</td>
<td>86.5±22.6</td>
<td>0.9±0.2</td>
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<tr>
<td>Cefepoxide</td>
<td>Ikawa et al. (2007) [33]</td>
<td>Patients after abdominal surgery (10)</td>
<td>Plasma and PF after first dose</td>
<td>Total 20.5</td>
<td>Total 15.1</td>
<td>189.9±32.0</td>
<td>174.1±36.0</td>
<td>0.9±0.1</td>
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* All the PK studies identified report parameters from either non-compartmental or compartmental analysis. All PK data are presented with standardized unit of measurement and whenever necessary, conversion was carried out. For data reported by body weight, a weight of 70kg was used in the re-calculation.

* Data from compartmental analysis are reported as total value from all compartments.

* This study reports CL as 0.036 x creatinine clearance (Clcr) + 4.88, with Clcr reported as 89.9±22.3.

* This study reports only Cmax or random concentrations and cannot be contrasted with the other studies. The authors reported a tissue:plasma ratio of 46.7±25.3 at 1 h±15 min, 56.4±24.1 at 2 h±15 min, and 83.1±46.6 at 3 h±15 min.

** AUC = area under the curve; CI = continuous infusion; CL = clearance; IB = intermittent bolus; II = intermittent infusion; NA = not available; PF = peritoneal fluid; Vd = volume of distribution; Vss = volume at steady state.
Impaired Penetration: Abdominal Abscess. Another challenge in the management of IAIs is the formation of an abscess. This may result from an immune defense mechanism causing the release of macrophages and neutrophils into the peritoneal cavity, as well as activation of the coagulation and complement cascades. Bacteria remain viable, as the abscess environment is not conducive to antibiotic activity. Antibiotic penetration is impaired as a result of limited perfusion in the presence of fibrin clots and the abscess wall [43]. The acidic environment of the abscess [44] may cause therapeutic failure of aminoglycosides, with in vitro studies demonstrating a reduced bactericidal effect. In vitro studies have shown that at pH 5.5, amikacin and netilmicin had practically no bactericidal effect on *Pseudomonas aeruginosa* [45].

Even though an abscess may be managed with antibiotic therapy alone, patients with both larger intra-abdominal abscesses (>6.5 cm) and pyrexia have a greater likelihood of antibiotic failure, and therefore, drainage or other source control is required [46].

*Pharmacokinetics: Changes in clearance*

*Organ dysfunction.* As discussed above, patients with a large intra-abdominal fluid volume are at risk of intra-abdominal hypertension (IAH) [47]. The pressure within the abdomen normally is atmospheric (<7 mm Hg) or sub-atmospheric (i.e., negative), but the presence of some form of intra-abdominal pathology may increase the pressure in the abdominal compartment. Hypoperfusion of the gastrointestinal tract is reported at or above an intra-abdominal pressure (IAP) of 12 mm Hg [48]. Intra-abdominal hypertension reduces abdominal wall blood flow because of the higher arteriolar and venous resistance, which will lead to intestinal mucosal hypoperfusion and ischemia. Persistent IAH could later result in development of multiple organ dysfunction; for example, it could cause hepatic and gastrointestinal effects by impairing lymphatic flow and produce renal dysfunction as a result of a decreased glomerular filtration rate [49]. Thus, IAH can lead to multiple organ dysfunction syndrome (MODS), and it has been reported that the incidence of MODS is as high as 90% compared with 31.5% in patients without acute compartment syndrome secondary to IAH [47]. In the presence of MODS, antibiotic doses may need to be adjusted to minimize the likelihood of drug accumulation and toxicity if the affected organ is responsible for antibiotic elimination [50,51].

*Clearance by Abdominal Surgical Drains*

It has been suggested that indwelling surgical drains are a frequently overlooked cause of antibiotic loss in critically ill patients [9,52]. However, most studies documenting the presence of antibiotics in drainage fluid were for the main purpose of understanding drug penetration to specific sites. Thus, these studies provide little information about the extent of drug loss from these drains or the PK characteristics of drugs in patients with indwelling surgical drains or whether the PK differs from that in patients without drains.

*Specific Antibiotic Classes*

The studies are grouped according to antibiotic class. Data were available from patients with IAI and also from patients who had undergone abdominal surgery; where possible, the results are compared.
Carbapenems

Meropenem is the only carbapenem that has had its PK studied in patients with IAI, with data on intra-abdominal penetration of other carbapenems coming from abdominal surgery patients. Bedikian et al. [15] compared the pharmacokinetics of meropenem in patients with IAI and healthy volunteers [17] and observed that the $V_d$ in the patients had doubled, the AUC was 25% lower, and the clearance (CL) twice as high as in healthy volunteers. However, because patients with organ impairment, life-threatening infection, septic shock and immunodeficiency, and long-term therapy were excluded, this study may not reflect the likely spectrum of critically ill patients that may be encountered. The $V_d$ is likely to remain augmented, although CL values may be significantly lower in some patients. Unfortunately, this study did not confirm antibiotic penetration into the peritoneal fluid (the site of infection). Karijgin et al. [16] also studied meropenem but described a reduced CL, with $V_d$ similar to that reported by Bedikian et al. Further PD analysis using PK simulations suggested that a dose of 3 g/day produces an AUC ratio of peritoneal fluid to plasma of 0.78 and achieves concentrations that exceed an MIC of 4 mcg/mL in both plasma and peritoneal fluid for 87% of the dosing interval. Because the majority of infections are localized in the extracellular fluid [40], doses that can achieve a high ratio of peritoneal fluid to plasma concentration are most likely to attain therapeutic antibiotic concentrations for the treatment of IAI.

Other studies on carbapenems, which include imipenem, doripenem, biapenem, and ertapenem, were performed in patients who had undergone abdominal surgery. Imipenem [18] showed a peritoneal:plasma AUC ratio similar to that of doripenem [19], 0.82 and 0.84, respectively. No ratio is available for biapenem [21] and ertapenem [22] (see Table 1).

The PK data from compartmental analysis for carbapenems showed that imipenem has the highest total CL compared with doripenem and biapenem. Both imipenem and doripenem have higher total CLs in these patients than in healthy volunteers [20,53]. Compartmental analysis also revealed elevated distribution clearances from the central to the peritoneal compartment, which may indicate good peritoneal penetration or high fluid volumes in the peritoneal compartment. Available imipenem data suggest that the minimum dosage required to attain at least an 80% probability of bactericidal activity at MICs of 1, 2, 4, 8, and 16 mcg/mL are 500 mg q 12 h, 1,000 mg q 12 h, 1,000 mg q 8 h, and 1,000 mg q 6 h, respectively [18]. For doripenem, the percentage of drug concentration that exceeds the MIC ($T_{>\text{MIC}}$) is slightly greater in peritoneal exudate than in serum [19]; however, this difference is unlikely to mandate different dosing. Confounding the interpretation of the ertapenem PK study is the sampling times, with only random serum concentrations reported [22]. As such, comparison with other studies is not possible. The great extent of protein binding of ertapenem (~95%) would necessitate the measurement of unbound (pharmacologically active) concentrations, which was not done [22].

Penicillins

Piperacillin and mezlocillin are the only two penicillins that are formulated with tazobactam in hospitalized patients with complicated IAI [24]. No difference in relevant PK parameters was found for the two infusion methods. When compared with healthy volunteers [25], the $V_d$ in the patients was two times greater, with CL largely unchanged. However, no samples were obtained from the peritoneal fluid, and therefore, this study did not confirm antibiotic penetration into that fluid. In another study, by Wittman and Schassan [14], in abdominal surgery patients, serial serum and peritoneal fluid concentrations were reported at different time intervals for eight beta-lactams. No Cmax or AUC data were provided. However, the peritoneal fluid concentration was reported at 2 h, and the ratio of the peritoneal fluid:plasma concentration 2 h after administration was 0.83 and 0.74 for piperacillin and mezlocillin, respectively.

Cephalosporins

Five cephalosporin antibiotics have been studied, although only two studies were conducted in patients with IAI [26,54]. The first study [26] was non-randomized and compared the PK of CI with II administration of ceftazidime. The PK parameters of $V_d$ and CL within the two groups were not statistically significantly different, but the AUC value in peritoneal exudate was higher in the CI group, and this difference was statistically significant on Day 2. The peritoneal exudate:plasma AUC ratio was higher in the CI group (56%–64%) than in the II group (33%–35%), but this difference was not statistically significant. Other data have shown that the AUC ratio of peritoneal exudates:plasma decreases over time (~0.6 on Day 2 and ~0.3 on day 4). The low ratio may have resulted from dilution of the peritoneal fluid as a result of continuous lavage, which resulted in rapid peritoneal ceftazidime clearance. However, drainage clearance was reported to be minor, 1% on Day 2 and 0.6% on Day 5, whereas the total ceftazidime CL was almost half that reported in healthy volunteers [47] (see Table 1).

A study with cefozopran (co-formulated with sulbactam) [46] described a half-life 3.9 times that observed in healthy volunteers [30] because of a 50% larger $V_d$ and a 43% lower CL. However, analysis of unbound concentrations was not undertaken in this study, which would have been significantly more relevant, as cefozopran is highly protein bound (95%). Further, no samples were obtained from peritoneal fluid, which would have been indicative of antibiotic effects at the site of infection. Other studies [14,31–33] have been performed in patients after abdominal surgery. In these studies, the AUC ratio of peritoneal exudates:plasma was ~90% for ceftazime, cefozopran, and cefotiam (cefozopran and cefotiam are available only in certain countries; e.g., China and Japan). Very high CL values of these drugs were observed.

For cefepime, 3-h infusions of 1 g q 8 h and 2 g q 12 h achieved a $T_{>\text{MIC}}$ above 85% for an MIC of 4 mcg/mL in peritoneal fluid [31]. The MIC data were derived from susceptibility surveillances of surgical infections from four major types of bacteria that cause post-operative IAI: *Escherichia coli*, *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, and *Enterobacter cloacae*. Higher CL and lower AUC values were noted than in healthy volunteers [55]. A regimen of 1 g q 8 h for cefotiam achieved a $T_{>\text{MIC}}$ above 80%, based on MIC data derived from local susceptibility surveillances of surgical infections. No pharmacodynamic analysis is available for
patients have shown lower Vd values, indicating more rapid clearance in peritoneal fluid, although the duration of these concentrations remains unknown.

Summary of Pharmacokinetic Data

The PK studies including IAI patients consistently show higher Vd values than in healthy volunteers except for ceftazidime [54]. The increment of Vd was twice as high for both meropenem [15,16] and piperacillin [24] and 20% higher for ceftazidime [26]. Despite these PK differences in healthy volunteers, because of the high susceptibility of the majority of pathogens causing IAI, a loading dose in response to this increased Vd would be required only on suspicion of a less susceptible bacterium (e.g., P. aeruginosa) [4].

On the contrary, PK studies including abdominal surgery patients have shown lower Vd values, indicating more rapid clearance than in healthy volunteers. Specifically, CL was four times greater for imipenem [18], three times greater for cefepime [31], and two times greater for doripenem [19]. The increased CL associated with the post-operative state suggests the need for more frequent dosing of beta-lactam antibiotics.

Approaches to Dosing in IAI

The importance of dose optimization of antibiotics in treating infection has been highlighted by various studies [16,56–59]. For critically ill patients with complicated IAI, optimizing antibiotic therapy is challenging. Dosing guidance from the product insert is obtained from well-controlled clinical trials in patients without significant pathologies and does not account for the complex pathophysiology of these patients [60,61]. As is evidenced above, antibiotic concentrations at the infection site and drug clearance can be variable between antibiotics. Major changes of these parameters will affect antibiotic concentrations and therefore bacterial killing. Changes in distribution through volume expansion may cause a dilution effect for hydrophilic antibiotics, thereby necessitating larger doses, as shown in those PK studies involving patients with IAI; higher Vd values were noted than in healthy volunteers [15,16,24]. There is a lack of data on the presence and effect of impaired penetration and possible antibiotic clearance through surgical drains, suggesting that further studies be conducted. As discussed above, the prescription of antibiotics that attain a higher peritoneal fluid:plasma ratio is suggested for this patient population, although such data are not readily available from all the studies reviewed. Where data suggest that antibiotic penetration into the peritoneum may be low, higher empiric doses to increase peritoneal fluid concentrations should be considered. Nevertheless, as studies describing antibiotic PK at the site of IAI are limited, more research is suggested to determine whether individualized dosing based on PK/PD does in fact improve clinical outcome. However, when susceptibility data are available, standard doses are likely to be sufficient because many bacteria causing IAI are highly susceptible, and PD targets are still achieved in the peritoneal fluid. Other factors, such as the presence of hypoalbuminemia [50,62] and impaired or augmented renal function [63–65], phenomena commonly seen in critically ill patients, also may lead to changes in plasma concentrations of antibiotics [66].

Conclusion

There are marked changes in the PK parameters of beta-lactam antibiotics in patients with intra-abdominal disease. The majority of these alterations lead to decreases in antibiotic concentrations, and therefore, dosage individualization or the development of revised evidence-based dosing guidelines is required for these patients. The variability and unpredictability of PK in patients with intra-abdominal disease may support monitoring of blood antibiotic concentrations to guide dosing. Such dose optimization should be considered important, as absence of appropriate dosing adjustment can lead to antibiotic resistance, therapeutic failure, or both. In this context, the data from the PK studies in this review can enable the clinician to tailor dosing in this patient population. We suggest further research to determine the clinical outcomes of patient-specific dosing.

References


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Three references cited in the table were not included with the reference list. We found two; we could not find Jules et al. 1988. Please provide it.