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Continuous versus Intermittent Intravenous Administration of Antibacterials with Time-Dependent Action

A Systematic Review of Pharmacokinetic and Pharmacodynamic Parameters

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Abstract

We performed a systematic review of randomised clinical trials to evaluate the comparative pharmacokinetic and pharmacodynamic properties of the continuous versus intermittent mode of intravenous administration of various antibacterials. Data were identified from PubMed (January 1950 to January 2005), Current Contents, the Cochrane central register of controlled trials, and references from relevant articles and reviews. Seventeen randomised clinical trials comparing continuous with intermittent intravenous administration of the same antibacterial regimen and examining the pharmacokinetic and pharmacodynamic properties

were included in this systematic review. We reviewed data regarding the clinical setting, number of participants, antibacterial agents and dosages used, as well as maximum serum concentration (C_{max}), trough serum concentration (C_{min}), steady-state or plateau serum concentration (C_{ss}), area under the concentration-time curve (AUC), time above the minimum inhibitory concentration (MIC) [T > MIC], AUC : MIC, elimination rate constant, elimination half-life, volume of distribution and systematic clearance. The mean C_{max} of the intermittently administered antibacterials was higher compared with C_{ss} achieved by the continuous infusion of the same antibacterial in all eligible studies (C_{max} was on average 5.5 times higher than C_{ss}, range 1.9–11.2). C_{ss} was on average 5.8 times higher than the C_{min} of the intermittently administered antibacterials (range 1.2–15.6). In three of six studies the length of time that the drug concentration was above the MIC of the responsible pathogens was longer in patients receiving the antibacterials continuously.

In conclusion, the reviewed data suggest that the continuous intravenous infusion of antibacterials with time-dependent bacterial killing seems to be superior than the intermittent intravenous administration, from a pharmacodynamic point of view, at least when treating bacteria with high MIC values for the studied antibacterials.

In general, the intermittent intravenous administration of antibacterials represents the most common method of antibacterial prescription used by clinicians and the most frequent instruction for administration suggested by pharmaceutical companies. However, the optimal dose administration strategy of antimicrobial agents for the treatment of serious infections remains controversial. During the 1970s and 1980s several investigators examined the effectiveness, and pharmacokinetic and pharmacodynamic properties of alternative modes of antibacterial administration, namely continuous 24-hour infusion.[1-6] This interest in the continuous intravenous administration of antibacterials has been revived during the last few years, mainly because of the emergence of multidrug-resistant bacteria and the limitations of the currently available therapeutic choices.[7-9]

The comprehension of the pharmacodynamic principles of drugs gained during the last few decades has led to the classification of the antimicrobial agents into two main categories: (i) concentration-dependent antibacterials, such as aminoglycosides and fluoroquinolones; and (ii) the concentration-independent or time-dependent antibacterials, such as β-lactams, macrolides, clindamycin, linezolid, quinupristin/dalfopristin and vancomycin.[10] Different dose administration strategies for antibacterials may optimise their pharmacokinetic and pharmacodynamic parameters, improve outcomes and overcome the problem of antimicrobial resistance according to whether they exert a concentration-dependent or -independent bacterial killing.[11] Several studies in animals and fewer in humans have attempted to assess the value of the continuous intravenous infusion of various antibacterials compared with the current intermittent administration. The resulting data have been controversial.[12-16]

We previously performed a meta-analysis of randomised controlled trials that compared the clinical outcomes (effectiveness and toxicity) obtained via continuous and intermittent antibacterial

administration.[17] In this article we report on data gathered by reviewing randomised clinical trials, focusing specifically on the pharmacokinetic and/or pharmacodynamic properties of different classes of antibacterials administered by continuous infusion or by intermittent bolus. The main objective of this systematic review was to compare the pharmacokinetic and pharmacodynamic parameters of antibacterials with time-dependent bacterial killing obtained by the two modes of dose administration.

1. Methods of Literature Review and Data Selection

Relevant studies for this systematic review were identified from PubMed (January 1950 to January 2005), Current Contents, the Cochrane central register of controlled trials, and references from relevant articles and review papers. Search terms included "continuous", "intravenous", "antibiotics", "intermittent", "bolus", "dosing", "infusion", "discontinuous" and "administration". Abstracts presented at international conferences were not searched.

We performed literature searches and examined the identified relevant studies for inclusion in further analysis of data on the pharmacokinetic and/or pharmacodynamic properties of antibacterials. A study was considered eligible for a full review of the reported data if it: (i) was a randomised clinical trial; (ii) compared the continuous with the intermittent mode of intravenous administration of the same antibacterial; and (iii) assessed the pharmacokinetic and/or pharmacodynamic properties of both modes of administration. No restriction in language was set. Experimental trials, trials concerning antifungal, antiviral or antiparasitic agents, as well as surgical prophylaxis trials were excluded. In addition, trials that involved the aminoglycosides were not included in the analyses on the basis of previous studies that showed that continuous infusion of these medications can be too toxic and, thus, is not clinically applicable.

The following data were extracted from each study: clinical settings, number of participants in each intervention arm, antibacterial agents and dosages used, as well as the pharmacokinetic and/or pharmacodynamic parameters reported in the studies, including maximum serum concentration (C_{max}), trough serum concentration (C_{min}), steady-state or plateau serum concentration (C_{ss}), area under the concentration-time curve (AUC), time above the minimum inhibitory concentration (MIC) [T > MIC], AUC : MIC, elimination rate constant, elimination half-life, volume of distribution and systematic clearance.

The main outcome measures examined were the C_{max} and C_{min} of the drug, C_{ss}, the AUC from 0 to 24 hours (AUC_{24}), T > MIC, AUC : MIC, the volume of distribution, systematic clearance, elimination half-life and elimination rate constant.

1.1 Trial Characteristics

Our literature search strategy revealed 75 possible clinical and/or pharmacokinetic-pharmacodynamic studies regarding the continuous intravenous infusion of antibacterial agents; 47 of 75 studies were comparative studies and were examined further.[1-9,12-16,18-50] Twenty-eight were noncomparative studies and were excluded at this stage.[51-78] From these 47 comparative studies, 20 were excluded from the analysis: 13 that focused exclusively on clinical outcome data, 3 trials that compared the rate of prevention of surgical site infections after continuous or intermittent infusion of antibacterials, 2 that examined cost effectiveness and 2 that studied the administration of amphotericin B and gentamicin.[1-5,8,13-15,24,25,27,29,33,36,37,39,40,48,50] The remaining 27 comparative studies reported pharmacokinetic and/or pharmacodynamic results for the two modes of antibacterial administration (continuous or intermittent). Of these 27 studies, 7 did not provide sufficient comparative data about the predefined outcome measures and 3 studies did not have a

randomised design; these 10 studies were not considered further in this review.[6,9,16,19,23,34,35,42,44,46] Subsequently, 17 randomised clinical trials were included in this analysis that compared pharmacokinetic and/or pharmacodynamic data of antibacterials administered by the continuous or intermittent intravenous mode.[7,12,18,20-22,26,28,30-32,38,41,43,45,47,49]

All 17 selected studies were conducted in adults: 11 trials involved in-hospital patients, while the remaining 6 studied healthy volunteers. Seven of the 11 trials were conducted in intensive care units and the other 4 in medical wards. Consequently, the majority of the studied patients were critically ill with severe infections. In addition, one study referred to cystic fibrosis patients with acute pulmonary infection due to *Pseudomonas aeruginosa* strains. Furthermore, the majority of the trials were conducted in the US[12,21,22,28,31,41,43,47] and funded either by pharmaceutical companies or by national health institutes.[7,18,20-22,28,41,47,49] Fifteen trials involved the β-lactams (six for ceftazidime, three for cefepime, three for piperacillin/tazobactam and one each for cefpirome, meropenem and piperacillin), and two trials involved glycopeptides (vancomycin). The responsible pathogens of the infections in most of the studies were Gram-negative bacilli.

2. Pharmacodynamic Parameters

Table I depicts the characteristics of the 14 individual studies analysed for the pharmacodynamic outcomes of various antibacterials administered intermittently or continuously. As expected, the mean C_{max} values of the intermittently administered antibacterials were higher than the C_{ss} values achieved by continuous administration of the same antibacterial in all eligible studies (C_{max} was on average 5.5 times higher than C_{ss}, range 1.9–11.2). In addition, C_{ss} was on average 5.8 times higher than the C_{min} of the intermittently administered antibacterials (range 1.2–15.6). Five trials used relatively fewer total daily doses of the studied drugs with continuous than with intermittent administration.[12,21,22,28,45] Subgroup analysis of the trials that used equal total daily doses in both treatment groups (intermittent and continuous) revealed that C_{max} was on average 4.7 times higher than C_{ss} (range 1.9–8.3) and C_{ss} was on average 6.3 times higher than C_{min} (range 1.9–15.6). Similar results were obtained in a subset analysis of the trials that involved the β-lactams exclusively (mean C_{max}/C_{ss}: 5.8 and mean C_{ss}/C_{min}: 6.5). A loading dose was administered prior to the continuous infusion of the antibacterials in 7 of the 14 trials.

It is interesting to note that there is considerable variation in the comparisons of the reported AUC values obtained by the two methods of intravenous antibacterial administration in each trial. For example, eight trials reported higher AUC values when the antibacterial was administered by intermittent bolus compared with continuous infusion (seven involved the β-lactams and one vancomycin), while three trials that involved the cephalosporins and vancomycin reported the opposite (the differences did not reach statistical significance).[21,26,31]

Table I presents only the T > MIC values from infected patients and not the healthy volunteers and, thus, represent everyday clinical practice. Six trials reported T > MIC values: four for cephalosporins (two ceftazidime and two cefepime), one for a carbapenem (meropenem) and one for a glycopeptide (vancomycin). This pharmacodynamic parameter describes the length of time that the serum drug concentration is above the MIC of the causative organism and is expressed as percentage of the dose administration interval (five trials) or as hours (one trial). No differences were observed in three of the six trials.[31,32,45] The responsible pathogens in these studies included Gram-negative bacteria, such as *Klebsiella* spp., *Enterobacter* spp., *Salmonella* spp., *Proteus mirabilis* and *Haemophilus influenzae*, as well as Gram-positive bacteria, such as *Staphylococcus aureus*. The MIC values for the studied

Table I. Characteristics of eligible randomised clinical trials included in the comparisons of the pharmacodynamic parameters

Study (year)	Study population	Number of pts		Antibacterial dosage		AUC_{24} (μg • h/mL) [mean ± SD (range)]		Serum concentration (μg/mL) [mean ± SD (range)]			T > MIC (% of dosing interval or h)	
		I	C	I	C	I	C	I		C	I	C
								C_{max}	C_{min}	C_{ss}		
Mouton et al.[38] (1990)	Healthy volunteers	8	8	Ceft 25 mg/kg q8h	Ceft 15 mg/kg ld → 60 mg/kg/24h	285.4 ± 22.7	21.3 ± 3.0	ND	ND	ND	ND	ND
Nicolau et al.[41] (1996)	Healthy volunteers	12 (gp 1) 12 (gp 2)	12 (gp 3) 12 (gp 4)	Ceft 1g q8h (gp 1) Ceft 1g q12h (gp 2)	Ceft 3 g/24h (gp 3) Ceft 2 g/24h (gp 4)	476.4 ± 138.5 (gp 1) 305.1 ± 70.9 (gp 2)	419.9 ± 108.7 (gp 3) 298.9 ± 70.4 (gp 4)	82.05 ± 22.91 (gp 1) 85.78 ± 29.48 (gp 2)	ND	18.15 ± 4.51 (gp 3) 12.77 ± 2.95 (gp 4)	ND	ND
Benko et al.[12] (1996)	Critically ill pts with suspected Gram-negative infections	6	6	Ceft 2g q8h	Ceft 2g ld → 3 g/24h	331 ± 165*	112 ± 56*	124.4 ± 52.6	25 ± 17.5	29.7 ± 17.4	100% for 92% of pts	100% for all pts
Hanes et al.[28] (2000)	Critically ill trauma pts	14	17	Ceft 2g q8h	Ceft 2g ld → 60 mg/kg/24h	ND	ND	90.9 ± 44.3	3.7 ± 3.9	19.2 ± 8.6	100% except in one pt	100% for all pts
Buijk et al.[20] (2002)	Pts with severe intra-abdominal infections	6	12	Ceft 1.5g q8h	Ceft 1g ld → 4.5 g/24h	1064 (505–1950) on d2 1166 (644–1496) on d4	1131 (505–2230) on d2 1098 (581–2233) on d4	88.7 (58.3–124.8) on d2 104.4 (94.6–127.8) on d4	19.4 (5.6–68.4) on d2 23.7 (7.1–41.3) on d4	47.1 (21.1–92.9) on d2 45.1 (24.4–93.1) on d4	ND	ND
Georges et al.[26] (1999)	Critical care pts (preliminary results)	9	9	Cef 2g q12h	Cef 4 g/24h	473	624	ND	ND	ND	20.7 ± 3h*	23.8 ± 0.2h*
Burgess et al.[21] (2000)	Healthy volunteers	12	6 (gp 1) 6 (gp 2)	Cef 2g q12h	Cef 3 g/24h (gp 1) Cef 4 g/24h (gp 2)	357 ± 95*	285 ± 46* (gp 1) 411 ± 45* (gp 2)	112.9 ± 21.1	1.3 ± 0.5	13.9 ± 3.8 (gp 1) 20.3 ± 3.3 (gp 2)	ND	ND

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Table I. Contd

Study (year)	Study population	Number of pts		Antibacterial dosage		AUC_{24} (μg • h/mL) [mean ± SD (range)]		Serum concentration (μg/mL) [mean ± SD (range)]			T > MIC (% of dosing interval or h)	
		I	C	I	C	I	C	I		C	I	C
								C_{max}	C_{min}	C_{ss}		
Jaruratana-sirikul et al.[32] (2002)	Pts with Gram-negative bacilli bacteraemia	5	5	Cef 2g q12h	Cef 4 g/24h	ND	ND	233.09 ± 65.37	4.74 ± 3.99	49.8 ± 18.4 (peak) 41.42 ± 16.48 (trough)	100%	100%
Hollenstein et al.[30] (2000)	Healthy volunteers	6	6	Cefp 2g as a single dose for 10 min	Cefp 2g over 12h	230.7 ± 29.8	175.0 ± 18.6	114.2 ± 19.3	4.1 ± 0.5	38.1 ± 5.3 (peak) 19.0 ± 1.9 (trough)	ND	ND
Richerson et al.[43] (1999)	Healthy volunteers	12	12	Pip/taz 4.5g q6h	500 mg/h based on the pip component	354	ND	232 (pip)	ND	28.0 (pip)	ND	ND
Burgess and Waldrep[22] (2002)	Healthy volunteers	11 (gp 1)	11 (gp 2) 11 (gp 3)	Pip/taz 3g/ 0.375g q6h (gp 1)	Pip/taz 6g/ 0.75g (gp 2) Pip/taz 12g/ 1.5g (gp 3)	926 ± 162 (pip)	330 ± 109* (gp 2) 731 ± 140* (gp 3) [pip]	179.8 ± 43.5* (pip)	ND	16.0 ± 5.0 (gp 2) 37.2 ± 6.8 (gp 3) [pip]	ND	ND
Thalhammer et al.[45] (1999)	Critically ill pts	15	15	Mer 2g q8h	Mer 2g ld → 3g	193.8 ± 21.1*	117.5 ± 12.9*	110.1 ± 6.9	8.5 ± 1.0	11.9 ± 5.0	100%	100%
James et al.[31] (1996)	Pts with suspected or documented Gram-positive infections	5	5	Van 1g q12h	Van 500mg ld → 2g	AUBC: MSSA 528.4 ± 263.7; MRSA 531.4 ± 247.1	AUBC: MSSA 547.5 ± 390.7; MRSA 548.4 ± 293.4	53.4 ± 19.3	8.4 ± 5.9	20.2 ± 11.1	100%	100%
Wysocki et al.[49] (2001)	Pts with severe *Staphylococcal* infections	58	61	Van 15 mg/ kg q12h	Van 15 mg/kg ld → 30 mg/ kg	653 ± 232	577 ± 120	ND	15 ± 9	24 ± 8	ND	ND

AUBC = area under the bactericidal curve; **AUC_{24}** = area under the concentration-time curve from 0 to 24 hours; **C** = continuous infusion; **Cef** = cefepime; **Cefp** = cefpirome; **Ceft** = ceftazidime; **C_{max}** = maximum serum concentration; **C_{min}** = trough concentration; **C_{ss}** = plateau concentration; **d*x*** = day *x*; **gp** = group; **I** = intermittent dose administration; **ld** = loading dose; **Mer** = meropenem; **MRSA** = meticillin-resistant *Staphylococcus auerus*; **MSSA** = meticillin-susceptible *S. aureus*; **ND** = no data reported; **pip/taz** = piperacillin/ tazobactam; **pt(s)** = patient(s); **q*x*h** = every *x* hours; **T > MIC** = time above the minimum inhibitory concentration value; **Van** = vancomycin; → indicates followed by; * indicates statistical significance ($p < 0.05$).

antibacterials were significantly below 1 μg/mL for these bacteria. Although the results of these three studies were similar, several additional results need mentioning. For example, the observed T > MIC of 8 μg/mL in patients with Gram-negative bacteraemia receiving intermittent cefepime 4g was 81.7% of the dose administration interval. In the continuous group, the C_{ss} for cefepime was more than four times the MIC of 8 μg/mL for 100% of the dose administration interval.[32] In addition, continuous intravenous infusion or intermittent administration of meropenem in critically ill patients produced exactly the same results for T > MIC with only 50% of the intermittently administered dose.[45]

T > MIC was higher for the patients receiving continuous infusion of the antibacterials in the remaining three trials.[12,26,28] Specifically, in two studies involving critically ill patients,[12,28] T > MIC was 100% of the dose administration interval in all patients treated with continuous infusion of ceftazidime compared with 92% for the patients in the intermittent group. Interestingly, the patients in the continuous group received half of the total daily dosage of ceftazidime received by those in the intermittent group in one of these studies.[12] In the same setting in another trial, continuous infusion of cefepime 4g was found to produce serum concentrations above the MIC values of the causative organisms for 23.8 ± 0.2 hours and for 20.7 ± 3 hours when it was administered intermittently ($p < 0.01$). Moreover, the time that the cefepime concentration was above five times the MIC in this study was statistically significantly longer in the continuous than the intermittent group (23.61 ± 0.6 vs 16.6 ± 6 hours; $p < 0.01$).[26] Of note, a study in patients with severe intra-abdominal infections reported that continuous infusion of ceftazidime resulted in concentrations in the exudate that exceeded four times the MIC of the responsible pathogens for 100% of the dose administration interval. In addition, these concentrations were above the MIC of 16 μg/mL for 92% of the dose administration interval. The observed concentrations in the group of patients that received ceftazidime intermittently were 88% and 44%, respectively.[20]

3. Pharmacokinetic Parameters

Table II summarises key aspects of the ten trials that were analysed for the pharmacokinetic outcomes of various antibacterials administered by the intermittent or continuous mode, including the intervention, sample size, antibacterial and dosage used. In six of the ten trials the antibacterial dosages were identical for the two modes of administration; consequently, their results could be further compared.[20-22,38,41,47] All of these studies involved the β-lactams; two were conducted in patients and the remaining four in healthy volunteers. The reported pharmacokinetic parameters were similar in the intermittent and continuous groups and were unaffected by the method of administration in the majority of the examined studies.

Within the subset of four trials that used unequal doses in the continuous and intermittent treatment regimens,[7,18,28,45] differences were found in three with regard to the systematic clearance of the medications.[7,18,45] In a study that assessed the pharmacokinetic and pharmacodynamic properties of continuous or intermittent intravenous administration of ceftazidime in patients with septicaemic melioidosis, the difference in systematic clearance reached statistical significance ($p < 0.05$). The investigators attributed this to the slight variations in creatinine clearance at randomisation (median creatinine clearance in the intermittent group was 23 vs 38 mL/min in the continuous group).[18] In addition, another study demonstrated that continuous infusion of 15% lower than the intermittent mean total daily dose of piperacillin/tazobactam in patients with community- or hospital-acquired infections resulted in higher piperacillin clearance values. This occurred because of the nonlinear pharmacokinetic

Table II. Characteristics of eligible randomised clinical trials included in the comparisons of the pharmacokinetic parameters

Study (year)	Study population	Number of pts		Antibacterial dosage		Volume of distribution (L/kg) [mean ± SD (range)]		Systematic clearance (L//h) [mean ± SD (range)]		Elimination half-life (h) [mean ± SD (range)]		Elimination rate constant (h^{-1}) [mean ± SD (range)]	
		I	C	I	C	I	C	I	C	I	C	I	C
Mouton et al.[38] (1990)	Healthy volunteers	8	8	Ceft 25 mg/kg q8h	Ceft 15 mg/kg ld → 60 mg/kg/24h	0.18 ± 0.02	ND	8.05 ± 1.54	7.91 ± 1.26	1.58 ± 0.09	ND	ND	ND
Nicolau et al.[41] (1996)	Healthy volunteers	12 (gp 1) 12 (gp 2)	12 (gp 3) 12 (gp 4)	Ceft 1g q8h (gp 1) Ceft 1g q12h (gp 2)	Ceft 3 g/24h (gp 3) Ceft 2 g/24h (gp 4)	ND	ND	6.73 ± 1.67 (gp 1) 6.91 ± 1.68 (gp 2)	7.28 ± 1.75 (gp 3) 6.83 ± 1.48 (gp 4)	1.74 ± 0.07 (gp 1) 1.67 ± 0.13 (gp 2)	ND	ND	ND
Hanes et al.[28] (2000)	Critically ill trauma pts	14	17	Ceft 2g q8h	Ceft 2g ld → 60 mg/kg/24h	0.32 ± 0.14	ND	9.79 ± 4.45	10.29 ± 3.192	1.72 ± 0.71	ND	0.46 ± 0.15	ND
Angus et al.[18] (2000)[a]	Pts with septicaemic melioidosis	11	10	Ceft 40 mg/kg q8h	Ceft 12 mg/kg ld → 4 mg/kg/h	0.45 (0.25–0.57)	0.49 (0.24–0.57)	1.89* (0.35–1.13)	6.23* (2.66–8.75)	11.89 (1.95–44.71)	3.59 (2.65–5.78)	3.48 (0.93–21.3)	11.58 (7.2–15.72)
Buijk et al.[20] (2002)	Pts with severe intra-abdominal infections	6	12	Ceft 1.5g q8h	Ceft 1g ld → by 4.5 g/24h	0.28 (0.15–0.44)	ND	5.1 (2.3–8.9) on d2 4.0 (2.0–7.0) on d4	4.1 (1.4–8.9) on d2 4.2 (1.6–7.7) on d4	4.2 (1.3–12.3)	ND	ND	ND
Burgess et al.[21] (2000)	Healthy volunteers	12	6 (gp 1) 6 (gp 2)	Cef 2g q12h	Cef 3 g/24h (gp 1) Cef 4 g/24h (gp 2)	ND	ND	12.4 ± 5.1	10.7 ± 1.6 (gp 1) 9.8 ± 1.1 (gp 2)	2.6 ± 0.4	1.9 ± 0.8 (gp 1) 2.3 ± 0.7 (gp 2)	ND	ND
Burgess and Waldrep[22] (2002)	Healthy volunteers	11 (gp 1)	11 (gp 2) 11 (gp 3)	Pip/taz 3g/0.375g q6h (gp 1)	Pip/taz 6g/0.75g q24h (gp 2) Pip/taz 12g/1.5g q24h (gp 3)	ND	ND	13.3 ± 2.3 (gp 1) [pip]	17.1 ± 5.2 (gp 2) 13.9 ± 2.9 (gp 3) [pip]	ND	ND	ND	ND
Vinks et al.[47] (2003)	Pts with cystic fibrosis and acute pulmonary infections due to *Pseudomonas aeruginosa*	4	5	Pip/taz 4g/0.5g q6h	Pip/taz 16g/2g q24h	0.24 ± 0.09	ND	13.1 ± 2.3*	24.4 ± 11.7*	1.2 ± 0.9	ND	ND	ND
Buck et al.[7] (2005)	Pts with hospital or community acquired infections	12	12	Pip/taz 4g/0.5g q8h	Pip/taz 2g/0.5g ld → pip/taz 8g/1g q24h	0.45 (pip) 0.54 (taz)	0.37 (pip) 0.35 (taz)	5.7 (pip) 7.4 (taz)	8.9 (pip) 7.4 (taz)	ND	ND	ND	ND
Thalhammer et al.[45] (1999)	Critically ill pts	15	15	Mer 2g q8h	Mer 2g ld → 3 g/24h	0.38 ± 0.05	0.37 ± 0.08	9.4 ± 1.2*	7.7 ± 1.4*	2.4 ± 0.7	ND	0.32 ± 0.12	ND

a All values of this trial are expressed as median (range).

C = continuous infusion; **Cef** = cefepime; **Ceft** = ceftazidime; **d*x*** = day *x*; **gp** = group; **I** = intermittent dose administration; **ld** = loading dose; **Mer** = meropenem; **ND** = no data reported; **pip/taz** = piperacillin/tazobactam; **pt(s)** = patient(s); **q*x*h** = every *x* hours; → indicates followed by; * indicates statistical significance ($p < 0.05$).

behaviour of piperacillin in the continuous treatment group.[7] Similar results were also reported for piperacillin in another study of cystic fibrosis patients.[47] Finally, intravenous administration of meropenem in critically ill patients showed statistically significant differences in the clearance of the medication according to the method of administration (9.4 ± 1.2 vs 7.7 ± 1.4 L/h [mean ± SD] in the intermittent and continuous groups, respectively; p = 0.01).[45]

4. Implications of the Published Evidence

In general, the administration of antibacterial therapy intermittently or continuously resulted in no significant differences in pharmacodynamic outcomes in three of six studies provided that the MIC values for the target organisms were close to the concentrations attained by the examined antibacterials. However, lower total daily doses of antibacterials with time-dependent bacterial killing, such as β-lactams, were needed to achieve the same pharmacodynamic outcomes with continuous infusion than with an intermittent regimen. In addition, the method of administration influenced the pharmacokinetic and pharmacodynamic outcomes when bacteria with higher MIC values were the cause of infection. Moreover, continuous infusion of time-dependent antibacterials appeared to be a valuable therapeutic option in difficult to treat infections as this method of administration achieved higher tissue site concentrations and more favourable pharmacodynamic parameters at the site of the infection than did intermittent administration.

Recent advances in the understanding of pharmacokinetic and pharmacodynamic properties of the antibacterials have led to new insights into dose administration strategies. Parameters such as AUC : MIC, C_{max} : MIC and T > MIC have been identified as factors that are closely related to clinical and microbiological outcomes.[10] The effectiveness of the time-dependent (or concentration-independent) agents increases as the T > MIC (measuring serum or, preferably, tissue site concentrations of the antibacterial) for the target pathogen increases. This can be accomplished with continuous antibacterial administration or with more frequent dose administration.[79] Although vancomycin, macrolides (especially azithromycin) and quinupristin/dalfopristin exhibit a time-dependent bacterial killing, as a result of the longer post-antibiotic effects that they exert compared with β-lactams, the AUC : MIC seems to best correlate with efficacy for these agents.

Studies of animals and humans have demonstrated that for concentration-dependent antibacterials (aminoglycosides and fluoroquinolones) a C_{max} : MIC ratio of 8–12 is needed for the successful killing of various pathogens.[80,81] Moreover, the target AUC_{24} : MIC of free drug has been found to be different for Gram-positive and Gram-negative microorganisms. For example, the AUC_{24} : MIC for free drug should be at least 25–35 for fluoroquinolones in *Streptococcus pneumoniae* infections.[82] However, this ratio should be >100 to obtain sufficient rates of bacteriological and clinical cure against Gram-negative bacteria.[11,83,84] Experimental studies have also shown that the concentration of time-dependent antibacterials does not need to be above the MIC for 100% of the dose administration interval to produce maximum bactericidal activity.[10] In addition, this pharmacodynamic parameter, T > MIC, seems to depend on the individual pathogen. A T > MIC of approximately 60–70% or 40–50% of the dose administration interval is generally needed for optimum activity against susceptible Gram-negative or -positive microorganisms, respectively.[22] It is important to note that most of these studies have examined the cephalosporins, penicillins and carbapenems.

A better outcome, although statistically non-significant, was observed with the continuous intravenous administration of time-dependent antibacter-

ials in a meta-analysis of relevant randomised controlled trials that we performed; the pooled odds ratio for clinical failure was 0.80 (95% CI 0.55, 1.16) for continuous versus intermittent intravenous administration. Interestingly, when a subset of trials that used the same total antibacterial dose in both intervention arms was analysed, clinical failure was lower in the continuous group of patients, a statistically significant difference (pooled odds ratio 0.70; 95% CI 0.5, 0.98). No differences were found for mortality and nephrotoxicity; the pooled odds ratio for mortality and nephrotoxicity was 0.89 (95% CI 0.48, 1.64) and 0.91 (95% CI 0.56, 1.47), respectively, for the continuous versus the intermittent intravenous administration of antibacterials.[17] There are also a few reports indicating that the continuous intravenous administration of antibacterials may be a valuable therapeutic strategy against multidrug-resistant pathogens and that they may reduce the development of antibacterial resistance.[16,78,85] In addition, continuous intravenous administration is a more cost-effective treatment than intermittent administration with respect to drug, labour and supply costs, as well as costs related to the monitoring of serum antibacterial concentrations.[8,15,29,37] However, continuous intravenous infusion of antibacterials requires a dedicated intravenous line and, thus, other intravenous access is needed for the administration of other medications. It also has some limitations concerning the stability of the drug after exposure to environmental conditions for up to 24 hours and the potential incompatibility with coadministered drugs.

5. Limitations of the Interpretation of the Reviewed Data

Several limitations of this systematic review should be acknowledged. First, the sample size of the eligible trials was relatively small. Moreover, the trials examined different populations (healthy volunteers and patients), which could impact on the pharmacokinetic and/or pharmacodynamic properties of the examined medications. The sites of the infections and the responsible pathogens also varied among the identified studies. In addition, a few of the included trials used a crossover design that could result in a misleading pharmacokinetic and/or pharmacodynamic assessment of the antibacterials. However, all of the trials used a washout period to circumvent these pitfalls.

Furthermore, a validity assessment of the individual studies included in this systematic review was not performed. It should also be acknowledged that not enough data were available in the reviewed studies for free drug concentrations due to protein binding, an important parameter with potential effect on clinical outcomes. MIC values, T > MIC and AUC **:** MIC were also not measured in the majority of the included trials. In addition, pharmacokinetic and/or pharmacodynamic indices were not linked to the original clinical or microbiological outcomes or to the original resistance development in any of the studies.

6. Conclusions

The method of antibacterial administration seems to be of greater importance when treating bacteria with high MIC values. Continuous infusion of antibacterials with time-dependent bacterial killing results in similar pharmacodynamic outcomes as intermittent administration; however, fewer total daily doses are needed in infections caused by pathogens with MIC values close to the concentrations attained by the examined drugs. Randomised controlled trials are needed to further establish the potential effects of the method of intravenous administration (intermittent or continuous) on the pharmacokinetic and pharmacodynamic properties of antibacterials, the clinical and bacteriological outcomes, and on the prevention of development of antimicrobial resistance. While new data are awaited, clinicians should take into account the pharmacokinetic and pharmacodynamic properties

of antibacterials and the optimum method of their administration, at least in patients with infections caused by multidrug-resistant bacteria.

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