Better outcomes through continuous infusion of time-dependent antibiotics to critically ill patients?

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Purpose of review

Increasing interest is being directed toward possible benefits associated with continuous infusion of time-dependent antibiotics such as β-lactams and vancomycin to critically ill patients. The background, emerging evidence and practical considerations associated with continuous infusions are discussed.

Recent findings

One large retrospective cohort study has found clinical outcome benefits of administering a β-lactam antibiotic by extended infusion compared with bolus administration. This complements a smaller randomized controlled trial comparing continuous infusion and intermittent bolus administration. For vancomycin, clinical outcome benefits have only been shown in a ventilator-associated pneumonia cohort of critically ill patients. No clinical outcome studies have been conducted for other time-dependent antibiotics.

Summary

Continuous infusion of vancomycin and β-lactam antibiotics enables faster and more consistent attainment of therapeutic levels compared with intermittent bolus dosing. Although the clinical benefits have not been conclusively shown at this time, compelling pharmacokinetic/pharmacodynamic support for continuous infusion nevertheless exists. Given that critically ill patients may develop very large volumes of distribution as well as supranormal drug clearances, individualized therapy through the use of therapeutic drug monitoring is required. A definitive determination of the relative clinical efficacy of intermittent bolus and continuous administration of β-lactams or vancomycin will only be achieved after a large-scale multicenter randomized controlled trial has been performed.

Keywords

clinical outcomes, continuous infusion, pharmacodynamics, pharmacokinetics, therapeutic drug monitoring

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Introduction

The problems associated with escalating antibiotic resistance and decreased development of antibiotics with novel mechanisms of action has necessitated more research into existing antibiotics. Specifically, studies [1,2] that seek to maximize antibiotic activity from altered dosing regimens are subject to increasing attention. Studies characterizing improved penicillin activity with more frequent dosing were performed as early as the late 1940s. Over the past 20 years, researchers and clinicians have developed an improved understanding of bacterial-kill characteristics, which has led to a rediscovered interest in this area of altered antibiotic dosing.

Pharmacodynamic studies have broadly classified different antibiotic classes to have either concentration-dependent or time-dependent bacterial killing characteristics (see Table 1). For concentration-dependent antibiotics, a high ratio of the peak concentration in a dosing period (C_{max}) to the minimum inhibitory concentration (MIC) of the pathogen (C_{max}:MIC) enables maximal bacterial killing [3]. These antibiotics also have a postantibiotic effect [4]. As such, large infrequent doses of these antibiotics will enable optimal antibacterial activity.

In 2007, the use of continuous infusions for administration of β-lactams, a family of time-dependent antibiotics, was well reviewed in *Current Opinion in Critical Care* by Mouton and Vinks [5••]. Time-dependent antibiotics have been shown to have maximal activity when the antibiotic concentration is maintained above the MIC ($T > MIC$). It follows that more frequent dosing, or dosing by extended infusion or continuous infusion should seek to achieve

Table 1 Pharmacodynamic bacterial kill characteristics of selected antibiotics

Pharmacodynamic kill characteristic	Optimal pharmacodynamic parameter	Antibiotics
Concentration-dependent	C_{max} : MIC	Aminoglycosides
		Fluoroquinolones
		Nitroimidazoles (e.g. metronidazole)
		Polymyxins (e.g. colistin)
Time-dependent	$T >$ MIC	β-Lactams
		Oxazolidinones
		Some macrolides (erythromycin, clarithromycin)
		Lincosamides (e.g. clindamycin)

such pharmacodynamic targets more successfully than intermittent bolus dosing [6]. In the context of critically ill patients, in whom early and appropriate antibiotic therapy has been shown to be an essential factor for improving clinical outcomes [7–13], an increasing amount of research is being committed to this area. Furthermore, an evaluation of recent data on the utility of continuous infusion for other time-dependent antibiotics such as vancomycin is also needed. In this overview, the clinical utility of administering time-dependent antibiotics by continuous infusion will be explored with special emphasis on emerging data. Given the recent review by Mouton and Vinks on β-lactams [5••], we will focus mostly on new data in this area.

β-Lactams

β-Lactam antibiotics include penicillins, cephalosporins, carbapenems and monobactams. Pharmacodynamically, in-vivo experiments have described a bacterial killing that is slow and related to the time for which the antibiotic concentration exceeds the MIC of the infecting pathogen [3]. Studies [14] have shown that bacterial killing is maximized when the β-lactam concentration is maintained at 4–5 × MIC. Specific target T more than MICs correlated with maximal bacterial killing have been determined for each of the β-lactam classes of antibiotic, penicillins ($T >$ MICs 50–60% of dosing interval), cephalosporins ($T >$ MICs 60–70% of dosing interval), carbapenems ($T >$ MICs 20–40% of dosing interval) and monobactams ($T >$ MIC 50–60%) [15].

Infusion versus intermittent dosing: pharmacokinetics in critically ill

The pharmacokinetics of β-lactams are different in critically ill patients compared with normal ward patients. Critically ill patients can develop increased volumes of distribution (V_d) and/or increased drug clearance. This can result in lower β-lactam trough concentrations [16–19]. In particular, low antibiotic levels have been shown to correlate with the development of increased creatinine clearance as a result of concomitant treatments to critically ill patients (e.g. increased cardiac output from fluid loading and inotrope administration) [16]. As such, extended or continuous infusions have been proposed, and subsequently shown to achieve higher antibiotic trough concentrations [6]. Recent studies by De Jongh *et al.* [20] and Langgartner *et al.* [21] further this understanding.

De Jongh *et al.* [20] evaluated the pharmacokinetic characteristics of temocillin (a penicillin stable to most extended-spectrum β-lactamases) administered by intermittent bolus or continuous dosing, in critically ill patients. The authors found the minimum concentration observed after an intermittent dose (C_{min}; 28 mg/l) to be significantly less than the steady state concentrations (C_{ss}) in plasma of continuous infusion (73 mg/l). With MICs of isolated organisms ranging from 2 to 16 mg/l, continuous infusion of temocillin achieves a plasma C_{ss} that is 4 × MIC of the least susceptible organism, which should enable maximal bacterial killing.

Langgartner *et al.* [21] found that a continuous infusion dose of piperacillin–sulbactam that was 33% lower than an intermittent bolus dose achieved trough concentrations (26 versus 12 mg/l) higher than *Pseudomonas aeruginosa* pharmacodynamic breakpoints (8–16 mg/l). An ongoing shortcoming of some pharmacokinetic studies is the use of trough concentrations as a pharmacodynamic endpoint rather than the specific $\%T$ more than MIC for the study antibiotic. Specifically, this errant reporting disadvantages results for intermittent bolus dosing regimens in which C_{min} is likely to be much less than concentrations after 30–60% of the dosing interval.

Pharmacokinetic/pharmacodynamic data

The difficulty of conducting appropriate studies comparing clinical outcomes of continuous infusion versus intermittent bolus dosing of time-dependent antibiotics (see below) can be remedied with pharmacokinetic/pharmacodynamic analysis of pseudoclinical data from in-vitro or ex-vivo studies. Recent studies have used different forms of pharmacokinetic/pharmacodynamic modeling to relate target pharmacodynamic antibiotic exposures to susceptibility data to compare the efficacy of different dosing regimens. Sakka *et al.* [22••] compared a 33% lower continuous infusion dose with intermittent bolus dosing of imipenem–cilastatin in 20 critically ill patients using population pharmacokinetic analysis. The authors reported that continuous infusion would achieve 90% success for organisms with a MIC of 2–4 mg/l compared with 90% success for intermittent bolus dosing for organisms with a MIC of 1–2 mg/l.

A comprehensive mathematical analysis of different piperacillin/tazobactam doses to achieve pharmacodynamic targets was undertaken by Kim *et al.* [23]. Using MICs of isolates obtained from the author's institution, a comparison of 30-min infusion (3.375 gm over 30-min 4-hourly), extended infusion (4.5 gm over 4-h 6-hourly) and continuous infusion (18 g over 24-h) was undertaken to show that extended infusion and continuous infusion attained higher pharmacodynamic targets (90% when MIC 32 mg/l) compared with bolus 30-min infusion (90% when MIC 8 mg/l). This information suggests equivalence of extended and continuous infusions for attaining pharmacodynamic targets. Clinical outcome benefits supporting use of extended infusion or continuous infusion of β-lactams are still lacking although evidence is growing.

Tissue penetration

Antibiotic tissue penetration is essential for effective antibiotic therapy as most infections are thought to occur in tissue [24]. No published data could be found that directly compare subcutaneous or muscle antibiotic concentrations when administered by intermittent bolus or continuous dosing. We have in-house data that compare the serum and tissue pharmacokinetics of piperacillin in critically ill patients when administered by either intermittent bolus or continuous administration (J.A. Roberts, M.S. Roberts, T.A. Robertson, *et al.* Piperacillin penetration into tissue of critically ill patients with sepsis – bolus vs. continuous administration?, in preparation). We used microdialysis to identify higher unbound trough concentrations in subcutaneous tissue that were less variable than the concentrations observed with intermittent bolus dosing. A pharmacodynamic analysis (endpoint for continuous infusion $T >$ MIC 100% and bolus dosing $T >$ MIC 60%) showed that continuous infusion achieved better pharmacodynamic targets in tissue than intermittent bolus dosing. Such information is valuable as extracellular fluid in tissues is the source of most infections [24,25•,26] and because antibiotic penetration is likely to be highly variable between critically ill patients of different levels of sickness severity (J.A. Roberts, M.S. Roberts, T.A. Robertson, *et al.* Piperacillin penetration into tissue of critically ill patients with sepsis – bolus vs. continuous administration?, in preparation) [27].

Although other data on comparative tissue penetration of infusion and intermittent bolus dosing are sparse [28], available data suggest that target trough concentrations are more consistently achieved using continuous infusions. Boselli *et al.* [29] have published separate studies comparing piperacillin penetration into epithelial lining fluid when administered by intermittent bolus and continuous dosing [30]. As expected, the data suggest similar trough concentrations of piperacillin from the same daily dose from either dosing method (13.6 mg/l continuous infusion versus 12.7 mg/l bolus dosing).

Clinical outcome data

The review by Mouton and Vinks [5••] details a number of prospective randomized controlled trials comparing continuous infusion and intermittent bolus dosing of β-lactams. All of the cited studies were underpowered and only the *a priori* analysis by Roberts *et al.* [31] of patients receiving 4-or-more days therapy showed advantages for continuous infusion of ceftriaxone over intermittent bolus administration. The intention-to-treat analysis found equivalence between both dosing methods.

A recent, large retrospective cohort study of 194 patients by Lodise *et al.* [32••] compared extended infusion (4-h) of piperacillin–tazobactam with bolus administration (infusion over 30-min) in patients with *P. aeruginosa* infections. The authors found that in the most severely ill patients [Acute Physiology and Chronic Health Evaluation (APACHE) II score >17], the 14-day mortality rate was lower in the extended-infusion group (12.2 versus 31.6%; $P = 0.04$) and the median duration of hospital stay after collection of samples for culture was shorter in the extended-infusion group (21 versus 38 days; $P = 0.02$).

Although compelling pharmacokinetic–pharmacodynamic data favor extended infusion or continuous infusion of β-lactams because of more consistent achievement of target concentrations, there still remain insufficient clinical outcome data to recommend a widespread change from intermittent bolus dosing. For clinical efficacy of continuous infusion β-lactam therapy to be achieved, therapeutic drug monitoring (TDM) maybe necessary because the altered V_d and clearance of critically ill patients may mean that empiric doses never achieve therapeutic concentrations [33]. The opportunity for therapeutic failure would be increased in patients that are infected by pathogens with a high MIC. Such individualized dosing by use of TDM is already commonplace for vancomycin.

Vancomycin

Vancomycin exhibits time-dependent bactericidal activity against most gram-positive bacteria. It is, however, bacteriostatic against enterococci. In in-vitro studies vancomycin shows no concentration-dependent killing effect and has a short to moderate postantibiotic effect against gram-positive cocci [34]. Experimental models using neutropenic mice with peritonitis have, however, shown some concentration-dependent (C_{max}/MIC) activity with advantages also evident when the area under the concentration–time curve (AUC) to MIC ratio (AUC/MIC) is maximized

[35]. Because of these varied findings, the optimal dosing regimen for vancomycin dosing remains unclear: intermittent dosing or continuous infusion?

Infusion versus intermittent dosing: pharmacokinetics in critically ill

The pharmacokinetics of vancomycin can be significantly altered in critically ill patients compared with normal ward patients [36,37]. As for β-lactams, increased V_d and/or increased drug clearance can result in lower vancomycin concentrations [38]. As such, administration by extended infusion or continuous infusion may enable more consistent attainment of target concentrations with corresponding therapeutic advantages.

Pharmacokinetic/pharmacodynamic data

Prompt initiation of appropriate antibiotic therapy is considered crucial to optimize clinical outcomes [39]. In a prospective multicenter randomized study, Wysocki *et al.* compared continuous infusion of vancomycin with intermittent infusion in 119 critically ill patients with severe methicillin-resistant Staphylococcal infections [17]. In patients receiving continuous infusion, target concentrations (20–25 mg/l) were faster achieved than intermittent dosing (mean 36 versus 51 h; $P = 0.029$). In addition, the variability between patients in both the observed AUC and the total daily dose given over 10 days of treatment was lower with the continuous infusion approach. The differences in other pharmacokinetic–pharmacodynamic indices (C_{min}/MIC, AUC/MIC) were not considered.

Kitzis and Goldstein [40] reported data from a retrospective cohort of 1737 patients treated with vancomycin for staphylococcal infections. Trough vancomycin serum levels after either two to four separate doses ($n = 780$) or administration by continuous infusion ($n = 957$) were substantially higher in the continuous infusion group. At the first monitoring assay, 65.6% of patients in the intermittent infusion group did not reach target concentrations (≥15 mg/l) compared with 30.0% in the continuous infusion arm. This was confirmed on the basis of a clinical study evaluating the efficacy and toxicity of high-dose vancomycin therapy for methicillin-resistant *Staphylococcus aureus* (MRSA) infections [41]. Among patients in whom the target drug concentrations (defined as a trough level at least four times the MIC) were not achieved within 72 h the response rate was 20% lower (56 versus 76%; $P = 0.05$). Therefore, when administered in continuous infusion vancomycin C_{ss} should at least be five to six times the MIC of the infecting microorganism, or not be given continuously at all.

Administration by intermittent dosing has been shown to result in more variable concentrations. In patients receiving extended vancomycin courses Vuagnat *et al.* [42] observed higher variability in serum concentrations in the intermittent infusion group. Similar results were found by James *et al.* [43].

Much of the above data was challenged by an analysis of a retrospective cohort of 94 patients with MRSA pneumonia [44]. In this study, Jeffres *et al.* compared observed pharmacokinetic data and clinical outcomes in patients receiving vancomycin. This study suggested that aggressive dosing strategies (>15 mg/l) may not offer clinical advantages. Unfortunately, the study was devoid of pharmacodynamic data (MICs) and as such the recommendations were based on incomplete data. In a subsequent letter to the editor, Potoski and Paterson [45] correctly stated that pharmacokinetic–pharmacodynamic indices should be used to correlate antibiotic exposures and efficacy as opposed to just pharmacokinetic data alone.

Tissue penetration

Vancomycin is considered to have inconsistent distribution throughout body tissues. Data on poor lung penetration of vancomycin suggests the opportunity for suboptimal outcomes for pneumonia treated with vancomycin [46,47]. This contrasts data by Byl *et al.* in patients post lung surgery that found vancomycin levels in pleural fluid to be identical to plasma levels. Albanese *et al.* [48] investigated the cerebrospinal fluid (CSF) penetration of vancomycin administered by continuous infusion, and observed that penetration is increased three-fold in patients with meningitis (0.48 serum/CSF ratio meningitis patients versus 0.18 nonmeningitis). Another study by Ricard *et al.* [49] compared trough plasma levels (25.2 mg/l) to CSF levels (7.2 mg/l) of vancomycin administered by intermittent dosing. The authors observed a positive correlation ($R = 0.68$; $P = 0.01$) suggesting that increasing plasma levels of vancomycin will result in increased CSF levels.

The majority of the data suggest that continuous infusion enables faster attainment of more consistent target concentrations, although there are few clinical data to support these apparent benefits at this time.

Clinical outcome data

A small study by Di Filippo *et al.* [50] compared improvements in surrogate clinical endpoints for 25 patients randomized to receive vancomycin by intermittent or continuous administration. The authors observed more improvements in organ function and leucocyte response when vancomycin was continuously infused although no differences in disease evolution were observed. The largest prospective clinical outcome study comparing intermittent and continuous administration of vancomycin was performed by Wysocki *et al.* [51] in 119 critically ill patients. The authors found no

significant differences in terms of microbiological or clinical outcomes.

In a multicenter cohort of 75 critically ill patients with ventilator-associated pneumonia, Rello *et al.* [52] reported lower mortality rates among patients receiving vancomycin in continuous infusion (25 versus 55%; $P = 0.03$). A multivariable logistic regression model confirmed that continuous infusion of vancomycin was associated with improved survival (odds ratio for mortality, 0.22; 95% confidence interval 0.1–0.8). As far as we know, this is the only study to announce better survival among patients receiving vancomycin by continuous infusion. Caution is, however, recommended as this study was not designed to compare different dosing regimens, and as a consequence elementary pharmacodynamic data are lacking [23].

Other antibiotics

Few studies on continuous infusion of other time-dependent antibiotics have been undertaken. Adembri *et al.* [53•] compared the pharmacokinetic–pharmacodynamic characteristics of linezolid when administered by intermittent bolus dosing and continuous infusion. Using T more than MIC of 75% for maximal bactericidal activity as the pharmacodynamic endpoint the authors concluded that continuous infusion of linezolid achieved greater T more than MIC and AUC/MIC targets. The authors also found much less variability in concentrations using continuous infusion. No studies that compare clinical endpoints for linezolid administered by intermittent bolus or continuous dosing have been performed.

An in-vitro study by Tan *et al.* [54] examined potential benefits of administering the concentration-dependent antibiotic colistin by continuous infusion to a multidrug-resistant *Acinetobacter baumannii* species. No pharmacodynamic benefits were found.

Competing interests for continuous infusion of antibiotics

Other factors that a clinician must consider as part of the prescribing process for continuous infusion of a time-dependent antibiotic include antibiotic stability, intravenous line compatibility with coadministered drugs and tolerability.

Antibiotic stability

Vancomycin and most β-lactams are stable for at least 24-h in intravenous solutions. Some β-lactams are, however, not sufficiently stable and may require multiple infusions (e.g. meropenem; 3×8-h infusions [55,56]) in a 24-h period. To reduce the possibility of suboptimal antibiotic concentrations, the stability of the reconstituted product must be verified before an infusion is attempted.

Line compatibility

Given that continuous infusions require continual line access, compatibility with other drugs may become an issue. Wherever data are not available for both prescribed drugs, the potential formation of inactive salts or degradation of the antibiotic can be avoided by drug administration through separate lines. Wherever there is insufficient line access to allow separate simultaneous administration, use of extended-antibiotic infusions could be considered.

Tolerability

Few data are available that suggest improved tolerability with intermittent bolus or continuous administration. Given the wide therapeutic window of β-lactams, both methods of administration should be equivalent. Adverse reactions associated with the same daily dose of vancomycin administered by intermittent infusion for treatment of osteomyelitis resulted in more adverse drug reactions in the intermittent group (42.9 versus 8.7%; $P = 0.03$) in a study by Vuagnat *et al.* [42]. Drug reactions included acute kidney injury, allergic reactions, and phlebitis. In the large prospective study by Wysocki *et al.* [51], no differences in rates of nephrotoxicity were observed.

Continuous infusions: verdict?

Data for vancomycin and β-lactams show that continuous infusion enables faster and more consistent attainment of therapeutic levels compared with intermittent bolus dosing. Although the clinical benefits have not been conclusively shown at this time, compelling pharmacokinetic/pharmacodynamic support for continuous infusion nevertheless exists. Given that critically ill patients may develop very large volumes of distribution as well as supranormal drug clearances, individualized therapy through use of TDM is required.

Optimal therapy for any antibiotic will be best achieved through comparison of pharmacokinetic concentration (and/or AUC data) to pharmacodynamic MIC data to enable dose adjustments that follow with optimal dose–exposure relationships from previous pharmacokinetic/pharmacodynamic studies. For β-lactams and vancomycin administered by continuous infusion, this requires C_{ss}/MIC ratio of 4–5. A definitive determination of the relative clinical efficacy of intermittent bolus and continuous administration of β-lactams or vancomycin will only be achieved after a large-scale multicenter randomized controlled trial has been performed.

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References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

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Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 468–469).

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