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Review

Is continuous infusion of β-lactam antibiotics worthwhile?—efficacy and pharmacokinetic considerations

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The most important pharmacodynamic parameter for β-lactam antibiotics has been shown to be the time above the MIC, which is used as an argument to administer β-lactam antibiotics by continuous infusion. Studies *in vitro* and in laboratory animals comparing efficacy of continuous and intermittent infusion of β-lactam antibiotics generally show continuous infusion to be more efficacious. While comparative trials in humans are scarce and a significant difference was only found in subgroup analysis in one study, several case-reports support the use of continuous infusion. Arguments in favour and against continuous infusion are discussed. Although dose-ranging studies have not yet been performed in humans, the results from in-vitro and in-vivo experiments indicate that 4 × MIC for the infecting bacterium would be the target concentration. Pharmacokinetic studies which have been performed in humans during continuous infusion show that serum concentrations can be predicted from total clearance or, using population pharmacokinetic modelling, the elimination rate constant as obtained during intermittent infusion. A nomogram is presented which allows calculation of the daily dose to obtain the target steady state blood concentrations suggested by the susceptibility of the infecting bacterium, usually 4 × MIC. For bacteria with a low MIC, the daily dose may be substantially lower than that used in conventional dosing regimens, while in infections which are difficult to treat as a result of more resistant bacteria, continuous infusion may be more effective than an equivalent bolus dose.

Introduction

Several pharmacodynamic parameters of antimicrobial agents have been correlated with efficacy or outcome. The most important such pharmacodynamic parameter for β-lactam antibiotics has been shown to be the time above MIC (Drusano, 1991; Craig & Ebert, 1992). This finding is used as an argument to administer β-lactam antibiotics by continuous infusion. In this article the arguments in favour and against continuous infusion are discussed with emphasis on clinical relevance of the issues raised.

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Studies *in vitro* and in laboratory animals

In-vitro studies of the pharmacodynamics of β-lactam antibiotics have shown that killing of bacteria, in particular Gram-negative aerobic rods, is slow, time dependent, and maximal at relatively low concentrations (Vogelman & Craig, 1986). Concentrations much higher than the MIC provide no extra benefit. These observations have led to the hypothesis that continuously maintained concentrations above a certain level, related to the MIC for the bacterium against which therapy is directed, would be more efficacious than the high peak and trough concentrations obtained with an intermittent dosing regimen. High peak concentrations have no value, and growth of bacteria resumes when concentrations decline to below the MIC. This is in constrast to, for instance, the pharmacodynamic behaviour of the aminoglycosides, where efficacy is concentration dependent.

Efficacy studies in laboratory animals are in agreement with these in-vitro findings. Several groups have performed studies comparing intermittent dosing regimens with continuous infusion. The results of these studies have been summarised by Craig & Ebert (1992). In one graph, summarising all published data, the daily dose needed to treat 50% of the animals successfully (the ED_{50}) during continuous infusion was compared with that needed by intermittent infusion to obtain the same efficacy. If both treatment regimens yielded equal results, the slope of the equal potency line would be unity, being a function of the MIC for the relevant bacterium, and the intercept would be zero. Instead, the line was shifted to the right. Overall, the daily doses needed to obtain the same efficacy were eight-fold higher during intermittent infusion regimens than with continuous infusion. In another experimental setting, to demonstrate that time above the MIC is a most important pharmacodynamic parameter for the efficacy of β-lactams, Onyeji *et al.* (1994) used different dosing regimens of ceftabuten and cefaclor, administering the same total daily dosage as between one and sixteen doses. The percentage survival of the animals used increased linearly with the frequency of dosing and the time above the MIC. A similar result was obtained when pneumococci with varying MICs were used in a mouse peritonitis model (Knudsen, Frimodt-Moller & Espersen, 1995). In that study, a direct relationship between ED_{50} could be found with time above the MIC but not with other pharmacodynamic parameters.

One of the problems in extrapolating these results from animals to humans, is the different pharmacokinetics in the animals used. In rodents, the half-life of most β-lactams is approximately 20 min, which is much shorter than in humans. Even with an intermittent dosing regimen of four times daily, concentrations in serum decline rapidly, and fall below efficacious concentrations within 1 to 2 h. If only the time above the MIC is considered, it would compare with a once daily dose in humans, which with a few exceptions, is generally considered completely inadequate.

One way to deal with this problem, is to simulate human pharmacokinetics in an in-vitro model, and to study efficacy during continuous and intermittent infusion. Results from these studies also showed increased efficacy during continuous infusion when *Pseudomonas aeruginosa* infections were treated with ceftazidime (Mouton & den Hollander, 1994; Cappelletty *et al.*, 1995). Other approaches which have been used successfully, are manipulation of the study animals by producing renal dysfunction to decrease total body clearance (Giacomini, Roberts & Levy, 1981) or administration of fractionized decreasing doses (Fluckiger, Segessenmann & Gerber, 1991). Results from these studies are generally in agreement with earlier findings.

Clinical efficacy studies

To determine whether the time the serum concentration is above the MIC, among other parameters, is an important pharmacodynamic parameter for β-lactams in humans, Schentag *et al.* (1984) studied the efficacy of cefmenoxime in patients with Gram-negative pneumonia, and correlated the time serum concentrations were above the MIC with bacterial eradication. They found a significant relationship between time to eradication of the bacteria and time above the MIC.

Reports on the efficacy of continuous infusion compared to intermittent administration in humans are still scarce. Only two randomised trials have compared the efficacy of β-lactams given by these two dosing-regimens, but definite conclusions from these trials could not be made. In a French study (Lagast, Meunier-Carpentier & Klasterski, 1983), 45 bacteraemic patients were treated with cefoperazone either by intermittent administration or by continuous infusion, but no statistically significant differences in efficacy were found between the two regimens. The power of this study, however, was quite low. In the study of Bodey, Ketchel & Rodriguez (1979), the efficacy of continuous versus intermittent infusion of cefamandole, in combination with carbenicillin, was compared. Although no overall significant difference was found between the two groups, subgroup analysis showed that the patients with persisting neutropenia and/or the patients with organisms susceptible to cefamandole did significantly better when receiving cefamandole as a continuous infusion. This significant finding in a small number of patients suggest that continuous infusion could be of substantial benefit. Efficacy of continuous infusion of ceftazidime was studied in patients with cystic fibrosis. Although these were non-controlled studies, treatment was efficacious. A few case reports also support the use of continuous infusions of ceftazidime in cystic fibrosis (Daenen & de Vries-Hospers, 1988; David & Devlin, 1989; Kuzemko & Crawford, 1989).

Continuous infusion

Argument against

There appear to be some reasons not to give β-lactams continuously, although most of these are more of theoretical interest than practical importance. It is conceivable that, in some situations, intermittent dosing would result in higher concentrations at the site of infection than would continuous infusion. One would be infection at a site with a rate-limiting active transport mechanism eliminating the antibiotic from the site. During continuous infusion, the antibiotic would be eliminated from the site continuously at a maximum rate, resulting in persisting low concentrations, while during intermittent infusion a maximum rate of elimination would still result in efficacious concentrations being maintained for some time. Examples would be infections in eye or cerebrospinal fluid. However, the kinetics of the enzymes make this scenario appropriate only over a particular range of antibiotic concentrations and then would apply only for those β-lactams which are handled by such elimination mechanisms.

Another situation would be if antibiotic elimination from a site was due to β-lactamases, again with a rate-limiting step. For example, while an antibiotic was diffusing to the centre of an abscess, β-lactamase-producing bacteria could degrade it, perhaps resulting in antibiotic concentrations near zero during continuous infusion,

while, because of the rate-limiting nature of the elimination, efficacious concentrations might be reached for part of the time during intermittent infusion.

In the study by Oyenji *et al.* (1994), it was found that cefaclor exhibited a marked inoculum effect against the four pathogens studied, and that there was concentration dependent killing at a large inoculum. The other test-drug, ceftibuten, did not show such an effect. From these observations, it follows that not all β-lactams show the same pharmacodynamic behaviour. Before deciding whether an individual compound can, or will, be given as a continuous infusion, its precise pharmacodynamic behaviour should be known; this also holds true for intermittent infusion.

Lastly, two of the more practical problems which have to be considered, are the stability of the compound to be administered and the costs of the pump which has to be used. Several antibiotics are very unstable at room temperature and thus cannot be given as a continuous infusion. Thus, if an antibiotic is given as continuous infusion, its stability should be considered. For others, such as penicillin, degradation products can cause hypersensitivity reactions (Smith, Dewdney & Wheeler, 1971).

At which concentration should we aim?

The important question of which concentration should be obtained during continuous infusion of β-lactam antibiotics is not yet fully answered. From the results of time-kill curves, it seems that a maximum effect is reached at 4 × MIC for the target bacterium. A concentration of 4 × MIC was also needed for efficacy in in-vitro pharmacokinetic models (Mouton & den Hollander, 1994) and, in a recent study to determine the efficacious in-vivo concentrations of ceftazidime in an experimental *P. aeruginosa* rabbit endocarditis model, Xiong *et al.* (1994) also found 4 × MIC to be a possible therapeutic goal. Four times the MIC would, therefore, seem to be the concentration to aim at during continuous infusion. However, dose-ranging studies have not yet been performed for continuous dosing regimens *in vivo*. In the studies of Roosendaal *et al.* (1985, 1986), the efficacy of continuous infusion is expressed not only as the ED_{50}, but survival per group per daily dose is presented as well, which permits calculation of the dose needed for efficacy. They studied efficacy of ceftazidime in a rat pneumonia model due to *Klebsiella pneumoniae*, starting therapy either 5 h (moderate infection) or 34 h (severe infection) after inoculation of the bacteria in the lung. When the animals had developed a severe infection, after 34 h, bacteraemia and/or sepsis was present in at least some animals. Furthermore, concentrations of ceftazidime in serum were determined. The serum concentration of ceftazidime needed during continuous infusion to obtain 50% efficacy in normal rats was between one-sixth and one-third the MIC, for the infecting *K. pneumoniae*, depending on the severity of the infection. However, the concentration needed to obtain 100% efficacy (ED_{100}) was dependent not only on the severity of infection but also whether the animals were leucopenic or not. In normal rats, the ED_{100} to treat animals with moderate infection was approximately one-third of the MIC for the *K. pneumoniae* strain and in severe disease was around six times the MIC, while in neutropenic animals, continuous concentrations of 2 × MIC were necessary to obtain 100% survival in the moderate infection group. This indicates that it is not only the MIC for the bacterium that should be considered, but also the severity and location of the infection that needs treatment. Although the results from these animal studies

are not directly comparable to infections in humans, the results do indicate that there is a relation to the MIC during (severe) infection.

If the MIC is taken as the benchmark, it follows that, when treating a patient with continuous infusion of an antibiotic, knowledge of the MIC for the bacterium is more important than during intermittent infusion, and of more importance than solely a laboratory report of susceptibility or resistance. The new semi-automatic devices, such as the Vitek and Microscan systems, which are being used increasingly in clinical laboratories, determine a type of 'MIC' and their results could possibly be used in clinical practice in the future for a finer attunement of the dose needed. For microorganisms with a low MIC, the daily dose can then be lowered substantially (Craig, 1993).

There are two other important issues to be considered, tissue penetration and protein binding. Although the concentration of an antimicrobial agent in serum may be known, this could be different in other body compartments (Barza & Cuchural, 1985). Since β-lactams, in general, distribute into the extracellular body compartment, it is to be expected that, if there is no active transport, at steady state, the concentration of the free fraction of the drug is the same in the various body-compartments. Studies from blister fluid show that, generally, penetration of β-lactams into such fluid is good, and shows consistent results (Wise, 1986). However, concentrations at the site of infection may be lower as was discussed above. Secondly, since only the free fraction of the drug is active, and indeed in animal models was shown to be of importance in relation to efficacy (Merrikin, Briant & Rolinson, 1983), this is the concentration which should be taken into account when calculating dose in relation to serum concentrations. Extracellular tissue fluid contains less protein (about one-third) than serum, and total concentrations (but not the free fraction) will thus be lower in that compartment (Wise, 1983). The concentration profile in tissue was shown to be similar to that in serum when only the free fraction of the drug was taken into account (Kunst & Mattie, 1978; Mattie, Hoogeterp & Hermans, 1987). In studies in human volunteers, comparing concentration profiles in serum and blister fluid of ceftazidime (Mouton *et al.*, 1990) and meropenem (Mouton & Michel, 1991) during continuous infusion, total concentrations in blister fluid were slightly lower.

Pharmacokinetic considerations

The clinically important practical question which arises, is: what dose needs to be administered to obtain the target concentration? To answer this question, the pharmacokinetics of the β-lactam should be known. Ceftazidime is one of the few β-lactams which has been studied extensively during continuous infusion, both in volunteers and in different patient groups. The results of these studies are summarised in the Table. There is a large variation in concentrations reached at steady state in relation to the dose given, as a result of differences in total body clearance.

The concentrations reached in patients with cystic fibrosis (CF) provide a good example. It has been shown in numerous studies examining intermittent infusion, that these patients have an increased total body clearance and a larger volume of distribution as compared to controls for many drugs, including most β-lactam antibiotics (Spino, 1991). As a result, when administered in standard dosages, serum concentrations are lower and the half-life shorter in CF patients than in other groups. The reasons for these

Table. Pharmacokinetics of ceftazidime during continuous infusion in different patient populations

Patient population	No. of patients	Age (years)	Dose (mg/kg)	TBC[a] (L/h/kg)	C_{ss}	References
Healthy volunteers	8	23 6 ± 2.4 (20–29)[b]	15 mg/kg load; 60 mg/kg/24 h	0.113 ± 0.018	21.3 ± 3.0	Mouton *et al* (1990)
Healthy volunteers	12	NS	2 g/24 h 3 g/24 h	NS	12.8 ± 3.0 18.2 ± 4.5	Nicolau *et al* (1994)
Healthy volunteers	3	21 ± 2	4 g/24 h 6 g/24 h	NS	34.3 ± 4.9 43.5 ± 4.7	Rio *et al.* (1994)
Neutropenic patients (bone marrow transplants)	13	41.7 ± 10 7	4.1 ± 1.0 g/24 h	0.126 ± 0.045	21.4 ± 5.4	Akkerman *et al.* (1992)
Leukaemia patients (acute myeloid leukaemia)	12	67.3 (LBM) (51–75)[b]	100 mg/kg/24 h	0.12 (7.8–12.7)	37.0 (26.4–81.8)	Daenen *et al.* (1995)
Neutropenic children	14	7.5 ± 4.5	100 mg/kg/24 h	0.20 ± 0.07	21.5 ± 7.4	Le Norman *et al.* (1993)
Intensive care patients	12	64 ± 7	65 mg/kg/24 h	0.108 ± 0.054	40 ± 18	Castela *et al.* (1994)
	6	64 ± 11	60 mg/kg/24 h	0.144 ± 0.090	25 ± 18	
Burn patients	3	24–47	4 g/24 h	(8.6; per kg?)	19.4 ± 6.8	Rio *et al.* (1994)
	3	31–54	6 g/24 h	(7.0)	35.8 ± 3.3	
Cystic fibrosis	9		100 mg/kg load 200 mg/kg/24 h	(0.15)	55.9 ± 19.5 (8 h) 63.4 ± 13.2 (24 h) 55.1 ± 26.1 (48 h) 52.9 ± 18.4 (72 h)	David & Devlin (1989)
Cystic fibrosis	6	9–25	108 mg/kg/24 h 82 mg/kg/24 h	(0.11) (0.13) (0.12) (0.16)	9am: 39.4 (30.8–52.5) 27.1 (15.0–39.2) 5pm: 38.3 (27.3–48.9) 21.3 (18.9–23.7)	Kuzemko & Crawford (1989)
Cystic fibrosis	10	19.6 (10–32)[a]	200 mg/kg/24 h	(0.14)	59.3 ± 24.1	Byl *et al* (1992)
Cystic fibrosis	9	24.8 ± 7.4 (19–38)[a]	100 mg/kg/24 h	0.154 ± 0.019	25.4 ± 4.5	Mouton *et al.* (1992)
Cystic fibrosis	8	25.6 ± 2.6 (22–30)[a]	100 mg/kg/24 h	0.152 ± 0.014	28.7 ± 5.0 (range)	Vinks *et al.* (1994)

NS, Not stated.
[a]If clearance values were not given in the reference, they were calculated from dose divided by mean C_{ss} and given between parentheses.
[b]Range.

differences in clearance and volume of distribution remain debatable (Hedman *et al.*, 1988; Spino, 1991).

The pharmacokinetics of ceftazidime during continuous infusion have been investigated in CF patients (Table). From these studies it has become clear that higher daily dosages are needed in order to obtain comparable serum concentrations during continuous infusion in CF patients. Studying the pharmacokinetics of continuous infusion of penicillin and cloxacillin, Visser *et al.* (1993) found a large variation in steady state concentrations, which could be explained largely by differences in renal function. The findings in these studies indicate that there should, *a priori* at least, be a reasonable estimate of both the total clearance and the target concentration of the antibiotic in the individual patient.

Dose calculations

When it is known what concentrations to aim for, it is relatively easy to calculate which dose should be given. Pharmacokinetic behavior of β-lactams in serum during continuous infusion is easy to conceive. When the input per unit of time is known (continuous infusion) and the output is known (total body clearance) one can calculate the serum concentrations achieved as: serum concentration = dose/total body clearance.

Conversely, when the target concentration is known the necessary dose can be calculated if the total body clearance (TBC) of the drug is known. The elimination rate constant (K_e), as often reported for intermittent infusion, can be used to calculate the TBC, which itself is a function of the K_e and the volume of distribution (V_d) of the drug: $TBC = K_e \times V_d$, if there is no important rate-limiting step in the elimination process.

The mean values of TBC, K_e and V_d, are known for most drugs (e.g. Mammen, 1990; Klepser *et al.*, 1995). For drugs which are cleared almost completely by glomerular filtration, an estimate of the clearance from the creatinine clearance should be satisfactory. This holds true also for drugs for which the TBC is merely a function of creatinine clearance, such as meropenem (Mouton & van den Anker, 1995). However, since these parameters may vary between different patient groups, for instance intensive care patients, mean values per patient group would be even more informative (Table). For some drugs with a high tubular excretion rate, such as penicillin and cloxacillin, however, other factors such as the saturability of tubular elimination may play an important role in determining the plasma concentrations during continuous infusion. For these drugs, drug specific nomograms can be of use (Visser *et al.*, 1993).

A more sophisticated method to estimate the TBC, K_e and V_d for a particular patient would be to use population pharmacokinetic models. In these models, clearance or elimination rate is related to parameters such as renal function and the volume of distribution is described as a function of bodyweight or lean body mass. Individual pharmacokinetic parameters and serum concentrations can be predicted accurately from population pharmacokinetics. This was recently shown, for instance, for continuous infusion of ceftazidime in a CF population (Vinks *et al.*, 1995*a*). Although there is variation between individuals, the clearances found during continuous infusion are generally in agreement with those found during intermittent infusion. For drugs cleared by both renal and extrarenal pathways, for instance meropenem, the same conclusion can be drawn (Mouton & Michel, 1991). In a similar study in CF patients

(Vinks *et al.*, 1995*b*), there was no significant difference between the TBC of aztreonam during both treatment regimens.

From these studies it is clear that, although there is variation between groups of patients, the concentrations reached during continuous infusion for most drugs do not differ between patients by more than a factor of two, provided there is no renal insufficiency. If time above the MIC is taken as the pharmacodynamic parameter for β-lactams, it seems to be more important to know the MIC (which is usually determined to within ± 1 dilution) for the infecting bacterium than the precise pharmacokinetic characteristics of the individual patient. The reported MIC for the bacterium and calculated pharmacokinetic parameters in the patient can then both be used to determine the dose necessary to obtain the desired concentration.

As indicated above, there is a direct inverse relationship between total body clearance and dose. Figure shows a nomogram translating total body clearance into dose during continuous infusion in relation to the MIC. From this nomogram, the daily dose to be administered can be read as a function from the total body clearance (known or estimated) and the target concentration. For example, if the target concentration is set at 4 mg/L in a patient with a total body clearance of 180 mL/min, the total daily dose should be 1000 mg, i.e. approximately 40 mg/h. In this example, the MIC of the

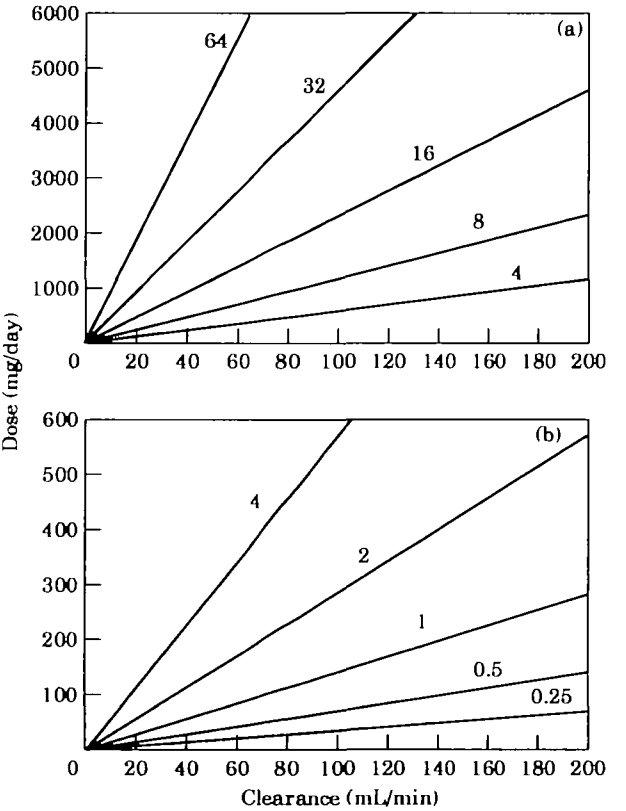

Figure. Nomogram for dose-adjustments during continuous infusion. When the total body clearance and the target concentrations are known, the total daily dose, given as a continuous infusion can be read from the y-axis

bacterium might typically have been 1 mg/L with the antibiotic having a low degree of protein-binding.

Conclusion

It is concluded that, although there are no clinical trials showing continuous infusion to be superior over intermittent infusion, there are at least theoretical arguments, results of animal studies in favour and case reports supporting efficacy of continuous infusion. From the nomogram presented, it should be easy to calculate daily doses, including in patients with a decreased clearance. Further clinical trials should be undertaken to show efficacy in different patient groups and dose-ranging studies are needed to determine the relationship between MIC and the concentration needed during continuous infusion in specific circumstances. Although 4 × MIC is a practical goal, this value is dependent both on the host and the infecting bacterium.

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