REVIEW

Is there a rationale for the continuous infusion of cefepime? A multidisciplinary approach

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This review is the fruit of multidisciplinary discussions concerning the continuous administration of β-lactams, with a special focus on cefepime. Pooling of the analyses and viewpoints of all members of the group, based on a review of the literature on this subject, has made it possible to test the hypothesis concerning the applicability of this method of administering cefepime. Cefepime is a cephalosporin for injection which exhibits a broader spectrum of activity than that of older, third-generation cephalosporins for injection (cefotaxime, ceftriaxone, ceftazidime). The specific activity of cefepime is based on its more rapid penetration (probably due to its zwitterionic structure, this molecule being both positively and negatively charged) through the outer membrane of Gram-negative bacteria, its greater affinity for penicillin-binding proteins, its weak affinity for β-lactamases, and its stability versus certain β-lactamases, particularly derepressed cephalosporinases. The stability of cefepime in various solutions intended for parenteral administration has been studied, and the results obtained demonstrated the good compatibility of cefepime with these different solutions. These results thus permit the administration of cefepime in a continuous infusion over a 24-h period, using two consecutive syringes.

Keywords β-lactamas, cefepime, cephalosporins, continuous infusion, dosage regimen

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IN VITRO AND EXPERIMENTAL RATIONALE: THE STATE OF THE ART

Pharmacokinetic/pharmacodynamic data

The concept of continuous infusion is based on knowledge of antibiotic pharmacodynamics. When aminoglycosides and fluoroquinolones are considered as concentration-dependent antibiotics, β-lactam antibiotics exhibit time-dependent bactericidal activity. Therefore, the goal of therapy is to maintain serum drug concentrations above the minimum inhibitory concentration ($T >$ MIC) for the relevant pathogen over most of the dosing interval [1,2]. Consequently, for therapeutic purposes, it seems justified to update the data in favor of continuous infusion with β-lactam antibiotics, in particular with cefepime, considering its activity mechanism and spectrum.

As early as 1946, Jawetz [3] observed that maintaining 'detectable' blood concentrations of penicillin was an essential element in therapeutic success; to meet this need, he therefore thought it desirable to recommend repeated administrations at short intervals or the use of continuous infusion, without, however, being able to confirm that this approach was essential, whatever the clinical situation. Nearly 40 years later, research teams working with the aid of various animal models of infection were able to demonstrate [2,4] that the pharmacodynamic parameter most predictive of the therapeutic success of β-lactams,

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and particularly cephalosporins, was $T > \text{MIC}$. Different studies showed that in vivo bacteriostatic activity was usually attained if the serum concentration of the antibiotic remained higher than the MIC for a period equal to 30–40% of the interval of administration, this being independent of the site of infection (thigh, lung, peritoneum). In a given model of infection (same animal, site of infection and bacterial strain), this percentage of time was smaller for penicillins and carbapenems than for cephalosporins; this corresponds to differences in the bactericidal rate observed with these compounds, since carbapenems act more rapidly and cephalosporins act more slowly. However, in cases of infections caused by Gram-positive cocci, particular species (enterobacteria) or specific strains (*Pseudomonas aeruginosa*), it appears that a much more sustained rate of administration, and thus a longer $T > \text{MIC}$, are essential for therapeutic success. From in vitro data and animal studies, the minimal desired concentration at steady state (C_{SS}) for maximization of the bactericidal activity seems to be $4 \times \text{MIC}$ [5–8]. This concentration is not reached for the total dosing interval with the conventional dosage of cefepime, ceftazidime or imipenem, as demonstrated by Navas et al. in most febrile, neutropenic patients [9].

An experimental model [10] was used to determine the pharmacokinetics of cefepime in the rat during multiple organ function failure. The pulmonary concentrations were significantly reduced by comparison with the healthy control animals, despite similar plasma concentrations. This indicates that the use of a standard dosage, aimed at achieving the recommended plasma concentrations, may result in insufficient tissue levels.

The tissue penetration of cephalosporins administered in a continuous infusion was studied with an experimental model of fibrin clots in the rabbit. The injection of a high dose of cefuroxime or latamoxef by intravenous bolus resulted in better penetration than the repeated administration of small doses, or continuous infusion [11–13]. In contrast, in the rat, there was no difference between the penetration of ceftazidime into different tissues in the body following a bolus or continuous infusion; better penetration of this antibiotic was observed in pleural exudates after continuous infusion [14]. In a model of suction blister fluid in humans, the rate of ceftazidime penetration following continuous infusion was lower than that achieved with intermittent infusions (84.5% versus 101.5%) [15]. This difference was less marked with cefepime: 106% with continuous infusion versus 113% with intermittent infusion [16]. This decrease in extravascular diffusion is slight, and could probably be prevented by a loading dose.

Selection of mutants

Any antibiotic therapy is capable of selecting resistant bacteria in a patient or in his environment.

The selection of resistant mutants is the principal cause of bacteriologic failure when treating an initially sensitive Gram-negative bacterial infection with a cephalosporin.

The most frequently incriminated mechanism is the production of chromosomal cephalosporinase. In the event of mutation, hyperproduction of this cephalosporinase is observed (referred to as derepression), which leads to destruction of the antibiotic and a marked rise in MIC values. Cephalosporins are among those compounds most affected by this problem, together with aztreonam. Cefpirome, cefepime and, particularly, imipenem are much more stable, showing a very moderate increase in MIC when compared with older cephalosporins [17].

Resistant mutants are selected by stages; each stage corresponds to the incidence of a given mutation and a maximum concentration above which mutants are no longer seen. It is important to be aware of this maximum concentration, or mutation prevention concentration (MPC), because as long as the concentration of the antibiotic at the site of infection exceeds this level, the risk of selecting a resistant mutant is virtually nil [18–21].

Knowledge of the pharmacokinetics of an antibiotic, its MIC versus specific bacterial species, its incidence of mutation and its MPC, enables a valid prediction of the risk of selecting a resistant mutant. It is thus possible to determine the optimum dose and most appropriate method of administration. The time during which the concentration of the antibiotic is greater than the MIC and less than the MPC is called the window of selection; the bigger this window, the higher the MPC/MIC ratio, and the longer the half-life of the antibiotic.

Numerous studies have considered the selection of resistant mutants in vitro, either in a liquid medium or on a solid substrate.

In a comparative study, Fung-Tomc et al. [19] compared the selective activity of ceftazidime,

ceftriaxone, cefpirome and cefepime against ten sensitive strains of *Enterobacter cloacae* (MIC 0.12–0.25 mg/L). The median MIC exceeded 8 mg/L after 1 day with ceftriaxone, 3 days with ceftazidime, 4 days with cefpirome, and 6 days with cefepime. Atleast four mechanisms of resistance were obtained as a function of the antibiotic employed; the principal mechanisms included the isolated hyperproduction of chromosomal cephalosporinase, and a reduction in the porin Omp-39 of the outer membrane. In most of the clones, these two mechanisms of resistance were found in association.

In the case of *P. aeruginosa*, although cefepime has an activity which is usually weaker than or equal to that of ceftazidime, Gradelski et al. [18] observed a more rapid increase in the geometric mean of cefepime MIC values until day 4, in comparison with ceftazidime. However, by day 7, the means reached 8.7 mg/L for cefepime versus 45 mg/L for ceftazidime. In an unpublished study performed on a solid substrate, Kitzis et al. compared ceftazidime and cefepime in five strains of *P. aeruginosa*. Versus a fully sensitive strain (MIC for cefepime: 2 mg/L), an incidence of between 10^{-7} and 10^{-9} of resistant mutants was obtained in 24 h, with an MIC not exceeding 32 mg/L for cefepime and reaching 128 mg/L for ceftazidime and piperacillin.

The risk of selecting a strain with high-level resistance thus appears from several studies to be much lower with cefepime than with ceftazidime or cefotaxime [19–22]. A few epidemiologic studies have also demonstrated that the first-line use of cefepime for the treatment of nosocomial infections appears to be associated with a reduction in the percentage of *Enterobacter* or *Citrobacter* strains resistant to both ceftazidime and cefepime [23–27]. However, the risk of selecting resistant mutants is not absent, particularly when the microorganism is already endowed with a resistance mechanism, and more generally with *P. aeruginosa* [28–32]. Under these conditions, the MIC values attained may rapidly exceed the capabilities of therapy.

Analysis of all the in vitro data concerning the selection of resistant mutants strongly suggests that continuous infusions of cefepime should be used as a therapeutic schedule. Indeed, maintaining the currently recommended method of administration (1 or 2 g every 12 or 8 h) leads to the presence, for at least 6 h after each injection, of serum levels between the MIC of a sensitive strain (0.03–0.25 mg/L) and the MPC; this window of selection thus implies a risk of selecting a resistant mutant. In contrast, the administration of cefepime in a continuous infusion reduces the window of selection to 6 h, and this only during the first and last administrations of the antibiotic.

In addition, it would be very simple to eliminate the few resistant mutants present in the entire bacterial population from the start, by administering a loading dose of cefepime. A similar effect could be obtained through the simultaneous use of an antibiotic against which no cross-resistance has been observed: this is the case for aminoglycosides, but not for fluoroquinolones [33,34].

CLINICAL DATA

Clinical studies aimed at demonstrating the superior or even equivalent efficacy of continous infusion versus intermittent infusion, depending on the mode of administration, are methodologically difficult to implement. Indeed, it is necessary to study a very large number of patients to reach a clear conclusion, which probably explains why few studies comparing these two methods of administration can be found in the literature. Only two randomized, comparative studies have been published. The study by Bodey et al. [35] compared the efficacies of continuous and intermittent infusions of cefamandole in a population of neutropenic subjects with infections at different sites. The second study, by Lagast et al. [36], involved the use of cefoperazone. In both the infections treated had been caused by Gram-negative bacilli. The study conducted by Bodey et al. demonstrated superior or equivalent clinical efficacy of the continuous infusion versus intermittent infusion, depending on the subgroup analyzed. Lagast et al. demonstrated identical efficacies of continuous and intermittent infusion of cefoperazone.

Most published studies are pharmacokinetic studies in patients in whom the variability of the pharmacokinetics justifies serum concentration monitoring.

Three types of clinical situations have been principally investigated: critically ill patients, or those suffering from neutropenia or cystic fibrosis. Findings in the literature have suggested the efficacy of continuous infusions in patients with neutropenia [37] or those with cystic fibrosis [38]

who constituted treatment failures under conventional therapy.

Critically ill patients

Most studies target pharmacokinetic data. Critically ill patients are often infected by multiresistant microorganisms, with high MIC values. In an in vitro pharmacokinetic model, Mouton and den Hollander [39] showed that it was necessary to attain concentrations of at least four to five times the MIC to inhibit the growth of *P. aeruginosa*. Various pharmacokinetic studies have demonstrated the variability of plasma concentrations, and notably the residual level (less than five times the MIC), in critically ill patients, and have concluded that continuous infusion, with or without a loading dose, made it possible to attain levels above the required concentrations [40,41]. Very few clinical studies have been published. In a preliminary study of cefepime [42], 18 patients were randomized and then received either 4 g in a continuous infusion (group 1) or 2 g every 12 h (group 2), in combination with amikacin, 20 mg/kg per day, in both groups. There were no significant differences in terms of the duration of ventilation or hospital stay, the cure rate, or the AUC/MIC ratio of cefepime at 12 and 24 h. In contrast, $T >$ MIC and the time for which the MIC values were above five times the MIC ($T > 5$ MIC) were significantly higher in the continuous infusion group: 23.84 h $\pm$ 0.2 h versus 20.7 h $\pm$ 3 h, and 23.61 h $\pm$ 0.6 h versus 16.6 h $\pm$ 6 h, respectively. These results, obtained in a small population of patients, demonstrated a pharmacokinetic advantage in the continuous infusion group.

A study by Nicolau et al. [43] compared the pharmacokinetics and efficacy of two methods of administration, continuous and intermittent, of ceftazidime in the treatment of nosocomial pneumonia. These authors demonstrated that there were no differences between the pharmacokinetic parameters with the two modes of administration: total clearance $CL_T = 142.5 \pm 59$ mL/min versus 133.2 ± 37 mL/min with intermittent infusion and continuous infusion, respectively. The pharmacodynamic results made it possible to demonstrate that, for the 46 microorganisms isolated and documented in 27 patients, continuous infusion was a method of administration which enabled optimization of ceftazidime therapy, in the knowledge that, whichever patient was considered, the $T >$ MIC parameter was 100% in the ceftazidime group with continuous infusion, while it ranged from 56% to 100% in patients included in the intermittent ceftazidime group.

Neutropenic patients

Occasional observations have been made which suggest the efficacy of continuous infusion in the event of therapeutic failure with intermittent administration [37,44].

A study by Daenen et al. [45] concerned 12 patients with acute myeloid leukemia who received 100 mg/kg per day ceftazidime following a loading dose of 500 mg. In all patients, the concentration at the steady state (>20 mg/L) was attained after between 180 and 240 min. Six patients responded to empirical treatment, four of them after 24–72 h of single-drug therapy, and two after the addition of vancomycin. The other six patients were considered to be non-responders; in four cases, the microorganism was not sensitive to ceftazidime. The authors laid emphasis upon drug interactions in the infusion lines that could render the antibiotic ineffective. In fact, the advantages of continuous infusion, as suggested by in vitro pharmacodynamic and pharmacokinetic studies, were not demonstrated in a large population of patients in whom the two modes of administration were compared.

Another study [46] enabled comparison of the population pharmacokinetics of cefepime in onco-hematologic neutropenic subjects with two modes of administration (intermittent and continuous infusion), to measure the interindividual variabilities of cefepime with regard to various pharmacokinetic parameters, to propose adaptable controls for cefepime doses based on specific population estimates in this type of patient, and to correlate the pharmacokinetic results with efficacy. From a pharmacokinetic point of view, there was no difference between the two methods of cefepime administration: total clearance $CL_T = 3.15 \pm 1.25$ L/h versus 4.58 ± 0.89 L/h, and apparent distribution volume $V_d = 11.40 \pm 1.33$ L versus 12.60 ± 0.98 L, respectively, for intermittent infusion and continuous infusion. These observations confirmed those described for aztreonam, meropenem and ceftazidime in neutropenic patients, and the pharmacokinetic specificities of these individuals when compared to those seen in healthy volunteers.

Patients with cystic fibrosis

Various studies [47,48] have demonstrated the pharmacokinetic modifications to β-lactams in cystic fibrosis patients: shortening of the half-life, increase in clearance, and lower concentration at the steady state. Superinfection episodes are caused by *P. aeruginosa* strains with high MIC values. With intermittent administration, a period exists between injections during which concentrations fall below the MIC, which is a factor favoring the selection of resistant strains. The use of continuous infusions was proposed as an alternative in the event of therapeutic failure [38]. Vinks et al. [49] demonstrated the value of continuous infusions of ceftazidime administered in the home to 17 patients. Ceftazidime was delivered via an infusion pump at a dose of 100 mg/kg per day for 3 weeks. The effects of this type of treatment were studied prospectively over a 2-year period. Of the 33 cycles of treatment received, 25 could be analyzed in 12 of the 17 patients. A clinical improvement was noted in 91% of patients, and persisted for 4–6 weeks in 70% of them. The number of cultures positive for *P. aeruginosa* diminished significantly during the period of treatment. The bacterial count had returned to pretreatment values within 4–6 weeks. Repeated treatments with ceftazidime as single-drug therapy did not significantly modify the sensitivity profile. Administration at home resulted in reductions in both direct and indirect costs.

All these studies enable us to conclude that, for antibiotics with a time-dependent bactericidal effect and a short elimination half-life, and in specific populations, continuous infusion constitutes an optimization of the therapeutic schedule.

INDIVIDUAL OR GENERALIZED DOSAGE: DOES THE USE OF CONTINUOUS INFUSION ENABLE THE OPTIMIZATION OF TREATMENT?

The variables modulating individual pharmacokinetic values are the status of the patient (age, body weight, vital functions, hemodynamic status), the type and site of infection, and the microorganism involved. These parameters must be taken into account when designing antibiotic therapy. They become determining factors for success in severe or particularly difficult clinical situations. The benefits expected of treatment adjusted as closely as possible to pharmacodynamic principles are clinical and ecological. They remain to be demonstrated. It is, however, possible to suggest that the technical problems of administration can be overcome. If this is the case, it is necessary to determine whether continuous administration is better, as good as or less effective than intermittent administration, and which is the best way to administer a β-lactam.

Patient status

The prescription of antibiotic therapy is currently based on general principles (daily dosage, body weight, rate of administration). Individualization of administration has, to date, only concerned dosage adjustments as a function of weight, diffusion requirements in certain types of difficult tissues (cerebrospinal fluid, bone, vegetations in infectious endocarditis), or the existence of major disturbances to the excretory functions or metabolic pathways of the antibiotic (renal impairment, liver impairment). The clinical situations are nevertheless particularly heterogeneous. Treatment optimization must ensure the best match between pharmacokinetic parameters, individual conditions and the bacteria responsible for the infection, while complying with pharmacodynamic and safety requirements.

Plasma pharmacokinetics

Plasma pharmacokinetic studies in patients with more or less severe infectious diseases who are receiving β-lactams have shown notable degrees of interindividual heterogeneity and significant differences in comparison with the data observed in healthy subjects.

In elderly patients with respiratory tract infections, receiving 1 g intravenously every 12 h, Kovarik et al. [50] found residual cefepime concentrations of 6.0 ± 4.9 mg/L, signifying that some patients exhibited concentrations in the order of 1 mg/L. The heterogeneity among the 10 patients was confirmed by half-life values, which ranged from 1.93 to 6.04 h, and area-under-the-curve (AUC) values which ranged from 173 to 480 mgh/L.

Benko et al. [51] compared the pharmacokinetic and pharmacodynamic parameters of ceftazidime administered via an intermittent or continuous infusion in critically ill patients. With the continuous

infusion of ceftazidime, pharmacodynamic parameters are equivalent to those observed with intermittent dosing, while utilizing one-half of the total daily dose.

Six patients with acute renal failure due to septic shock received cefepime at a dose of 2 g twice daily during continuous venovenous hemodiafiltration. Among these patients, Allaouchiche et al. [52] observed one with a C_{max} for cefepime of 11 mg/L, and undetectable concentrations after 6 h of administration.

Tissue pharmacokinetics

The tissue distribution and antibiotic concentrations in critically ill patients are poorly documented. In elderly subjects, Jonsson and Walder [53] observed considerable differences in ceftazidime concentrations in subcutaneous interstitial fluids during severe infectious disease. Following intermittent intravenous administration, the concentrations in tissue fluids ranged from 1.1 mg/L at the residual level (range: 0.1–2.3 mg/L) to 7.1 mg/L (range: 3.4–12.2 mg/L) at the peak. The lowest values on concentration curves were below 1 mg/L for most of the time. In some patients, the tissue concentrations were therefore very low.

Interindividual differences in concentrations are therefore of importance in critical, specific or complicated clinical circumstances. It is necessary to match dosages with modes of administration in order to optimize antibiotic therapy in these clinical situations. In this respect, the monitoring of plasma levels is essential. However, the target levels are unknown in the case of intermittent administration, and corrective strategies remain uncertain. It is clear that the continuous infusion of β-lactams constitutes a method of administration which enables adaptability to complex conditions, with more easily identifiable target values.

The site of infection

The tissue diffusion of antibiotics depends on numerous factors related to the compound: physicochemical and pharmacokinetic characteristics, and affinity or tropism of the antibiotic with respect to the tissue involved. The extravascular diffusion of β-lactam antibiotics does not require any biochemical transporter. This mechanism of passive diffusion is found for all tissues in the body, except for certain protected, or 'sanctuary', sites, as specified by Barza and Cuchural [54]: central nervous system, eye, and prostate gland. In principle, it may therefore be anticipated that the extravascular concentrations will be very similar to blood concentrations, particularly in the case of compounds which exhibit low protein binding, such as cefepime.

The microorganism

It appears that, in most cases, treatment of an infection with a β-lactam will be optimum if the plasma concentrations of the antibiotic exceed the MIC of the incriminated bacteria for a period of at least 30–40% of the interval of administration. However, the situation may vary under certain pathophysiologic circumstances. Indeed, because of the type of bacteria involved, or the particularly weakened terrain (neutropenia, critically ill, cystic fibrosis) in severe infections, it is necessary to cover considerably more than 50% of the administration interval [55].

WHAT VALUE SHOULD BE TARGETED FOR THE C_{SS}/MIC RATIO IN THE EVENT OF CONTINUOUS INFUSION?

If we refer to most studies of in vitro bactericidal kinetics, it appears quite clear that, with β-lactams, the bactericidal rate reaches a maximum at a concentration which is about four to six times the MIC. This ratio, $C_{ss}/MIC = 4$, has also been found in models simulating the pharmacokinetics of β-lactams [39], as well as in vivo in a model of rabbit endocarditis caused by *P. aeruginosa* and treated with ceftazidime [56]. With the same model, a comparative (intermittent versus continuous infusion) study by Robaux et al. confirmed that a C_{ss} around 4–5 $\times$ MIC was a reasonable therapeutic target in most clinical settings of severe *P. aeruginosa* infection, and was at least as efficacious as the traditional intermittent intravenous infusion [7].

In contrast, strains of *P. aeruginosa* isolated in cystic fibrosis patients required ceftazidime concentrations which were 10 (non-mucoid strains) to 50 (mucoid strains) times the MIC [8]. Various other findings seem to demonstrate that the choice of a target value is not simple. Indeed, earlier dose-ranging studies in rats with pneumonia caused by *Klebsiella pneumoniae* which were treated with continuous infusion showed that several parameters

could affect the choice of C_{ss}/MIC ratio: severity of infection, presence of neutropenia, site of infection, and sensitivity of the bacteria [57,58]. In these studies, the concentration necessary to attain 100% success rates ranged from 0.3 (moderate infection) to six times the MIC (severe infection or neutropenia). With the current state of knowledge, and although further investigations are necessary to refine a target C_{ss}/MIC value, it seems reasonable to recommend a value of at least four times the MIC.

PHARMACOLOGIC REQUIREMENTS TO OPTIMIZE TREATMENT BY CONTINUOUS INFUSION?

Loading dose

The loading dose is used at the initiation of treatment with a continuous infusion, mainly to enable the attainment of an effective concentration, i.e. between four and six times the MIC, from the first minutes of therapy. This method is usually preferred for antibiotics with a long half-life or those which bind strongly to proteins.

The question raised from the bacteriologic point of view is whether, in the absence of a loading dose and during continuous infusion, the interval required to reach an effective plasma concentration might be sufficient to select mutant strains with diminished sensitivity. Based on the MPC concept, Negri and Baquero [22] defined this risk for ceftazidime and cefepime versus *E. cloacae* which was hyperproducing β-lactamases. The risk was present from the beginning of the ceftazidime infusion, but only from 6 h after the cefepime infusion. An interval of about 45 min was necessary to exceed the MPC. It is impossible to specify whether this period was sufficient to allow the appearance of mutant strains.

Based on these results, it is possible to conclude that, if a loading dose is essential for ceftazidime, it is probably less important in the case of cefepime, but this view should nevertheless be reviewed with regard to the bacteriologic documentation and the window of selection, defined as the period during which the concentration of the antibiotic is higher than the MIC and lower than the MPC. It is probable that the higher the MIC of strains and the weaker the terrain of a non-neutropenic patient, the more justification there is for using a loading dose.

Monitoring for cefepime

It is indeed clearly stated in the Summarized Product Characteristics that the cefepime dosage must be adjusted to compensate for a lower rate of renal excretion. Because it enables better control of serum levels, the use of continuous infusion should reduce the level of neurologic toxicity. As for the other adverse events reported, their risk of onset will probably not be affected, as they are not related to the mode of product administration. To date, no adverse event which was probably attributable to cefepime has been reported in a patient receiving the drug in a continuous infusion. Cefepime may be assayed with the use of chromatographic (HPLC) and microbiological methods. However, because of the common use of multiple drug therapies, HPLC seems to be the most appropriate assay method.

The steady state for cefepime is attained 5 h after the initiation of continuous infusion. It is therefore not necessary to perform a plasma assay before then. After 5 h, an estimation of the steady-state concentration should allow evaluation of the validity of the initial dosage administered. With our current state of knowledge, the concentration at the steady state should, in most clinical situations, be between four and six times the MIC, but could reach ten to 50 times the MIC under certain special circumstances (e.g. *P. aeruginosa* in cystic fibrosis patients). In practice, a steady-state concentration of at least 15 mg/L, and close to 30 mg/L, should meet the requirements in the majority of situations.

Based on pharmacokinetic and pharmacodynamic data, the daily dosage of 4 g is suited to the most common clinical situations. The dosage of 6 g/day should be reserved for more difficult situations, in the case of strains with reduced sensitivity to cefepime, and in the context of individual dosage adjustment.

CONCLUSION

There is no absolute clinical proof of the superiority of continuous infusion over intermittent administration; there are only isolated clinical observations. The failure of antibiotic therapy in the most severe infections (terrain or pathogens implicated) does occur, and, in such patients, the method of administration must be optimized, to enable alignment of the pharmacokinetic/

pharmacodynamic ratio and the mode of administration. In these areas, clinical studies will not provide any answers, for methodological reasons.

There are numerous arguments in favor of continuous infusion: a better match with the pharmacodynamic parameters of β-lactams, better control of changes of levels in patients with unpredictable, variable pharmacokinetic constants, the possibility of treatment adjustment as a function of a defined therapeutic target (plasma concentrations at the steady state, C_{ss}/MIC ratio), ease of administration, and the prevention of overdose accidents. Furthermore, continuous infusion may contribute to reducing the risk of the emergence of resistant mutants during treatment.

Several in vitro and experimental findings have suggested that the therapeutic objective is to achieve plasma concentrations at the steady state which are four to six times the MIC of the incriminated microorganism. In the case of particular strains with a high MIC ($>$ 16 mg/L), this objective does not seem to be compatible with the toxicologic risks of most β-lactams.

A bolus of the antibiotic prior to the initiation of continuous infusion shortens the time needed to obtain active concentrations in the plasma. For cefepime, this loading dose should be 2 g in adults, followed by the continuous infusion of 4 g/24 h. The true value of the loading dose has not been demonstrated, but it appears to be reasonable in the most severely ill patients with a heavy infectious load.

Pharmacologic therapeutic monitoring (plasma assay at the steady state) is possible after about 5 h of infusion, and enables subsequent adjustment of the 24-h dosage as a function of the microorganism identified and the MIC of the antibiotic, the objective being a minimum level of four to six times the MIC value.

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