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Stability and compatibility study of cefepime in comparison with ceftazidime for potential administration by continuous infusion under conditions pertinent to ambulatory treatment of cystic fibrosis patients and to administration in intensive care units

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Cefepime has been examined for stability, potential liberation of degradation products and compatibility with other drugs under conditions mimicking its potential use by continuous infusion in cystic fibrosis and intensive care patients (5–12% w/v solutions; temperatures from 20 to 37°C; 1 h contact at 25°C with other drugs frequently co-administered by intravenous route to these types of patients). Ceftazidime was used as a comparator based on a previous normative study with this antibiotic for the same indications. Based on a limit of max. 10% degradation, cefepime can be considered stable for a maximum of 24 h at 25°C, but for only ~14 h at 30°C, and for <10 h at 37°C. Cefepime released so far unidentified degradation products if maintained at >30°C for >12 h as shown from a marked increase in pH and from the development of a strong red–purple colour. Incompatibilities were observed with erythromycin, propofol, midazolam, phenytoin, piritramide, theophylline, nicardipine, *N*-acetylcysteine and a concentrated solution of dobutamine. We conclude that: (i) cefepime cannot be used safely by continuous infusion if containers are kept for more than a few hours at 37°C (as will be the case for cystic fibrosis patients if using portable pumps carried under clothes); (ii) caution must be exercised in intensive care patients if the temperature and co-administration of other drugs is not kept under tight control. The nature and safety of the cefepime degradation products need to be studied further.

Keywords: stability, continuous infusion, degradation, compatibility

Introduction

β-Lactams are time-dependent antibiotics,[1] which implies that their activity is primarily related to the time during which their serum concentration remains above the MIC for the offending organism. Whereas studies with non-life-threatening infections have suggested that 50% of the dosing interval might be sufficient,[2] longer times (and up to 100% of the dosing interval) may be needed with difficult-to-treat organisms.[3] This has triggered efforts aimed at developing the use of continuous infusion of β-lactams in severe infections, an approach that, beyond its pharmacodynamic rationale,[4] may also offer pharmacoeconomic advantages.[5] Administration of ceftazidime by continuous infusion has accordingly been attempted in cystic fibrosis[6,7] and in intensive care.[8] Cefepime is a fourth-generation cephalosporin with a pharmacokinetic profile similar to that of ceftazidime,[9] but with increased affinity for penicillin-binding proteins,[10] improved activity against *Enterobacter* species and *Staphylococcus aureus*,[11,12] and reduced susceptibility to extended-spectrum β-lactamases.[13] These properties would make cefepime an attractive alternative in the clinical situations discussed above. Yet, only a limited amount of clinical data on the safety and efficacy of cefepime administered by continuous infusion are available so far.[14,15] More importantly, and in contrast to ceftazidime, no normative information is available concerning cefepime

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stability and compatibility under conditions fully pertinent to its potential clinical use by continuous infusion. In a recent study,[16] we observed only a minor (~10%) difference in the apparent stability of cefepime and ceftazidime upon incubation in aqueous media. Yet, only low concentrations (up to 5% maximum) of cefepime were used and these may not be adapted for intensive care patients. Moreover, we noted a marked change in colour of the solutions of cefepime upon storage, which raised the question of the liberation of potentially harmful degradation products. These points have been examined in the present study together with the compatibility of cefepime with other drugs that are commonly used in intensive care patients. Ceftazidime was used as a comparator.

Materials and methods

Overall design of the study

All conditions were aimed at mimicking the use of cefepime by continuous infusion in cystic fibrosis and intensive care patients. Based on the most accepted susceptibility breakpoint for cefepime (8 mg/L), a stable serum concentration of at least 20–40 mg/L was considered desirable,[3] meaning a daily dose of up to 6 g. Anticipated clinical practice implied that this daily dose would be placed in a single container (typically a 48 mL syringe, as used in commercially available motor-operated syringe pumps for intensive care patients, or a 125 mL motor-less elastomeric pump carried under clothes for cystic fibrosis patients), which would be left in place for a 24 h period. This led us to set the drug concentration in a 5–12% (w/v) range. After having determined that maintaining either cefepime or ceftazidime in solution at 37°C for more than a few hours caused appreciable degradation, we systematically investigated the 20–30°C (68–86°F) temperature range, which is the most frequently encountered in intensive care units. Compatibility studies were designed to take into account the situation most likely to cause unnoticed adverse effects, i.e. the β-lactam and another medication infused from distinct containers but through a common line using a Y-shaped connector. The drugs tested were selected based on a survey identifying those most frequently used via the intravenous route in intensive care patients in Belgium. These premises led us to adopt the methods described here.

Preparation of solutions and condition of storage

All solutions of cefepime and ceftazidime were freshly prepared using commercially available compounds. Dissolution was in water obtained from a Milli-Q Academic Ultrapure Water System (Millipore Corp., Bedford, MA, USA). No addition of NaCl or glucose was deemed necessary since the solutions were highly hypertonic. The solutions equilibrated spontaneously at ~pH 4.8 for cefepime, and at ~pH 7 for ceftazidime. No pH adjustment was attempted since: (i) preliminary studies, as well as private (during the review process of this paper, the Bristol-Myers Squibb Company communicated to one of us unpublished data on the pH–rate profile of cefepime degradation at 35°C, showing a typical U-shaped profile with maximum stability at ~pH 4–5) and published data,[17] showed that these conditions provided optimal stability; and (ii) no commercially available and/or pharmaceutically validated means of adjusting the pH of such concentrated solutions is presently available to the clinician. In the case of ceftazidime, for which the commercially available form contains sodium carbonate (118 mg/g of ceftazidime) and is stored in a CO_2-containing vial, care was taken to avoid CO_2 release and subsequent change of pH by running all experiments in closed and completely filled vials.

Compatibility studies

Each drug was prepared in solution (or diluted if supplied in solution) exactly as recommended for hospital usage in the corresponding Belgian *Notice Scientifique*[18] [i.e. the Summary of Product Characteristics (SPC) or following the corresponding supplier's documentation]. The final concentration and rate of infusion of each drug were those corresponding to recommendations for use in intensive care patients. The rate of infusion of the β-lactam (12% w/v) was set up at 2 mL/h. Based on these considerations, we calculated the concentrations of the antibiotic and of the co-administered drug that would be reached in the common line of the Y-shaped infusion set. Appropriately dosed mixtures were then prepared and left standing at 25°C for 1 h before being examined for physical compatibility. The latter was assessed by visual inspection using an LV 28 Liquid Viewer (P. W. Allen and Co. Ltd, Tewkesbury, UK) in comparison with a pure solution of cefepime (or ceftazidime) and distilled water. All mixtures showing visible signs of precipitation were considered as demonstrating physical incompatibility [and the presence of particles thereafter confirmed by light scattering analysis; Sub Micron Particle Analyser COULTER N 4 MD (Coulter Corp., Miami, FL, USA)]. All mixtures with no sign of precipitation were examined for their content of the corresponding β-lactam using HPLC analysis, and were considered as demonstrating chemical stability if the β-lactam concentration had not fallen below 90% of its nominal content.

Determination of cefepime and ceftazidime concentrations

We used a published HPLC method[19] with the following specific conditions: X-terra RP 18 column; elution buffer, 10 mM sodium acetate buffer pH 5/acetonitrile (95:5 v/v); flow rate 1 mL/min; UV detector, 258 nm for cefepime and 254 nm for ceftazidime. All analyses were made with a Waters 2690 System (Waters Corp., Milford, MA, USA) equipped with diode array detector and operated with the proprietary Waters

Millennium 32 software. Assays showed linearity from 1 to 200 mg/L [r^2 = 0.99; maximal coefficient of variation (based on the repetition of at least 30 determinations of the same samples), 4%]. All measurements were made against freshly prepared quality control solutions run with each series of assays. Each sample was assayed at least three times and the data pooled.

Other studies

pH was measured with an MP 225 pH meter (Metler-Toledo AG, Schwerzenbock, Switzerland) with calibration at each of the temperatures used. Absorbance spectra were obtained with a UVIKON 933 Double Beam UV/VIS Spectrophotometer (Bio-Tek Instruments Inc., Winooski, VT, USA) over a wavelength range of 200–800 nm and at a scan speed of 200 nm/min.

Materials

Cefepime was supplied by Bristol-Myers Squibb Belgium and ceftazidime by GlaxoSmithKline Belgium as the original, branded products (MAXIPIME and GLAZIDIM, respectively). All other drugs were obtained through the Hospital Pharmacy as the registered commercial product for parenteral use. Each drug was supplied by the corresponding marketing authorization holder of the original, branded product and complied with the Belgian or other applicable Pharmacopoeia. All products for chromatography were of HPLC grade and obtained from Sigma–Aldrich Corp. (Steinheim, Germany) or E. Merck AG (Darmstadt, Germany).

Statistical analyses

All experiments were carried out in triplicate (independent experiments), and all data points used to calculate means and standard deviations (S.D.). Two-way ANOVA analysis was carried out with the significance level set at 5%.

Results

Stability in aqueous media

In this first series of experiments, solutions of cefepime and ceftazidime were prepared at increasing concentrations from 5% to 12% and systematically exposed at fixed temperatures ranging from 20 to 37°C for increasing periods of time. Cefepime remained >95% stable at 20°C for up to 24 h at all concentrations but was unstable at 37°C (>10% degradation within 12 h) whatever its concentration (in the range studied). We therefore examined in more detail the influence of the temperature for 25°C and 30°C, which are of direct clinical interest. Figure 1 shows indeed that this range is critical since the loss of cefepime reached 10% within 24 h at 25°C (which

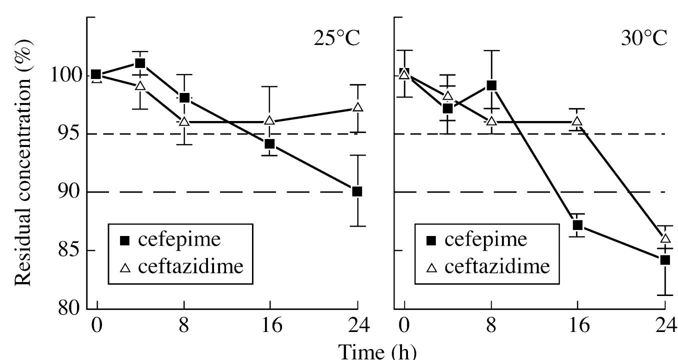

Figure 1. Stability of cefepime and ceftazidime (12% w/v) at 25 and 30°C. Each value is the mean ± S.D. of three independent determinations. The fine dotted line corresponds to the lowest limit of drug content for drug powders, based on the specifications of the 2000 edition of the *Pharmacopée Européenne*[38] and the corresponding recommendations of the European Agency for Evaluation of the Medicinal Products.[39] The thick dotted line corresponds to the lowest limits of drug content for ceftazidime solutions based on the 1995 edition of the United States Pharmacopeia.[20]

is the limit set up for ceftazidime solutions by the US Pharmacopeia;[20] note that neither the US nor the European Pharmacopoeia sets limits of degradation for cefepime in solution), and markedly exceeded this limit if incubation was carried out at 30°C. A two-way ANOVA analysis of the data presented in Figure 1 showed that cefepime and ceftazidime did not share a common behaviour, with ceftazidime demonstrating globally a greater stability at both 25°C (P = 0.04) and 30°C (P = 0.01). Meaningful differences were, however, only seen at 24 h for incubations at 25°C, and at 16 h for incubations at 30°C.

Change in pH

A marked difference was noted between cefepime and ceftazidime, with cefepime solutions showing a marked increase in pH progressing over time after an initial lag period of ~8–12 h. This change was temperature dependent. In contrast, almost no change in pH was seen with ceftazidime. Figure 2 shows typical results obtained at 37°C (with respect to time; this temperature was chosen to demonstrate clearly the characteristic lag period) and at 24 h (with respect to temperature) using a fixed concentration for both drugs (12%; less concentrated solutions were more susceptible to pH change due to the reduced buffering capacity of these diluted solutions). Again, no marked change in pH was seen with ceftazidime under similar conditions.

Change in colour

Freshly prepared solutions of cefepime display a light yellow colour that, according to the Belgian SPC,[18] must be considered normal for all cephalosporins and may change gradually

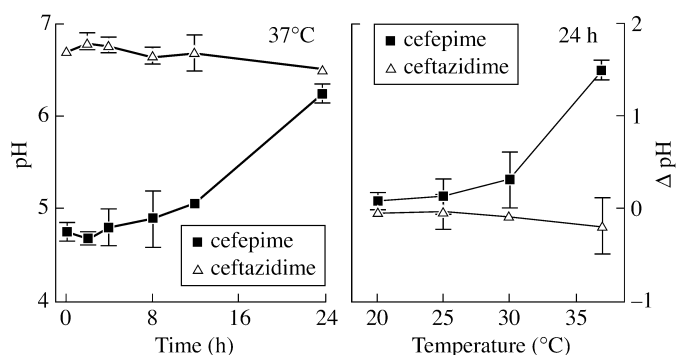

Figure 2. pH change of cefepime and ceftazidime solutions (12% w/v) upon incubation at 37°C for up to 24 h (left), or measured after 24 h incubation at increasing temperatures (right). Note that the ordinate in the left panel shows the actual pH values (which were quite different for ceftazidime and cefepime with freshly prepared solutions) whereas the right panel shows the change in pH upon incubation.

to amber yellow without loss of activity. Yet, we noted that the solutions of cefepime turned to red–purple if kept at 30°C for 12–16 h, whereas the solutions of ceftazidime remained yellow–amber. Spectrophotometry was therefore used to better characterize this change. Whereas complete scans from 200 to 800 nm were made, significant changes were seen only in the 420–550 nm range. The corresponding spectra are shown in Figure 3 for 12% solutions kept at 30°C for 16 and 24 h in comparison with that of freshly prepared solutions (0 h). Whereas only a low absorbance in the 420–440 nm region (corresponding to a pale yellow colour) was seen with unincubated solutions, a marked absorbance with a maximum at 490 nm (red) was noted at 16 h for cefepime. At 24 h, the absorbance of cefepime solutions had still increased and shifted to a maximum at 500 nm (red–purple). At the same time, the absorbance at 420–440 nm had completely disappeared. Figure 3 shows that these changes were much less marked with ceftazidime. In additional experiments, we observed that the change in colour of cefepime solutions was dependent upon the initial drug concentration and temperature (data not shown).

Compatibility studies

All initial studies were carried out using a 12% solution for both cefepime and ceftazidime and the corresponding results are presented in summary in Table 1. Among all antimicrobials tested, only erythromycin was incompatible with both cefepime and ceftazidime, whereas clarithromycin and vancomycin were incompatible with ceftazidime only. For all other drugs tested, incompatibilities were common to both cefepime and ceftazidime but the nature of the incompatibility (i.e. physical versus chemical) was sometimes different (for instance, incompatibility with midazolam was of a chemical nature for cefepime but of a physical nature for ceftazidime). The most severe chemical incompatibility was noted with theophylline (up to 25% degradation of cefepime after 1 h of contact). With respect to physical incompatibility, all samples showing visual evidence of precipitation also gave consistent readings when examined in an automatic particle analyser (data not shown). All these incompatibilities were concentration independent (within a range of clinically meaningful concentrations), except for dobutamine, for which concentrated solutions (250 mg/mL, as used for bolus administration) proved physically incompatible, whereas diluted solutions (1 mg/mL, as used for continuous infusion) showed neither physical nor chemical signs of incompatibility.

Discussion

β-Lactams are intrinsically unstable in water because of the high susceptibility of the β-lactam ring to hydrolysis through both acid- and base-mediated catalysis.[21] This

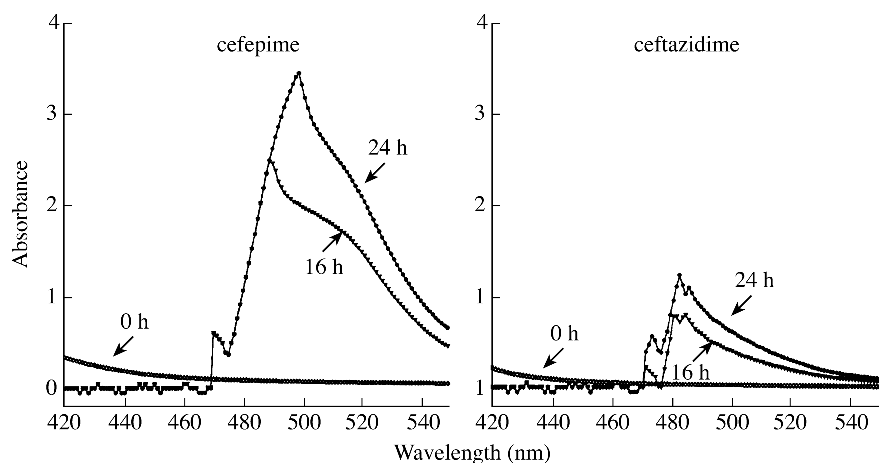

Figure 3. Absorption spectra of cefepime (left) and ceftazidime (right) solutions (12% w/v) upon incubation at 30°C for 16 and 24 h (0 h = freshly prepared solution).

Table 1. Conditions and results of compatibility studies of ceftazidime and cefepime with other drugs under conditions mimicking their co-administration through the same line of infusion[a]

Drug	Dose (mg)[b]	Volume per administration (mL)	Time of infusion (h)	Drug/β-lactam (cefepime/ceftazidime) weight ratio[c]	Result	
					ceftazidime	cefepime
Antiinfectives						
amikacin[d]	1500	100	0.25	25.25	c	c
tobramycin[d]	600	100	0.25	10.1	c	c
gentamicin[d]	600	100	0.25	10.1	c	c
vancomycin	1500	50	1	6.31	i (phys)	c
erythromycin	100	20	0.33	12.63	i (phys)	i (chem)
clarithromycin	500	10	0.33	6.31	i (phys)	c
fluconazole	200	100	0.5	1.68	c	c
Sedatives/anticonvulsivants/analgesics						
ketamine	480	48	24	0.08	c	c
propofol	300	300	24	0.05	i (phys)	i (phys)
sufentanil	0.12	24	24	2.1×10^{-5}	c	c
midazolam	600	120	24	0.11	i (phys)	i (chem)
valproic acid	1200	12	24	0.21	c	c
remifentanil	10	50	8.33	4.8×10^{-3}	c	c
phenytoin	750	15	0.25	12	i (phys)	i (phys)
morphine	5	5	1	0.02	c	c
piritramide	10	5	1	0.04	i (phys)	i (phys)
Bronchodilatators						
theophylline	200	10	0.33	2.39	i (chem)	i (chem)
Antihypertensives, vasodilators and other drugs acting on the sympathetic nervous system						
nicardipine	120	120	24	0.02	i (phys)	i (phys)
uradipil	2400	480	24	0.42	c	c
isosorbide dinitrate	6	30	1	0.02	c	c
furosemide	960	96	24	0.17	c	c
dopamine	0.4	1	0.016	0.1	c	c
dobutamine	0.84	0.84	0.016	0.21	i (phys)[e]	i (phys)[e]
adrenaline	0.5	10	0.33	0.0063	c	–
Hormones						
insulin	60 IU	0.6	3	0.08 IU/mg	c	c
methylprednisolone	500	10	0.5	4.0	c	c
Miscellaneous						
N-acetylcysteine	10 000	100	24	1.74	i (chem)	i(chem)
amino acid solution	18 000	1000	24	3.16	c	c

Key: c, chemically and physically compatible; i, incompatible; phys, physically incompatible (precipitate and presence of particles as shown by particle analyser); chem, chemically incompatible (<90% recovery; >10% loss of antibiotic compared with nominal content).
[a]Cefepime and ceftazidime were assumed to be administered at a daily dose of 6 g and to be infused at a rate of 4.17 mg/min (0.033 mL/min).
[b]Calculated (when appropriate) for a 70 kg male subject.
[c]In final infusate.
[d]Assuming a once-a-day schedule (30 min infusion).
[e]Precipitation at high concentration of dobutamine (250 mg/mL) but not at low concentration (1 mg/mL).

instability is potentially enhanced by an increase in drug concentration (combination of both intra- and intermolecular attack), and has been studied in detail for ceftazidime (see references 22 and 23 for recent publications), but only limited public data are available for cefepime.[17,24] Moreover, only a few studies[23,25–27] have used conditions strictly relevant to those that will be encountered in the clinics if using cefepime by continuous infusion (while the present contribution was being reviewed, one study quite similar to ours was presented as a poster).[28] Finally, no systematic comparison between

cefepime and other third- or fourth-generation cephalosporins has been made. Preliminary studies using diluted solutions[16] showed only marginal differences between ceftazidime and cefepime. Yet, and in contrast to ceftazidime, administration of cefepime by continuous infusion is not officially approved (see for example the US[29] and Belgian[18] SPCs), suggesting to us that additional studies are needed. The data presented in this paper actually demonstrate that the process of degradation of cefepime: (i) is not concentration dependent (unpublished data from the Bristol-Myers Squibb Company communicated to one of us during the reviewing of this paper show that degradation of cefepime is not concentration dependent; conversely, a recent study[30] showed that cefepime degradation in deproteinized plasma at 37°C was inversely related to its concentration, with half-lives varying between 3.66 and 6.89 h for concentrations spanning from 10 to 500 mg/L; note that these rates of degradation are considerably faster than those observed here in water); (ii) is marginally faster than that of ceftazidime (but additional experiments involving precise measures of rate constants are needed in this context). Yet, the changes in chemical composition of solutions of cefepime and ceftazidime occurring upon storage must be at least in part different, and could involve the liberation of so far unidentified products that may not be released from ceftazidime. This is evident from the marked increase in pH and the conspicuous change in colour noticed with cefepime, effects not seen to the same extent with ceftazidime. The degradation of cefepime includes cleavage of the C3 side chain and opening of the β-lactam ring, yielding 2-[[2-amino-4-thiazolyl((*Z*)-methoxyimino) acetyl]amino]ethanal and *N*-methylpyrrolidine.[28] These compounds are, however, colourless, and this degradation scheme is actually very similar to that of ceftazidime,[23] indicating that other reactions are likely to occur.[24] We could not, within the context of the present study, establish the nature of the coloured products and which chemical reaction(s) cause their liberation. Likewise, no quantification was attempted. These points will therefore need to be critically addressed in the future. Turning our attention to known products, and namely *N*-methyl-pyrrolidine [listed both by the US Environment Protection Agency (EPA; list 3: inerts of unknown toxicity)[31] and by the European Union (section I)[32] regulations concerning flavouring substances], we were faced with a lack of public toxicological data within the context of the evaluation of medicinal products. According to internal documents of the Bristol-Myers Squibb Company, administration of *N*-methyl-pyrrolidine at a dose of 50 mg/kg in monkeys (a daily dose that is ~25-fold higher than the maximum amount of *N*-methyl-pyrrolidine that could contaminate a daily dose of 6 g/day of cefepime assuming a 10% degradation) for 28–30 consecutive days caused ataxia and esotropia (cross-eyed appearance) during or shortly after treatment and with brief duration. No other overt signs of toxicity were apparent. No changes considered to be clearly related to the administration of *N*-methyl-pyrrolidine were detected in the clinicopathological data, gross necropsy findings or the histopathological examination. Lower doses caused no significant effect. *N*-Methyl-pyrrolidine is metabolized *in vivo* to *N*-methyl-pyrrolidine *N*-oxide,[33] for which only limited public safety data are available.[34] We know, however, that the extent of appearance of *N*-methyl-pyrrolidine *N*-oxide in the serum of patients receiving cefepime is in direct relation with the degree of their renal impairment.[35]

Whatever the chemical details of the degradation of cefepime, the present study also shows unambiguously that cefepime (or ceftazidime) cannot be administered by continuous infusion in cystic fibrosis patients with pumps carried under clothes, since the temperature of the solution is likely to exceed 25–30°C (recent data based on Arrhenius plot analyses show that 29.1°C is the upper limit for ensuring 90% cefepime intactness over 24 h).[28] These devices will therefore need to be changed at least every 8 h. Clear warnings must therefore be voiced in this context since clinical investigators seem to have ignored the potentially dangerous degradation of ceftazidime under these conditions.[7] Our warning needs to be even stronger for cefepime in view of the liberation of the so far unidentified degradation products as described above.

Moving now to the use of continuous infusion of cefepime and ceftazidime in intensive care units, it must be stressed that both drugs ought to be kept at temperatures preferably not exceeding 25°C. Effective control of the temperature in clinical wards will therefore be essential. Here also, additional warning must be given concerning cefepime in the absence of additional chemical studies concerning the nature of its degradation products. The occurrence of clinical signs of neurotoxicity in renally impaired patients receiving cefepime and other β-lactams without appropriate dosing corrections (see reference 36 for a recent report) raises questions in this context even though a cause to effect relationship has not been demonstrated.

Finally, our studies on drug compatibility indicate definite limitations in the routine use of continuous infusion with either cefepime or ceftazidime. It must be emphasized that chemical incompatibilities have not been characterized here beyond the mere observation of a decreased content of cefepime or ceftazidime in the solutions. The nature of the chemical compounds formed therefore needs to be studied in detail. Yet, it is clear that the incompatibilities seen here are more numerous than those mentioned in the official SPCs. The latter also contain information that varies between countries [and sometimes in a contradictory fashion; for instance, the official US Product Information (‘approved labelling’)[29] for cefepime mentions incompatibilities with vancomycin, gentamicin, tobramycin and theophylline, whereas the official Belgian *Notice Scientifique*[18] mentions only gentamicin as being incompatible but lists theophylline as compatible]. For

ceftazidime, only vancomycin incompatibility is listed in both SPCs and has been published as such.[37] These inconsistencies and the differences with our observations stem most likely from the fact that studies made in support of registration and used for establishing SPCs have not specifically considered the conditions under which continuous infusion would be implemented in the clinical arena as has been done here. As well as providing direct information to clinicians in this context, our data also illustrate the necessity of examining carefully the conditions of use of β-lactams if deviating from the originally foreseen and officially approved modes of administration.

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