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How To Minimize Toxic Exposure to Pyridine during Continuous Infusion of Ceftazidime in Patients with Cystic Fibrosis?

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Ceftazidime is particularly efficient against *Pseudomonas aeruginosa* in cystic fibrosis patients. Thus, the spontaneous production of pyridine, which is a toxic product, raises some concern. Our aim was to examine the kinetics of degradation of ceftazidime in portable infusion pumps either at 4°C, 22°C, or 33°C and to propose some recommendations in order to reduce the pyridine exposure. Two administration models were studied *in vitro*. In model 1, we administered 12 g of ceftazidime infused over 23 h (once-daily infusion) compared to 6 g infused over 11.5 h in model 2 (twice-daily regimen). Samples were collected at 0 h and then every 4 and 2 h after the shaping of portable infusion pumps in models 1 and 2, respectively. Both ceftazidime and pyridine were analyzed using an ultraviolet high-performance liquid chromatograph. Production of pyridine is highly depending on the temperature. The *in situ* production of pyridine per day of treatment decreases at a ratio close to 1/6 and 1/3 between 33°C and 4°C in models 1 and 2, respectively. Regardless of the conditions, the production of pyridine is significantly lower in model 2, whereas the total delivery amount of ceftazidime is significantly higher at 4°C and 33°C compared to that in model 1. According to a the precautionary principle, these findings lead to three major recommendations: (i) exposing a solution of ceftazidime to over 22°C should be strictly avoided, (ii) a divided dose of 6 g over 11.5 h instead of a once-daily administration is preferred, and (iii) infusion should be administered immediately after reconstitution.

Ceftazidime (CAZ) is one of the main anti-infective agents and is particularly efficient against *Pseudomonas aeruginosa* in cystic fibrosis (CF) patients. This major beta-lactam antibiotic, which has been on the market for many years, represents one of the main agents to treat acute pulmonary exacerbations (APE). In a recent survey, devoted to utilization of antipseudomonal beta-lactam antibiotics in the treatment of APE among Cystic Fibrosis Foundation-accredited care centers, ceftazidime appears as the most used beta-lactam analog, comprising 74/167 (44%) of all infusions, whether intermittent or extended (1).

One of the major disadvantages of CAZ is its instability, especially in aqueous solutions, due to the high susceptibility of the beta-lactam ring to spontaneous hydrolysis. This is also true for other beta-lactam analogs (2). Thus, the spontaneous production of pyridine (P), which is a toxic product, raises some concern (3–5). The chemical structures of ceftazidime and its main degradation product are depicted in Fig. 1. CAZ contains a pyridine group linked to C3 of its side chain.

Pyridine is a small basic heterocyclic organic compound (molar mass = 79.10 $g \cdot mol^{-1}$) with the chemical formula C_5H_5N. It is structurally related to benzene and also called azabenzene. Pyridine is widely used as a denaturant in alcohol and antifreeze mixtures, as a solvent for paint, rubber, and polycarbonate resins, and as an intermediate in the manufacture of insecticides, herbicides, and fungicides. It is used as an intermediate, solvent, and reagent in the preparation of vitamins and drugs, dyes, textile water repellants, and flavoring agents in food. Pyridine is a hazardous compound. Its toxicity profile has been studied in the context of various occupational exposures, usually by inhalation, dermal absorption, and swallowing, which may occur during P production or its use as a chemical intermediate or solvent (6–9). Pyridine has been characterized in humans as a central nervous system depressant, and it also may cause liver, kidney, and digestive disorders (6, 10). In 2-year drinking water studies, there was evidence of carcinogenic activity of pyridine in rats and mice (7). We will not discuss the available data related to the metabolism of P in humans (6, 10).

It is worth noting that the U.S. Pharmacopeia has a fixed upper limit of P in CAZ for intravenous (i.v.) infusion at 1.1 mg/ml, and no more than 0.4% and 0.3% of P is permitted in a sterile mixture of ceftazidime and sodium carbonate or arginine, respectively (11). Furthermore, the European Medicines Agency (EMEA) has defined a permitted daily exposure (PDE) as the maximum acceptable intake per day of residual solvent in pharmaceutical products. For P, this PDE was established at 2 mg per day (12).

The toxicological impact of the i.v. route remains unknown in humans. This is both worrying and logical, as there is obviously no valid reason to intentionally use this route or another for this type of product. Although reports of CAZ intolerance are fairly rare (13), we will see that we are also faced with an ethics question.

Our aim was to examine and to compare the kinetics of spontaneous degradation of CAZ in portable infusion pumps (PIP) at various temperatures and to propose some recommendations in order to reduce the P exposure during continuous infusion of ceftazidime in patients with cystic fibrosis. Two administration models were studied *in vitro*. In model 1, we administered 12 g of

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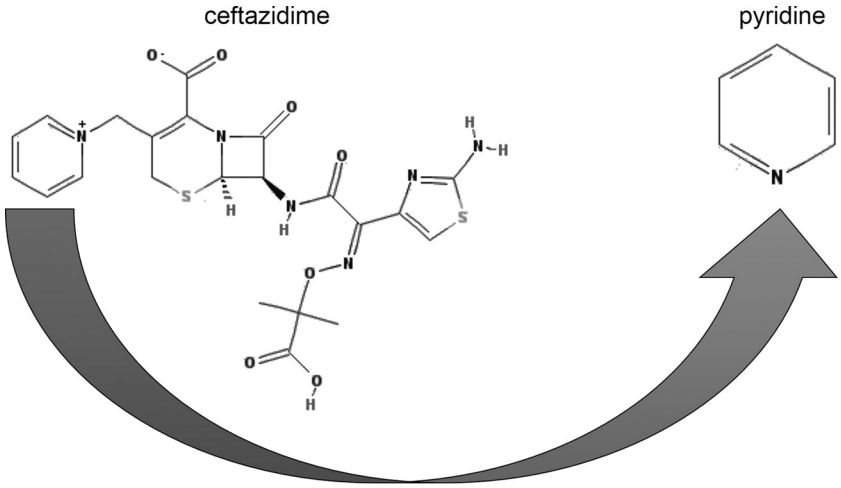

FIG 1 Spontaneous degradation of CAZ and *in situ* production of pyridine.

CAZ over 23 h with a once-daily infusion (ODD regimen) of the drug compared to 6 g over 11.5 h in model 2, which simulates a twice-daily regimen (BID regimen).

(Part of this work was presented at the 36th European Cystic Fibrosis Conference in Lisbon, Portugal, as a poster entitled "Ceftazidime continuous IV infusion in patients with cystic fibrosis and pyridine production" and as a poster at the 27th North American Cystic Fibrosis Conference in Salt Lake City, UT, entitled "How to reduce toxic exposure to pyridine during continuous infusion of ceftazidime in cystic fibrosis patients?").

MATERIALS AND METHODS

Study design. Throughout the study, we used the recommended dosing regimen commonly used in CF French reference centers and followed the study conducted by Hubert et al., i.e., a continuous infusion of 12 g of CAZ per day of treatment (14). In this work, the drug was administered using a PIP. There are several types of marketed devices that are commonly used in both hospitals and in homecare, as well as for ambulatory patients. We selected a pump model widely used, i.e., Infusor LV10 (Baxter reference no. 2C1702KD, batch no. 09C044 2011-12-31). Figure 2 presents a diagram of the device.

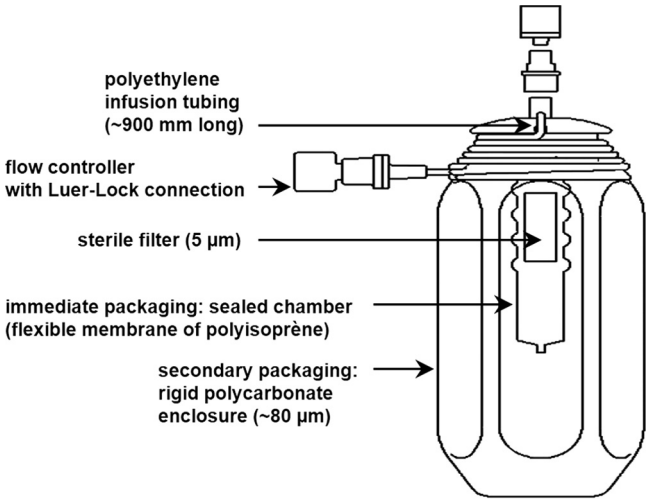

FIG 2 Schematic representation of a portable infusion pump (LV10 Baxter).

Two study models were developed and tested with the aim of accurately determining the kinetics of a coinfusion of CAZ and pyridine, its main degradation product. In the first model (model 1), 18 PIPs were filled with 12 g of ceftazidime (Fortum; GlaxoSmithKline, Marly-le-Roi, France) in a final volume of 230 ml of saline, which simulates an ODD regimen, i.e., 12 g of CAZ infused over 23 h. In model 2, 18 PIPs were loaded with 6 g of CAZ in a final volume of 115 ml of saline, which simulates a BID regimen, i.e., 6 g of CAZ infused over 11.5 h. In both cases, we estimated a time of 1 h per day as the time devoted to care, including the time for aminoglycoside antibiotics administration.

Initially, we examined the possible use of a divided daily infusion of CAZ, rather than the once-daily regimen, to reduce the risk of toxic exposure to P. In both models, the nominal concentration was 52.17 mg of CAZ/ml. Thirty-six devices and their infusion tubing (900-mm long) were stored either at 4°C (12/36 PIPs), simulating use of an autonomous refrigerant system, at 22°C (12/36 PIPs), simulating conditions of a temperate area or a conditioned space (12/36 PIPs), and at 33°C (12/36 PIPs), simulating storage close to the skin, under clothes, or under a blanket or duvet. In all cases, PIPs were protected from light, without any counterpressure. The flow controller was strictly maintained at 33°C using a thermostatically controlled sleeve.

Experimental protocol. Throughout the experiment, the samples of therapeutic solutions were collected and frozen extemporaneously at −80°C at 0 h and then every 4 h and 2 h after the shaping (compounding) of PIPs in models 1 and 2, respectively. To determine the residual volumes (RV) of therapeutic solution still present at the end of the experiments, the devices were weighed at 0 h and 23 h in model 1 and at 0 h and 11.5 h in model 2, i.e., with 36 weighing events for each group.

Sample pretreatment. Frozen samples were completely thawed and diluted in water for injection (dilution ratio = 1:1,000). To adjust dilution and avoid injection errors, α-picoline was added to the medium as an internal standard; its chemical structure is close to that of pyridine. We worked under cool conditions to prevent substantial evaporation of P and, consequently, to avoid further degradation of CAZ by chemical shift of the reaction. We were careful to avoid oxidation phenomena and subsequent changes of the pH of the medium by running all experiments in carefully stoppered and completely filled vials.

HPLC-UV conditions. Both CAZ and P were analyzed using a high-performance liquid chromatography with UV detection (HPLC-UV) validated method. Chromatographic separation was performed on a Dionex Ultimate 3000 series liquid chromatographic system equipped with a quaternary pump, a variable UV/visible detector, and an autosampler (Dionex, Voisins le Bretonneux, France). Chromatographic separation was performed with a Polaris (250 mm by 4.6 mm, particle diameter = 5 µm)

TABLE 1 Parameters calculated in model 1[a]

Storage temp (no. of devices)	Compound	C0 (g/liter)	C23 (g/liter)	AUC_{0-23} (g · h/liter)	$t_{1/2}$ (h)	Remaining vol (ml)	TDA[b] (g for CAZ, mg for pyridine)
4°C ($n = 6$)	CAZ	52.8 ± 2.2	51.7 ± 2.3	1,200.1 ± 19.4	312.4 ± 66.3	80.5 ± 7.1	7.5 ± 0.1
	Pyridine	0.057 ± 0.006	0.133 ± 0.066	2.50 ± 1.12	−21.6 ± 8.0	80.5 ± 7.1	16.3 ± 0.7
22°C ($n = 6$)	CAZ	53.9 ± 1.2	46.1 ± 1.0	1,207.1 ± 34.1	88.6 ± 17.2	<1.0	12.1 ± 0.3
	Pyridine	0.075 ± 0.014	0.425 ± 0.015	5.81 ± 0.1	−10.0 ± 0.3	<1.0	58.1 ± 0.1
33°C ($n = 6$)	CAZ	53.2 ± 1.8	43.0 ± 2.0	1,129.59 ± 49.8	76.8 ± 8.8	<1.0	11.3 ± 0.5
	Pyridine	0.064 ± 0.032	0.790 ± 0.007	9.54 ± 0.1	−6.7 ± 0.1	<1.0	91.5 ± 0.1

[a] Model 1 is characterized by 12 g of CAZ in 230 ml of saline, infused over 23 h via a portable infusion pump, studied in various conditions. The flow controller of the device was maintained at 33°C.
[b] TDA, total delivered amount. TDA was calculated by multiplying the AUC by the injected volume, i.e., volume of solution minus remaining volume, and dividing by time of infusion.

C_{18} column (Merck, Lyon, France). The mobile phase consisted of a mixture of ammonium acetate (25 mmol/liter) adjusted to pH 5.0 with acetic acid and acetonitrile (90:10, vol/vol) and was delivered at a rate of 1.8 ml per min. The mobile phase was filtered through a 0.45-μm-pore-size membrane (Millipore, Molsheim, France) and degassed prior to use. The column temperature was maintained at 30°C, while the autoinjector sample racks were maintained at 4°C. Detection was performed at 250 nm. The injection volume was 50 μl with a run time of 10 min. Data were recorded. Dionex Chromeleon (version 6.80) software was used for data collection and processing.

Validation parameters. The HPLC-UV method was optimized on the basis of previous studies (2–4, 14, 15). In particular, it seemed to us necessary to add an internal standard, i.e., α-picoline. Analytical validation of the methods was conducted in accordance with the recommendations of the Commission of the French Society of Pharmaceutical Science and Technology (SFSTP) (16, 17). Calculations of the validation parameters were based on six measurements per day for 3 days of four levels of quality control and were performed using the e.noval (version 3.0) software (Arlenda, Liège, Belgium). In brief, (i) for linearity, the slope and intercept are close to 1 and 0, respectively, confirming the absence of a proportional and constant systematic error in each model, and the correlation coefficients (R^2) were 0.9999 and 0.9994, respectively, for CAZ and P, (ii) repeatability values (intraseries variance) expressed in relative standard deviation (RSD %) were systematically below 1.7 and 3.4, respectively, for CAZ and P, (iii) intermediate precision values (the intra- and interseries variances sum) (RSD %) were systematically below 2.8 and 3.4, respectively, for CAZ and P, and (iv) trueness expressed in terms of recovery (%) ranged from 98.5 to 101 and from 96.7 to 110, respectively, for CAZ and P.

Data and statistical analysis. Model-independent kinetic parameters were calculated as follows for both CAZ and P: (i) initial (C0; mg/liter) and final (C23 and C11.5; mg/liter) concentrations, (ii) area under the concentration-time curve (AUC_{0-23} and $AUC_{0-11.5}$; g · h/liter), (iii) terminal half-life of the concentration-time curves ($t_{1/2}$; h), (iv) the total delivered amount of CAZ and P (TDA; g and mg, respectively), and (v) the remaining volume of therapeutic solution (RV) in the device after 23 (model 1) or 11.5 (model 2) hours. The results are expressed as the means ± standard deviations (SD) of the reference data. Comparisons of data were performed using a two-tailed Student *t* test. Data were analyzed using the Statistical Package for the Social Sciences (SPSS) software for Windows (version 17.0; SPSS Inc., Chicago, IL).

RESULTS

Kinetic parameters. As highlighted in Tables 1 and 2 and in Fig. 3, CAZ concentration decreased over the course of the experiments. This phenomenon was highly dependent on temperature.

In model 1, concentrations of CAZ measured after an infusion simulation of 23 h were 51.7 ± 2.3, 46.1 ± 1.0, and 43.0 ± 2.0 g/liter at 4°C, 22°C, and 33°C, respectively. The corresponding linear regression curves were as follows: $y = -0.40x + 53.1$ at 33°C, $y = -0.26x + 53.6$ at 22°C, and $y = -0.09x + 53.4$ at 4°C, where y and x are expressed in grams per milliliter and in hours, respectively. The charts in Fig. 3 and related regression models illustrate the linearity of the degradation phenomenon in each depicted situation. The decrease in CAZ concentration was esti-

TABLE 2 Parameters calculated in model 2[a]

Storage temp (no. of devices)	Compound	C0 (g/liter)	C11.5 (g/liter)	$AUC_{0-11.5}$ (g · h/liter)	$t_{1/2}$ (h)	Remaining vol (ml)	TDA[b] per day (g for CAZ, mg for pyridine)
4°C ($n = 6$)	CAZ	52.6 ± 0.8	52.4 ± 0.9	606.4 ± 5.7	1,551.5 ± 1,066.8	20.0 ± 5.0	10.0[d] ± 0.2
	Pyridine	0.036 ± 0.004	0.057 ± 0.008	0.56 ± 0.09	−15.9 ± 7.3	20.0 ± 5.0	9.3[e] ± 1.6
22°C ($n = 6$)	CAZ	53.8 ± 0.8	52.0 ± 0.7	618.8 ± 50.2	222.8 ± 50.2	<1.0	12.4 ± 0.4
	Pyridine	0.047 ± 0.007	0.173 ± 0.066	1.32 ± 0.50	−6.8 ± 2.6	<1.0	26.4[c] ± 10.2
33°C ($n = 6$)	CAZ	52.6 ± 2.2	50.0 ± 0.2	512.8 ± 6.3	126.0 ± 97.4	<1.0	10.3[d] ± 0.2
	Pyridine	0.034 ± 0.009	0.265 ± 0.002	1.52 ± 0.18	−3.9 ± 0.1	<1.0	30.4[d] ± 4.0

[a] Model 2 is characterized by 6 g of CAZ in 115 ml of saline, infused over 11.5 h via a portable infusion pump, studied in various conditions. The flow controller of the device was maintained at 33°C.
[b] TDA, total delivered amount. TDA was calculated by multiplying the AUC by the injected volume, i.e., volume of solution minus remaining volume, and dividing by time of infusion.
[c] $P = 0.015$, model 2 compared to model 1.
[d] $P < 0.001$, model 2 compared to model 1.
[e] $P = 0.033$, model 2 (6 g over 11.5 h 2 times per day) compared to model 1 (12 g over 23 h).

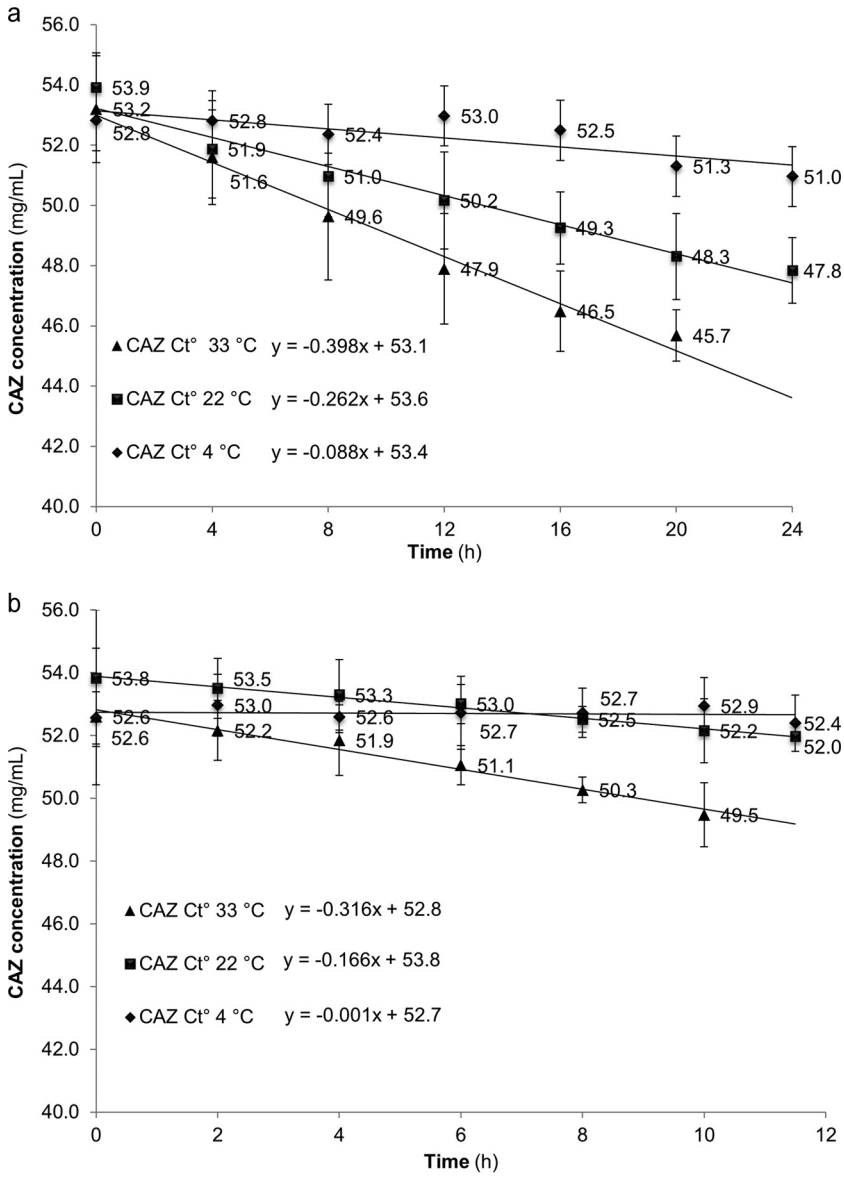

FIG 3 (a) Kinetics profiles of the degradation of CAZ in model 1, i.e., 12 g of CAZ infused over 23 h (ODD regimen); (b) kinetics profiles of the degradation of CAZ in model 2, i.e., 6 g of CAZ infused over 11.5 h (BID regimen).

mated at 2.1% (51.7 compared to 52.8 mg/ml), 14.5% (46.1 compared to 53.9 mg/ml), and 19.2% (43.0 compared to 53.2 mg/ml) of the initial (C0) concentration at 4°C, 22°C, and 33°C, respectively, which exceed, at 22°C and 33°C, the U.S. Pharmacopoeia limit of 10%. On the other hand, the infusion rate decreases by nearly 35% at 4°C. At the end of the experiment, a remaining volume of approximately 80.5 ml, equivalent to 4.2/12 g of CAZ, is still present in the device. In contrast, after 23 h or less, the devices maintained at 22°C and 33°C were always empty.

In model 2, the concentrations of CAZ measured after an infusion simulation of 11.5 h were 52.4 ± 0.9, 52.0 ± 0.7, and 50.0 ± 0.2 g/liter at 4°C, 22°C, and 33°C, respectively, according to the U.S. Pharmacopoeia limit of 10% (see above). The corresponding linear regression curves were as follows: $y = -0.32x + 52.8$ at 33°C, $y = -0.17x + 53.8$ at 22°C, and $y = -0.001x + 52.7$ at 4°C, where y and x are expressed in grams per milliliter and in hours, respectively. The infusion rate decreased by nearly 17% at 4°C. At the end of the experiment, a remaining volume of approximately 20.0 ml, equivalent to 1.04/6 g, and ~2.08 g per day of treatment of CAZ, was still present in the device. After 11.5 h, the devices maintained at 22°C and 33°C were empty.

Simultaneously, the P concentration gradually increased over the course of the experiment (Tables 1 and 2; Fig. 4). The corresponding regression models are depicted in Fig. 4. The speed of the chemical transformation is illustrated by the half-life values of the concentration-time curves, which have either positive (CAZ) or negative (pyridine) values. In model 1, it takes approximately 21.6 h at 4°C to double the P concentration in a medium at 4°C, approximately 10 h at 22°C, and almost 6.7 h at 33°C. In model 2, it takes approximately 15.9 h at 4°C to double the P concentration in a medium at 4°C, approximately 6.8 h at 22°C, and almost 3.9 h at 33°C.

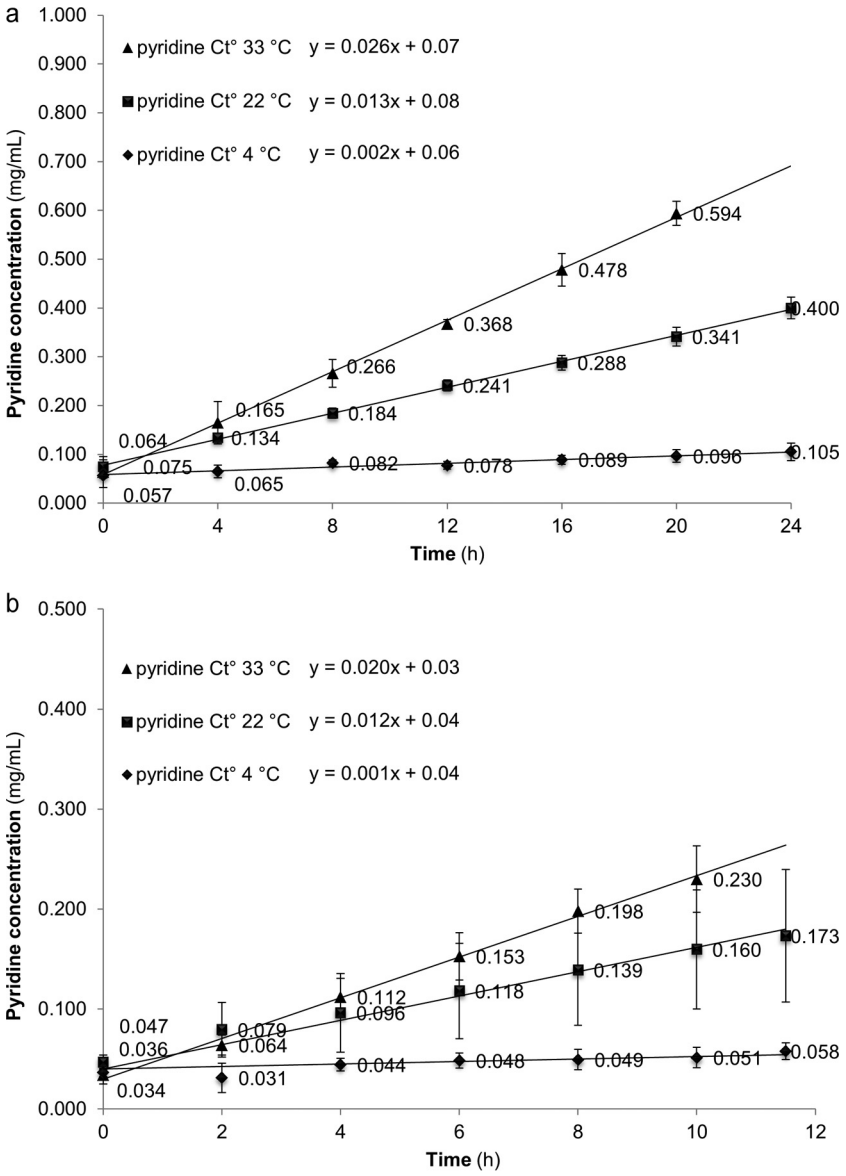

FIG 4 (a) Kinetics profiles of the production of pyridine in model 1, i.e., 12 g of CAZ infused over 23 h (ODD regimen); (b) kinetics profiles of the production of pyridine in model 2, i.e., 6 g of CAZ infused over 11.5 h (BID regimen).

Total delivered amounts. As shown in Tables 1 and 2 and within the same study model, the bioavailable fraction of CAZ, which corresponds to a total delivered amount, is significantly lower at 4°C than at the two other conditions ($P < 0.001$). As might be expected, the remaining volumes of therapeutic solutions are significantly higher at 4°C than at the two others conditions ($P < 0.0001$). In fact, the devices were always completely emptied after storage at 22°C and 33°C (Tables 1 and 2). The *in situ* production of P per day of treatment decreases at a ratio close to 1/6 and 1/3 between 33°C and 4°C in models 1 and 2, respectively. However, the TDA exceed systematically the permitted daily exposure (PDE) established at 2 mg per day by EMEA guidelines for residual solvents in pharmaceutical preparations (see the discussion above) (18). Regardless of the conditions, i.e., storage of the devices at 4°C, 22°C, and 33°C, the production of P is significantly lower in model 2 than in model 1, whereas the bioavailable amounts of CAZ are significantly higher at 4°C ($P < 0.0001$) and 33°C ($P = 0.001$). Conversely, at 22°C, the TDA values of CAZ per day of treatment are very similar in both models.

DISCUSSION

Among antibiotics, beta-lactam antibiotics are widely used in the treatment of APE (1) and demonstrate time-dependent pharmacodynamic properties. To achieve maximal microbiological efficacy, the residual blood concentration has to be three to four times the MIC of the pathogen and to remain above the MIC for ≥20% to 70% of the dosing interval (19). Increasing the concentration above this multiple does not improve the killing effect of the drug against the targeted pathogens (18, 20). The use of continuous infusion compared to intermittent infusion of beta-lactams in the treatment of APE remains a matter of controversy. In 2009, the CF Foundation (Bethesda, MD) concluded that there is insufficient

evidence to recommend the first option (21). In 2011, Prescott et al. evaluated the pharmacokinetics, efficacy, safety, stability, pharmacoeconomics, and quality-of-life effects of continuous-infusion antipseudomonal β-lactam therapy in patients with CF. This useful work was built on a literature review through MEDLINE from 1950 to December 2010 (22). According to these authors, the efficacy and safety studies available suggest that CAZ, administered as a continuous infusion for the treatment of CF pulmonary exacerbations, is safe and effective, has the potential to reduce the costs of treatment, and is preferred to intermittent infusion among the patients treated at home. As previously stated, this technical option is often selected in our common practice. Thus, our aim was not to start a controversial debate or discuss the basis of one option over another. The issue of the physicochemical stability of ceftazidime is clearly an upstream problem, especially when the main degradation product is pyridine, which is recognized as a toxic product.

In a multicenter, randomized, crossover study performed in 69 patients with moderate lung disease, we compared intermittent infusion and continuous infusion of CAZ for treating APE (14). The drug was administered at the relatively high dose of 200 mg/kg of body weight per day. Adverse effects were not significantly different between the two regimens, and we concluded that the continuous infusion did not increase the toxicity profile of the product and appeared to be as efficient as short infusions in patients with CF as a whole. The design of the study did not permit a simultaneous study of the stability of the drug administered at ambient temperature via portable infusion pumps. This issue will be the subject of a separate study. The connections between these issues have not been very carefully studied and discussed until now.

The effects of an acute P intoxication include dizziness, headache, lack of coordination, nausea, salivation, and loss of appetite. These disorders may progress into abdominal pain, pulmonary congestion, and unconsciousness (23). Evaluations of P as a possible carcinogenic agent indicated there is inadequate evidence in humans for its carcinogenicity. In contrast, there is some evidence of carcinogenic effects on animals (7, 23). Available data indicate that exposure to P in drinking water led to the reduction of sperm motility at all dose levels in mice and to an increased estrous cycle length at the highest dose level in rats (7). The toxicity profile of P administered by i.v. route has never been studied in humans. Indeed, there is no valid reason to intentionally use this route or another for a product such as P. As we can see, the apparently trivial issue of the infusion regimen of CAZ includes underestimated ethical aspects.

As stated in the introduction, it is worth noting that the U.S. Pharmacopeia has a fixed upper limit of P in CAZ for i.v. infusion at 1.1 mg/ml (11). On the other hand, the EMEA guideline for residual solvents in pharmaceutical preparations, which took effect in February 2009, recommends limited amounts of residual solvents in pharmaceuticals to ensure the safety of the patient (12). This guideline provides a list of solvents that are classified according to their toxicity in three classes. Pyridine is classified as a class 2, i.e., "Solvents to be limited," which is defined as nongenotoxic animal carcinogens or possible causative agents of other irreversible toxicity, such as neurotoxicity or teratogenicity and "solvents suspected of other significant but reversible toxicities"; the PDE of P was established at 2 mg per day.

These interlinked regulatory and ethical considerations led to the present examination of CAZ degradation and P production. As illustrated in Tables 1 and 2, (i) we confirm that the stability of CAZ is significantly better at low temperature, i.e., at 4°C rather than 22°C or 33°C (3–5), and that (ii) the production of P is unavoidable regardless of the operational conditions and (iii) the absolute amount of P produced per day of continuous infusion is significantly lower in model 2 (BID regimen) than in model 1 (ODD regimen). Finally, an acceptable compromise needs to be reached between a bioavailable and expected amount of delivered CAZ and the amount of P inevitably coinjected into the patient.

We have to consider at least five interlinked parameters, i.e., the algorithm of infusion, the temperature of the therapeutic solution, the nominal quantity (the dose) of CAZ into the device, the actually delivered dose of antibiotic, and the dose of P to which a patient will be exposed. These parameters should also be considered in the context that patients with CF receive multiple courses of antibiotics throughout a year and more generally throughout their lives. We demonstrate that P production is significantly lower at 4°C, especially when the daily dose is divided. The disadvantage of these relatively modest amounts of P being released in the medium is the sacrifice of a portion of therapeutic solution remaining in the device when infusion ends, i.e., 80.5 ± 7.1 ml or 4.2 g of CAZ and 40 ± 10.0 ml or 2 g of CAZ per day of treatment in model 1 and model 2, respectively. This phenomenon is the direct consequence of a contraction of the glass capillary tube inserted in the flow controller, despite it being heated at 33°C (data not shown). This is an illustration of the Hagen-Poiseuille law. In other words, if we demonstrate that an infusion at low temperature is the preferable solution, its implementation remains technically unfeasible at this time. This option might be realistic in the future, following the development of an autonomous and lightweight refrigerated system and the improvement of the performance of the distal flow controller.

Each year, approximately 40% of patients with CF are admitted to the hospital with APE. Half of these patients are admitted more than once per year, and a quarter are admitted three or more times each year (24). It is instructive to estimate the respective total amounts (quantities) of CAZ and P to which patients could be exposed annually on the basis of three courses of 15 days of treatment per year. Thus, in model 1 (ODD regimen), we calculate an estimated coinfusion of 486 g of CAZ and 4.12 g of P at 33°C compared to 522 g of CAZ and 2.5 g of P at 22°C. In model 2, we calculate an estimated coinfusion of 531 g of CAZ and 1.37 g of P at 33°C compared to 549 g of CAZ and 1.18 g of P at 22°C. In any case, the BID regimen is preferred, as it avoids exposing a solution of CAZ to temperatures greater than 22°C. As previously explained, the third condition (infusion at 4°C) is not feasible at this time.

The recommended dosages administered at Cystic Fibrosis French Reference Centers are historically based on the following European Consensus guideline, i.e., 150 to 250 mg/kg/day divided every 6 to 8 h (maximum of 12 g/day) and on studies performed at higher intermittent or continuous regimens that have demonstrated similar tolerability profiles and improved efficacy in the management of the APE episodes (14, 25–28). In contrast, it has been demonstrated that compared with an intermittent infusion dosing regimen, continuous-infusion beta-lactam therapy achieves the target serum concentration for susceptible organisms using a 41% to 50% lower total daily dose of CAZ (29, 30).

Conclusion. According to a the precautionary principle, these

findings lead to three major recommendations: (i) exposing a solution of CAZ to over 22°C, especially in the case of continuous infusion, should be strictly avoided; (ii) a divided dose of 6 g over 12 h or less (BID regimen) instead of a once-daily administration is preferred, and (iii) infusion should be administered immediately after reconstitution by saline. However, if infusion cannot occur immediately, we recommend keeping the solution in the refrigerator for as short a time as possible. Except for the algorithm parameters, the other recommendations are feasible for other modalities of injection of CAZ, e.g., a short or a very short infusion. Furthermore, given that the kinetics of the degradation of CAZ are first order, it is consistent to estimate that the amount of P coinjected on the basis of a 6 g BID regimen is approximately 3.2 times less than the value calculated in the case of the ODD regimen, when performed at 22°C. Because of the very concrete character of these recommendations, since April 2013, we decided to change our practices in favor of the BID regimen. Such changes in clinical practices have been explained clearly to caregivers and patients, and after 7 months, we have not encountered any particular problems.

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