STABILITY AND COMPATIBILITY OF ANTIBIOTICS IN PERITONEAL DIALYSIS SOLUTIONS APPLIED TO AUTOMATED PERITONEAL DIALYSIS IN THE PEDIATRIC POPULATION

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◆ **Objectives:** Assess the stability of several antibiotics in peritoneal dialysis (PD) solutions under common conditions of use in pediatrics, particularly in automated PD.

◆ **Methods:** Amoxicillin, cefazolin, cefepime, ceftazidime, imipenem, cotrimoxazole, tobramycin, vancomycin, and the association of ceftazidime + vancomycin and ceftazidime + tobramycin, were tested in 3 different PD solutions: bicarbonate/lactate solution with 2 glucose concentrations (Physioneal 1.36 and 3.86%; Baxter Healthcare Corporation, Deerfield, IL, USA) and an icodextrin-containing solution (Extraneal; Baxter Healthcare Corporation, Deerfield, IL, USA). Concentrations were those recommended in guidelines for the treatment of peritonitis in pediatrics. Physioneal bags were incubated at 37°C for 24 hours, whereas Extraneal bags were stored 12 hours at room temperature (22 ± 2°C) and then 12 hours at 37°C. Drug concentrations were determined using high performance liquid chromatography (HPLC). Each measure was taken in triplicate. Stability of antibiotics was defined as less than 10% degradation of the drug over time.

◆ **Results:** Cefazolin, cotrimoxazole, tobramycin, and vancomycin were stable under studied conditions. Ceftazidime was stable 24 hours in icodextrin, 12 hours in Physioneal 1.36% and 6 hours in Physioneal 3.86%. The association of tobramycin or vancomycin did not influence the stability of ceftazidime. Cefepime and amoxicillin were stable 6 h, 4 h, and 8 h in Physioneal 1.36%, 3.86% and Extraneal, respectively. The stability of imipenem was very low: 2 h in Physioneal and 6 h in Extraneal. Moreover, an increasingly yellow coloration was observed with the use of imipenem, whereas no color change or precipitation occurred in other bags.

◆ **Conclusion:** Cefazolin, tobramycin, cotrimoxazole, and vancomycin are stable in PD solutions up to 24 hours and can be administered in the PD bag for the treatment of peritonitis, even in automated PD under studied conditions. However, amoxicillin, cefepime, ceftazidime, and imipenem must be used with caution due to their lack of stability.

Infectious complications remain the most significant cause of morbidity in pediatric patients receiving chronic peritoneal dialysis (PD). More particularly, peritonitis and catheter-related infections are a major complication associated with automated PD (APD). Treatment of peritonitis in pediatric patients receiving PD is well documented. Consensus guidelines were updated and published in 2012 (1). One limit of APD is the need to keep dialysis solutions several hours at 37°C before use and, moreover, in some neonates and small children, a single bag of PD solution may be administered for up to 24 hours. In case of infection, intraperitoneal antibiotic administration is the gold standard (1). However, specific conditions surrounding administration of these preparations have not been studied (warmed to body temperature before use during many hours, compatibility with icodextrin, drug-drug interactions, etc.). Most of the previous studies have checked antibiotic stability in Dianeal (Baxter Healthcare Corporation, Deerfield, IL, USA) (2,3,4). In our study, we evaluated the stability of some antibiotics frequently recommended alone (amoxicillin, cefazolin, ceftazidime, cefepime cotrimoxazole (sulfamethoxazole + trimethoprim), imipenem, tobramycin, vancomycin), and in certain combinations (ceftazidime + vancomycin and ceftazidime + tobramycin) in 3 different PD solutions (Physioneal 40 1.36% and 3.86% [Baxter Healthcare Corporation, Deerfield, IL, USA] for 24 hours at 37°C, and Extraneal [Baxter Healthcare Corporation, Deerfield, IL, USA] for 12 hours at room temperature and then 12 hours at 37°C).

MATERIALS AND METHODS

A compatibility study is a concept that includes several parts: stability of the drug over a defined time (24 hours in our case), diluent stability, absorption into the container (drug container interaction), and, in the case of combinations, the drug-drug interactions.

Stability is defined in the United States Pharmacopeia (USP) as the extent to which a product retains, within specific limits and throughout its period of storage and use, the same properties and characteristics that it possessed at the time of its manufacture. Drug stability and diluent stability are incorporated in this definition.

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Absorption into the container was evaluated by measuring the difference between the expected target concentration (e.g. 50 mg/L) and the effective initial concentration obtained after adding the drug to the PD solution (e.g. 48.5 mg/L).

MATERIALS

The stability of the main antibiotics used in the treatment of peritonitis was determined in several PD fluids contained in Viaflex (Baxter Healthcare Corporation, Deerfield, IL, USA): a bicarbonate/lactate solution with physiological pH (Physioneal) with 2 different glucose concentrations (1.36% and 3.86%), and an icodextrin-containing solution (Extraneal). Physioneal solution was hermetically sealed inside a 2-chamber bag manufactured from medical grade plasticized polyvinyl chloride (PVC). The upper chamber was fitted with an injection port for drug admixture to the glucose with electrolytes solution. The lower chamber was fitted with a port for connection to a suitable administration set allowing dialysis operations. The bag was sealed inside a transparent overpouch obtained by thermic fusion and made of multilayer copolymers. The Extraneal solution was presented in a flexible PVC bag and was sterile, non-pyrogenic, and contained no bacteriostatic or antimicrobial agents or added buffers.

Antibiotics studied were amoxicillin, cefazolin, ceftazidime, cefepime, cotrimoxazole, imipenem, tobramycin, vancomycin, and the following combinations: ceftazidime + vancomycin and ceftazidime + tobramycin. Each drug was admixed and evaluated in 3 different 2.5-L bags of each PD solution tested: Physioneal 40 1.36 % and 3.86 %, and Extraneal.

EXPERIMENT DESIGN

The study was designed to mimic end-user conditions as closely as possible. Drugs available in powder (amoxicillin, cefazolin, ceftazidime, cefepime, imipenem, and vancomycin) were reconstituted as recommended in the product information. Tobramycin and cotrimoxazole were available in liquid form. Three different bags for each PD solution were used for injection of each drug and each dosage. Immediately before injection of the drug, the 2 chambers of Physioneal were mixed. A suitable volume of drug was injected through the injection port, using a sterile syringe, in order to reach the expected target concentration of each antibiotic. These expected concentrations corresponded to the maintenance dose indicated in the consensus guidelines for the prevention and treatment of catheter-related infections and peritonitis in pediatric patients receiving PD (1).

Physioneal bags were then incubated at 37°C for 24 hours, whereas Extraneal bags were stored 12 hours at room temperature ($22 \pm 2^\circ\text{C}$) and then 12 hours at 37°C. Prior to sampling, the bags were shaken gently by hand for 1 min, and samples (2 mL) were withdrawn from each bag immediately after preparation (baseline) and after 2, 4, 6, 12, and 24 hours. These 2-mL aliquots were frozen (-80°C) immediately after collection and stored until assay. All preparations were visually

inspected to detect precipitation, cloudiness, and change in color throughout the study period. The pH level was also monitored at baseline and at 12 and 24 hours after preparation.

ASSAY METHODS

Concentrations of all antibiotics were determined in triplicate using a high-performance liquid chromatography (HPLC). The chromatographic system (quaternary pump, autosampler, column manager, and photodiode Array Manager) consisted of a Waters Acquity UPLC (Waters, Milford, MA, USA). Chromatographic separations were achieved using Acquity UPLC BEH C18 column (2.1×150 mm, 1.7 mm), and UHPLC-grade reagents were used for all assays.

DATA ANALYSIS

For each analysis time, the average concentration and standard deviation of 3 bags were calculated. Drug concentrations were determined with a standard curve. The change in drug concentration was determined as the percent change between the registered signal and the signal of the initial concentration. A mean loss over 10% from baseline was taken as evidence of lack of stability (5).

Drug-drug interaction was assessed by measuring the stability of each drug alone and in combination. Time to reach 10% degradation and degradation percentage after 24 hours were compared in order to determine the influence of one drug on the other.

RESULTS

Imipenem solutions showed a yellow coloration that increased over time. All other solutions were clear in appearance and no color change or precipitation was observed throughout the study period.

Measured concentration at baseline and the percentage of difference between target concentration and measured concentration are reported in Table 1. Concentration differences were negligible.

Table 2 lists stability data of the drugs studied as single additives to PD solutions. Vancomycin, cotrimoxazole, cefazolin, and tobramycin were stable 24 hours in the 3 different bags under studied parameters. Ceftazidime and cefepime did not show degradation in Extraneal, whereas stability in Physioneal was less than 24 hours. Stability of amoxicillin and imipenem was weak in both Physioneal and Extraneal.

DRUG-DRUG INTERACTION

No changes in pH were noted throughout the study for all drugs in the 3 different bags. Stability of ceftazidime was assessed alone and in combination with tobramycin and vancomycin. Time to reach 10% degradation was the same for ceftazidime alone (12.8 hours) and combined with vancomycin (13 hours) or tobramycin (13 hours) in Physioneal

TABLE 1
Concentration and Percentage of Drugs in Peritoneal Dialysis Solutions at Baseline

	Target concentration (mg/L)	Physioneal 1.36% mg/L (% change)	Physioneal 3.86% mg/L (% change)	Extraneal mg/L (% change)
Amoxicillin	50	48.45 (-3.1%)	47.5 (-5.1%)	52.8 (+5.5%)
Cefazolin	125	121.2 (-3%)	118.1 (-5.5%)	126.3 (+1%)
Ceftazidime	125	127.9 (+2.3%)	125.8 (+0.7%)	132.2 (+5.8%)
Ceftazidime (+ tobramycin)	125	128.3 (+2.6%)	127.1 (+1.7%)	129.5 (+3.6%)
Ceftazidime (+ vancomycin)	125	126 (+0.8%)	123 (-1.6%)	127.5 (+2%)
Cefepime	125	119 (-4.2%)	116 (-7.2%)	123 (-1.6%)
Sulfamethoxazole	400	405.4 (+1.4%)	402.3 (+0.6%)	403.5 (+0.9%)
Trimethoprim	80	79.9 (-0.1%)	78.8 (-1.5%)	79.8 (-0.3%)
Imipenem	200	189 (-5.5%)	195 (-2.5%)	204 (+2%)
Imipenem	50	48 (-4%)	52.1 (+4.2%)	49.4 (-1.2%)
Tobramycin	4	4.2 (+4.6%)	3.8 (-3.8%)	4.2 (+5.4%)
Tobramycin (+ ceftazidime)	4	4.1 (+2.5%)	4.0 (+0.6%)	4.2 (+5.4%)
Vancomycin	30	29 (-3.3%)	28.4 (-5.5%)	28.9 (-3.9%)
Vancomycin (+ ceftazidime)	30	29.3 (-2.3%)	28.9 (-3.7%)	28.8 (-4%)

1.36% and was 4.8, 7.4, and 6.8 hours in Physioneal 3.86%, respectively.

After 24 hours, in Physioneal 1.36% and 3.86%, vancomycin and tobramycin have no effect on ceftazidime stability (Table 2). Stability of vancomycin and tobramycin was at least 24 hours alone or combined with ceftazidime. Importantly, no influence of one drug on another was found.

DISCUSSION

As discussed earlier, it is necessary to warm PD solutions to body temperature (37°C) before administration in order to minimize complications such as hypothermia and arrhythmia. However, warming up solutions, especially for extended periods of time, may result in significant drug degradation.

In the case of adsorption, which occurs when medication adheres to a container, a decrease of the drug concentration occurs in the solution. Alternatively, some medications may be absorbed into the container itself, also decreasing drug concentration (6). In contrast to drug degradation which is time-dependent, drug adsorption is faster and can already be seen at the mixing stage (5). In our study, the maximum difference between target concentration and measured concentration at baseline was 7.2% for cefepime in Physioneal 3.86%. This small difference between theoretical and measured concentrations can be attributed to overfill volume of the bags, or to syringe use, which is not as accurate as a pipette used in laboratory.

In our studied conditions, cefazolin, sulfamethoxazole, trimethoprim, tobramycin, and vancomycin were considered as stable in Physioneal as in Extraneal.

Imipenem is known to be unstable in various solutions. Its degradation is pH, concentration, and temperature dependant (7). Based on our results, imipenem shows a rapid degradation: 10% degradation is reached in 2 hours at 37°C in Physioneal. Whereas consensus guidelines recommend the

use of imipenem-cilastatin in PD solutions (loading dose of 250 mg/L and maintenance dose of 50 mg/L), this study shows that this drug is rapidly and extensively degraded in PD solutions, even before administration.

As found by others (8), ceftazidime remains stable in icodextrin for 24 hours. In Physioneal 1.36% and 3.86%, 10% degradation was reached in 12.8 and 6 hours at 37°C, respectively. Our results are consistent with previous published data (8). Studies about the stability of ceftazidime have shown that its stability is influenced by temperature (9). Many degradation products have been identified, notably pyridine.

In consensus guidelines for the prevention and treatment of catheter-related infections and peritonitis in pediatric patients receiving PD, cefepime is suggested as monotherapy for empiric treatment of peritonitis in centers in which that antibiotic is available and affordable (guideline 10.2 [1]). However, in our study, cefepime appears to be stable only 10 and 5 hours in Physioneal 1.36% and 3.86%, respectively. Caution must be taken in terms of preparation and conservation of the bags if this drug is used in Physioneal. In Extraneal, cefepime remains stable for 24 hours as published elsewhere (10).

The choice of antibiotic for the treatment of peritonitis in pediatric patients receiving PD is driven by consensus guidelines, identified pathogen, and its susceptibility. Even if the recommended intraperitoneal dosages of the antibiotics tested are usually several-fold higher than the minimal inhibitory concentrations (MICs) of most bacteria, results of our study show that antibiotics such as amoxicillin, cefepime, ceftazidime, and imipenem are quickly and extensively degraded *prior* to delivery, in warmed biocompatible fluids. This lack of stability, according to United States Pharmacopeia, and possibly toxic degradation products (pyridine for ceftazidime) could influence the efficacy of antibiotics *in vivo*. For these antibiotics, administration modalities, such as time of use of the bags, could be considered.

TABLE 2
Summary of Drug Stability*

	Physioneal 1.36%	Physioneal 3.86%	Extraneal
Amoxicillin (50 mg/L)	6 h 41% @ 24h	4 h 32% @ 24h	8 h 82% @ 24h
Cefazolin (125 mg/L)	>24 h 99% @ 24h	>24 h 92% @ 24h	>24 h 92% @ 24h
Ceftazidime (125 mg/L) (±tobramycin) (±vancomycin)	12.8 h 77% @ 24h	6 h 48% @ 24h	>24 h 92% @ 24h
Cefepime (125 mg/L)	10 h 60% @ 24h	5 h 29% @ 24h	>24 h 96 % @ 24h
Sulfamethoxazole (400 mg/L)	>24 h 97% @ 24h	>24 H 99% @ 24h	>24 h 100% @ 24h
Trimethoprim (80 mg/L)	>24 h 96% @ 24h	>24 h 100% @ 24h	>24 h 100% @ 24h
Imipenem (200 mg/L)	2 h 12% @ 24h	2 h 4% @ 24h	6 h 26% @ 24h
Imipenem (50 mg/L)	2 h 12% @ 24h	2 h 5% @ 24h	6 h 24% @ 24h
Tobramycin (4 mg/L) (±ceftazidime)	>24 h 91% @ 24h	>24 h 93% @ 24h	>24 h 91% @ 24h
Vancomycin (30 mg/L) (±ceftazidime)	>24 h 93% @ 24h	>24 h 91% @ 24h	>24 h 96% @ 24h

* Time (in hours) necessary to reach 10% of drug degradation and percentage of drug remaining after 24 hours.

CONCLUSION

The results of our study show that cefazolin, cotrimoxazole, tobramycin, and vancomycin are stable in PD solutions up to 24 hours and can be administered in the PD bag for the treatment of peritonitis, even in automated PD. However, antibiotics such as amoxicillin, ceftazidime, cefepime, and imipenem must be used with caution due to their lack of stability prior to administration. Our findings raise concerns about possible degradation of intraperitoneal antibiotics that may call into question the efficacy of these antibiotics *in vivo*.

DISCLOSURES

The authors have no financial conflicts of interest to declare.

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