Effect of Freezing on Stability of a Fortified 5 mg/mL Ticarcillin Ophthalmic Solution

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ABSTRACT

Background and Objective: Degradation of ticarcillin limits its shelf life under certain storage conditions. This study was undertaken to determine the stability of 5 mg/mL ticarcillin ophthalmic solution in 0.9% sodium chloride in frozen and unfrozen preparations.

Methods: Ticarcillin ophthalmic solutions were prepared in 0.9% sodium chloride. One set of samples was frozen (–20°C) for 9 weeks, thawed at room temperature, and stored for 15 days at either 4°C or room temperature (25°C), with or without protection from light. Another set of samples was stored, without freezing, for 15 days at either 4°C or room temperature (25°C), with or without protection from light. Physical and chemical analysis of the samples included visual inspection, determination of pH and osmolarity, reverse-phase liquid chromatographic analysis of the ticarcillin concentration (with ultraviolet light detection at 240 nm), and analysis of microbial growth. The stored solutions were opened twice a day to reproduce conditions of use after dispensing.

Results: Ticarcillin ophthalmic solutions (5 mg/mL) were physically stable during the study period, and there was no evidence of microbial growth. The samples that had not been previously frozen retained more than 90% of their initial ticarcillin concentration (with 95% confidence) for 7 days at 4°C and for 3 days at room temperature with or without protection from light. Samples that had been frozen for 9 weeks also retained more than 90% of their initial concentration (with 95% confidence) after thawing, for 6 days at 4°C and for 3 days at room temperature with or without protection from light.

Conclusions: Ticarcillin ophthalmic solutions can be made up in advance and stored frozen, without affecting the expiry date. The thawed solutions should be used within 3 days if stored at room temperature or 6 days if stored at 4°C. Freezing allows chemical and microbiological testing to be completed before use, if necessary.

Key words: ticarcillin disodium, ophthalmic solutions, stability, storage, high-performance liquid chromatography

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RÉSUMÉ

Historique et objectif : La dégradation de la ticarcilline limite la durée de conservation de celle-ci dans certaines conditions d'entreposage. Cette étude a été menée pour déterminer la stabilité de préparations gelées et non gelées de solutions ophtalmiques de ticarcilline disodique à 5 mg/mL dans du chlorure de sodium à 0,9 %.

Méthodes : Les solutions de ticarcilline disodique ont été préparées dans du chlorure de sodium à 0,9 %. Une série d'échantillons ont été congelés (–20 °C) pendant 9 semaines, décongelés à la température ambiante, puis entreposés pendant 15 jours à 4 °C ou à la température ambiante (25 °C), à l'abri ou non de la lumière. Une autre série d'échantillons ont été entreposés, sans être congelés, pendant 15 jours à 4 °C ou à la température ambiante (25 °C), à l'abri ou non de la lumière. L'analyse physique et chimique des échantillons a compris une inspection visuelle, une détermination du pH et de l'osmolarité, une analyse de la concentration en ticarcilline disodique au moyen d'une épreuve par chromatographie liquide en phase inverse (avec détection ultraviolette à 240 nm) ainsi qu'une analyse de croissance microbienne. Les solutions ainsi entreposées ont été ouvertes deux fois par jour afin de reproduire les conditions d'utilisation après leur distribution.

Résultats : Les solutions ophtalmiques de ticarcilline (5 mg/mL) sont demeurées physiquement stables durant la période de l'étude, et on n'a observé aucun signe de contamination microbienne. Les échantillons qui n'avaient pas été congelés ont conservé plus de 90 % de leur concentration initiale de ticarcilline (intervalle de confiance à 95 %) pendant 7 jours à 4 °C et pendant 3 jours à la température ambiante, à l'abri ou non de la lumière. Les échantillons qui avaient été congelés pendant 9 semaines ont conservé également plus de 90 % de leur concentration initiale (intervalle de confiance à 95 %) une fois décongelés, pendant 6 jours à 4 °C et pendant 3 jours à la température ambiante, à l'abri ou non de la lumière.

Conclusions : Les solutions ophtalmiques de ticarcilline peuvent être préparées à l'avance et congelées, sans que cela n'affecte leur durée de conservation. Une fois décongelées, les solutions doivent être utilisées dans les 3 jours si elles sont conservées à la température ambiante ou pendant 6 jours si elles sont conservées à 4 °C. La congélation permet de compléter les épreuves chimiques et microbiologiques avant l'utilisation, au besoin.

Mots clés : ticarcilline disodique, solutions ophtalmiques, stabilité, entreposage, chromatographie liquide à haute performance

INTRODUCTION

Ticarcillin is a semisynthetic penicillin with an extended spectrum of activity, used for the treatment of severe infections with gram-negative organisms. Because of its broad spectrum of activity against 70% to 80% of *Pseudomonas aeruginosa* strains and 60% to 90% of strains of *Proteus* species, it is administered locally for bacterial keratitis. *Pseudomonas* remains the most common genus of bacteria isolated in severe bacterial keratitis.[1] Ophthalmic solutions can deliver high concentrations of drug to the infected site. Hence, fortified antibiotic eye drop solutions (also called strengthened ophthalmic solutions), which contain high antibiotic concentrations, are prepared by hospital pharmacies when suitable sterile ophthalmic solutions are not available from a licensed manufacturer.[2] This is the situation for fortified ticarcillin ophthalmic solutions.

Several factors must be considered in preparing ophthalmic solutions. For instance, osmolarity and pH must be similar to those of tears, as these attributes of the solution affect local tolerance. Osmolarity should correspond to that of a 0.8% to 1.4% solution of sodium chloride (270 to 480 mOsm/L), and pH should be between 6.4 and 9.6 to avoid irritation. The ophthalmic solution should also be sterile.[3] Furthermore, because keratitis is potentially blinding, treatment is generally urgent. Hence, it was important to know if an ophthalmic solution could be prepared in advance and stored frozen so that it would be immediately available when required.

Several authors have reported the stability of ticarcillin solutions.[4-7] However, their results cannot be directly applied to the ophthalmic solution used in the authors' institution, because the concentrations of ticarcillin differed (60 mg/mL for Holmes and others,[4] 20 mg/mL for Das Gupta and Stewart,[5], 30 mg/mL for Zhang and Trissel,[6] and 25 mg/mL for Young and others,[7] as opposed to 5 mg/mL in the authors' institution). Furthermore, different containers (ethylene vinyl acetate or polyvinyl chloride [PVC], rather than glass) and different solutions for dilution (peritoneal dialysate in some instances, rather than 0.9% sodium chloride) were used in those studies.

The aim of this study was to define appropriate storage conditions and shelf life for 5 mg/mL ticarcillin ophthalmic solution prepared in 0.9% sodium chloride and stored in glass bottles with PVC caps, with or without prior freezing.

METHODS

Preparation of Ticarcillin Ophthalmic Solution

The ticarcillin ophthalmic solution was prepared aseptically in a vertical laminar air flow hood. Three 1-g bottles of commercially available ticarcillin disodium sterile lyophilized powder (SmithKline Beecham, Nanterre, France) were each reconstituted with 20 mL of sterile water for injection (Laboratoire Renaudin, Itxassou, France) and swirled to mix. Each 50 mg/mL solution was diluted 1:10 in 0.9% sodium chloride solution for injection (Laboratoire Renaudin, Itxassou, France) to obtain a final concentration of 5 mg/mL. The diluant (0.9% sodium chloride) was chosen to obtain pH and osmolarity compatible with ophthalmic administration (6.4 to 9.6 and 270 to 480 mOsm/L, respectively). The solution was filtered through a 0.22-µm Minisart filter (Sartorius, Goettingen, Germany) into 10-mL sterile glass bottles. Bottles were sealed with PVC caps by means of a separate sterile silicon dropper, to avoid contamination. No buffers or preservatives were added.

Storage Conditions for Stability Study

Forty-two bottles of the 5 mg/mL ticarcillin solution were prepared. Half of the bottles were designated for storage without prior freezing. Seven of these bottles were stored at room temperature (25°C) without protection from light, 7 bottles were stored at room temperature with protection from light, and 7 bottles were stored at 4°C. Three of the bottles stored under each set of conditions were used to measure pH and osmolarity on day 0 (immediately after preparation) and after 15 days of storage. Three other bottles stored under each set of conditions were sampled immediately after preparation and daily for up to 15 days, and the ticarcillin concentration in each was determined by high-performance liquid chromatography (HPLC; see below). The seventh bottle stored under each set of conditions was used for sterility testing and was sampled on day 0 (immediately after preparation) and after 15 days of storage.

The other 21 bottles of solution were stored at –20°C for 9 weeks. After removal from the freezer, 7 of these bottles were stored for 15 days at room temperature (25°C) without protection from light, 7 bottles were stored for 15 days at room temperature with protection from light, and 7 bottles were stored at 4°C. The 7 bottles stored under each set of conditions were used for measurement of pH and osmolarity, determination of ticarcillin concentration, and sterility testing as described above for unfrozen samples.

All of the samples were analyzed (for pH, osmolarity, and sterility) immediately after sampling. To reproduce conditions of clinical use, each bottle was opened twice daily during the 15-day storage period.

Preparation of Controls and Standards for HPLC Analysis

For preparation of standards, two 1-g bottles of sterile ticarcillin powder (SmithKline Beecham, Nanterre, France) were each dissolved in 20 mL of sterile water (Versol, Laboratoire Aguettant, Lyon, France). The first

solution corresponded to a 50 mg/mL stock solution. The second solution was further diluted in sterile water to obtain 3 control solutions (25, 125, and 250 µg/mL). All solutions were divided into 100-µL aliquots, which were frozen at –20°C. The concentration of ticarcillin in the frozen samples was compared (after thawing) with that of fresh solutions; the stability of the samples subjected to freezing was confirmed. Standards (0, 25, 50, 100, 125, 200, and 250 µg/mL) were prepared daily by dilution in sterile water of one of the stock samples, thawed extemporaneously. Standards and controls were analyzed on each study day.

Analysis of Ticarcillin Concentration

Ophthalmic solutions and standards were diluted in sterile water (Versol, Laboratoire Aguettant, Lyon, France). Ticarcillin concentration was measured by HPLC. The mobile phase consisted of a 10/90 (v/v) mixture of methanol (RP Normapur, Merck Eurolab, Fontenay sous Bois, France) and 0.01N ammonium acetate buffer (pH 6.7), prepared with ammonium acetate (Merck Eurolab, Fontenay sous Bois, France) and sterile water (Versol, Laboratoire Aguettant, Lyon, France), both of analytical grade. The flow rate of the mobile phase was set at 0.5 mL/min. A single 20-µL portion of each sample was injected by an automated sample injector (Waters 717, Millipore Corporation, Milford, Massachusetts) into an octadecylsilane column (LiChrospher 100 RP-18 carrier, 5-µm LiChroCART cartridge, 125 x 4 mm internal diameter, Merck, Darmstadt, Germany). Absorbance of the column effluent was monitored with an ultraviolet-visible absorbance detector (SpectraSYSTEM, Spectra-Physics Analytical Inc, Riviera Beach, Florida) at 240 nm. Chromatograms were analyzed using a chromatographic integrator (C-RS5A Shimadzu, Touzart et Matignon, Kyoto, Japan).

The stability study was conducted according to accepted standards.[8] The stability-indicating nature of the chromatographic method was tested by ensuring separation of the ticarcillin from degradation products. Degradation compounds were produced by dilution of the ophthalmic solution with 5N sodium hydroxide and application of heat (90°C for 15 minutes). The lack of analytical interference between sodium chloride solution and ticarcillin was also checked.

A calibration curve, based on the peak area ratio, was constructed covering a concentration range from 0 to 250 µg/mL. The precision of the method (intraday and interday variability) was tested by analysis (on one day) of 10 samples at 25 µg/mL and 10 samples at 220 µg/mL, as well as concentrations of 25, 50, 100, 125, 200, and 250 µg/mL tested daily over 6 days. To test accuracy, the mean deviation between nominal and observed concentrations (for 125 µg/mL samples) was calculated on 4 replicate samples.

Osmolarity, pH, and Visual Examination

Osmolarity was determined by an osmometer (model 3D3, Advanced Instruments, Inc, Norwood, Massachusetts). Quality controls (240 and 480 mOsm/L) were analyzed before each series of measurements. pH was measured with a digital pH meter (MP 230, Metler Toledo, Viroflay, France), calibrated with buffer solutions at pH 4 and 7 (Hanna Instrument calibrator solutions, Szeged, Hungary), at 25°C.

The ophthalmic solutions were visually inspected against a black background and a white background, with the naked eye, and compared with water to detect potential precipitates, crystals or colour changes.

Determination of osmolarity and pH and visual examination were performed on the day of preparation (before freezing, for samples that were frozen), and at the end of the study (day 15).

Sterility Testing

Sterility testing was performed according to European Pharmacopeia requirements.[9] Five millilitres of ophthalmic solution was diluted with 0.1% sterile peptone water to obtain 100 mL of solution. This solution was filtered through a cellulose membrane with 0.45-µm pore size (Millipore, Saint Quentin Yvelines, France). The membrane was rinsed 3 times with the sterile peptone water (200 mL) to eliminate the ticarcillin. This method was previously validated in the authors' laboratory using strains of *Staphylococcus aureus* and *Candida albicans*, according to European Pharmacopeia recommendations.

The membrane was aseptically cut into 2 pieces; each piece was incubated (at 20°C or 35°C) to test moisture and bacteriological growth (Sabourau glucose agar, AES Laboratoire, Combourg, France; Trypticas soy medium, Biomerieux, Craponne, France). Culture media were incubated and examined each day for 15 days.

Data Analysis and Statistical Calculations

The concentration of ticarcillin on day 0 (immediately after preparation [before freezing for samples stored at –20°C]) was taken as the reference value. Concentrations of ticarcillin measured in each sample were averaged (n = 3) for each study day and are expressed as percentages of the initial concentration obtained on day 0. Linear regression was used to estimate the relation between percent remaining and days of storage. The lower limit of this line, based on a 95% confidence interval (CI), was also determined. Ticarcillin concentrations on any day of analysis were considered acceptable or within acceptable limits if the concentration was greater than 90% of the initial (day 0) concentration and if the lower limit of the 95% CI exceeded 90%.

RESULTS

The analytical method was specific. No compound in the 0.9% sodium chloride or breakdown product eluted with retention times close to the ticarcillin peaks (Fig. 1). Degradation products eluted between 2 and 4.5 min, whereas 2 peaks corresponding to ticarcillin isomers eluted much later (retention times: 7.1 min and 8.5 min). The 2 ticarcillin peaks were integrated and their areas added. Peak shape was symmetric.

The method was linear over the range 0 to 250 µg/mL ($r^2 > 0.998$, $n = 4$). Intraday and interday variations were less than 1% and 3%, respectively, except for the 25 µg/mL solution (interday variation 5.7%). Mean deviations between the nominal and observed concentrations were below 2%.

Table 1 shows the percent of the initial ticarcillin concentration remaining in ophthalmic solutions that were prepared and then stored at 4°C and at room temperature (with or without protection from light). At least 90% of the initial concentration remained after 4 days at room temperature and 11 days at 4°C. However, application of confidence intervals indicated that the 90% limit can only be assured with 95% confidence if storage is limited to 3 days at room temperature or 7 days at 4°C. At room temperature, light had no influence on ticarcillin stability.

Table 2 shows the percent of the initial ticarcillin concentration remaining in ophthalmic solutions that were prepared and then stored frozen at –20°C for 9 weeks before thawing and storage at 4°C or at room temperature (with or without protection from light). At least 90% of the initial concentration remained after 4 days of storage at room temperature and 8 days of storage at 4°C. However, application of confidence intervals indicated that the 90% limit can only be assured with 95% confidence if storage is limited to 3 days at room temperature or 6 days at 4°C. These expiration periods are nearly identical with those for solutions that were never frozen.

No growth was observed in any solution. The pH remained stable during the 15-day study period. The mean pH was 6.9 for solutions that were frozen for 9 weeks before the 15-day study period and 6.8 for solutions that were never frozen. The osmolarity did not change over the study period. The average osmolarity was 350 mOsm/L for solutions that were frozen for 9 weeks before the 15-day study period and 340 mOsm/L for solutions that were never frozen. All solutions remained clear and colourless during the study period.

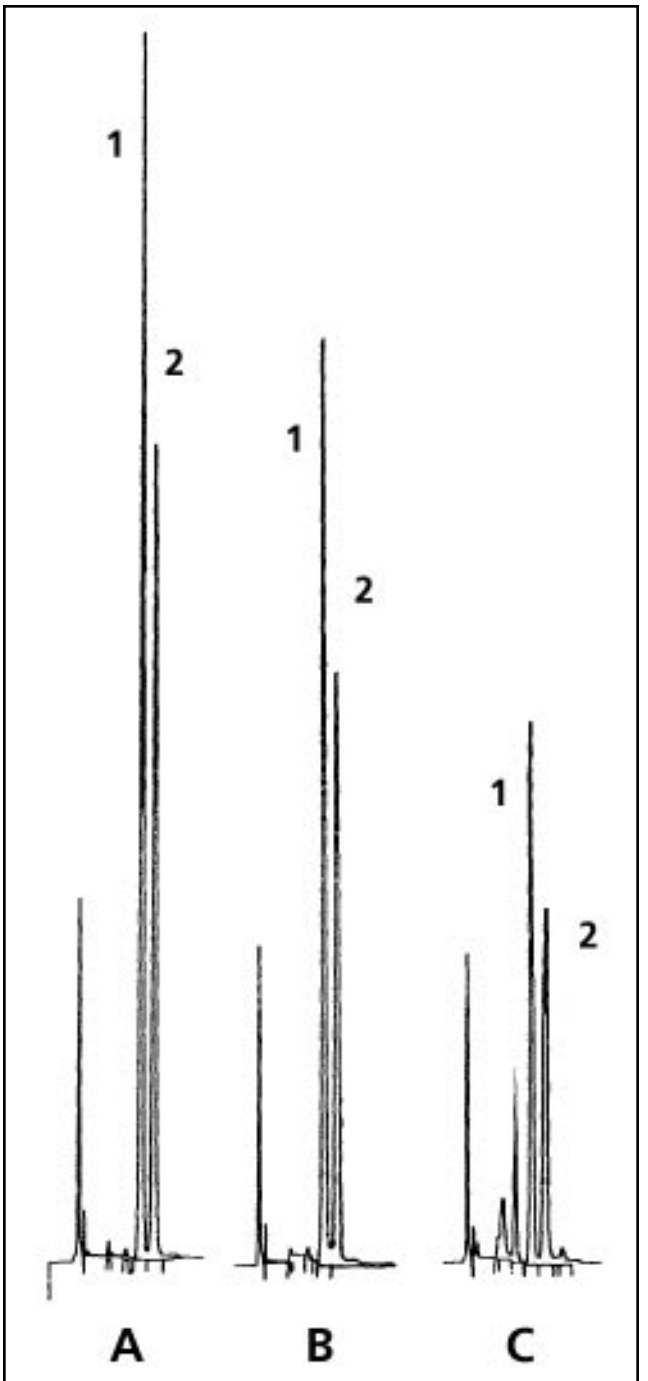

Figure 1. Typical chromatograms observed during the study. The peaks identified as 1 and 2 represent each of the ticarcillin isomers, which eluted at 7.1 and 8.5 min respectively. A: Ticarcillin disodium standard (5 mg/mL). B: Sample stored for 4 days at room temperature. The ticarcillin concentration was determined to be 44.5 µg/mL. C: Ticarcillin standard diluted with 5N sodium hydroxide and heated at 90°C for 15 min. Peaks of compounds presumed to be degradation products eluted between 2 and 4.5 min.

DISCUSSION

The authors have validated an analytical method to quantify ticarcillin in aqueous solution. This method was applied to study the stability of 5 mg/mL ticarcillin ophthalmic solutions. The osmolarity, pH, and sterility of solutions remained unchanged over the study period.

Table 1. Percentage of Initial Ticarcillin Concentration Remaining in Solutions Stored Without Freezing

Study Day	Storage Conditions; % of Initial Concentration Remaining*					
	Room Temperature, Protection from Light		Room Temperature, Exposure to Light		4°C	
0	100 ± 3.1	[4.9 mg/mL]†	100 ± 2.4	[5.2 mg/mL]†	100 ± 2.3	[5.2 mg/mL]†
1	96.7 ± 2.0	(96.8)	100.5 ± 1.2	(97.3)	100.4 ± 2.5	
2	95.6 ± 5.1	(90.8)	96.7 ± 3.2	(92.3)	101.7 ± 3.2	
3	95.6 ± 2.8	(90.9)	95.5 ± 5.3	(90.1)	96.6 ± 5.3	
4	90.6 ± 3.9	(87.2)	91.2 ± 2.6	(87.4)	96.2 ± 2.1	
5	88.6 ± 3.2	(85.4)	86.9 ± 2.4	(84.9)	93.5 ± 2.6	
6	90.7 ± 5.2	(80.6)	82.1 ± 8.2	(75.5)	96.9 ± 6.2	
7	90.1 ± 6.2		83.4 ± 5.6		96.9 ± 3.6	(90.0)
8	83.4 ± 3.8		80.2 ± 6.3		94.2 ± 3.5	(89.0)
9	75.7 ± 9.1		73.1 ± 5.2		93.2 ± 5.3	(85.8)
10	76.5 ± 10.5		73.7 ± 7.6		94.0 ± 6.2	(83.7)
11	73.5 ± 8.2		70.4 ± 10.1		92.7 ± 4.3	(84.7)
12	68.4 ± 6.4		64.6 ± 10.2		87.8 ± 3.2	
13	67.2 ± 8.3		62.9 ± 9.2		86.7 ± 10.2	
14	66.0 ± 7.5		61.0 ± 8.3		83.9 ± 8.3	
15	65.1 ± 10.0		68.1 ± 5.1		81.6 ± 3.2	

*Data are presented as the mean of 3 replicates ± standard deviation. The lower limit of the 95% confidence interval calculated from linear regression is shown in parentheses. Ticarcillin was diluted in 0.9% sodium chloride and stored in glass bottles at the specified temperature. The effect of protection from light was tested only for solutions stored at room temperature.
†Nominal initial concentration was 5 mg/mL. Actual concentration measured on day 0 (taken as 100%) is shown in square brackets.

Table 2. Percentage of Initial Ticarcillin Concentration Remaining in Solutions Frozen for 9 Weeks at –20°C

Study Day	Storage Conditions, % of initial concentration remaining*					
	Room Temperature, Protection from Light		Room Temperature, Exposure to Light		4°C	
0	100 ± 2.3	[5.1 mg/mL]†	100 ± 4.3	[4.8 mg/mL]†	100 ± 2.1	[4.8 mg/mL]†
Immediately after thawing	99.1 ± 5.2	(93.9)	98.3 ± 3.4	(97.0)	100.4 ± 1.5	
1	97.6 ± 2.3	(94.9)	101.3 ± 5.2	(92.4)	99.3 ± 5.3	
2	95.6 ± 5.2	(89.4)	96.8 ± 1.2	(94.4)	95.9 ± 2.1	
3	92.2 ± 1.2	(91.7)	95.6 ± 1.3	(91.7)	97.6 ± 2.1	
4	90.6 ± 1.6	(89.1)	91.2 ± 4.2	(85.9)	97.5 ± 2.0	(94.0)
5	86.5 ± 2.6	(85.7)	88.0 ± 2.3	(85.5)	97.3 ± 2.3	(92.2)
6	88.7 ± 5.3	(80.4)	82.0 ± 2.5		96.9 ± 2.6	(90.5)
7	85.2 ± 2.5		81.9 ± 2.2		96.5 ± 2.5	(89.2)
8	80.3 ± 8.2		80.0 ± 6.5		92.3 ± 2.4	(87.9)
9	83.4 ± 4.6		80.3 ± 4.3		87.5 ± 5.4	
10	75.7 ± 7.5		73.1 ± 5.6		87.5 ± 2.4	
11	76.5 ± 5.8		73.7 ± 8.3		86.3 ± 4.5	
12	74.2 ± 8.2		70.4 ± 8.3)		85.7 ± 4.5	
13	72.0 ± 8.3		66.5 ± 3.2		82.8 ± 2.6	
14	67.9 ± 8.2		65.5 ± 5.6		82.0 ± 6.5	
15	64.0 ± 3.4		63.7 ± 3.2		77.4 ± 4.7	

*Data are presented as the mean of 3 replicates ± standard deviation. The lower limit of the 95% confidence interval calculated from linear regression is shown in parentheses. Ticarcillin was diluted in 0.9% sodium chloride and stored in glass bottles at the specified temperature. The effect of protection from light was tested only for solutions stored at room temperature.
†Nominal initial concentration was 5 mg/mL. Actual concentration measured on day 0 (taken as 100%) is shown in square brackets.

With 95% confidence, the concentration of ticarcillin in solutions retained more than 90% of their initial concentration for 3 days when stored at room temperature or for 6 days when stored at 4°C. Prior freezing for 9 weeks at –20°C and protection from light for solutions stored at room temperature had a mild effect on the expiration period.

Stability studies of ticarcillin solutions have previously been reported.[4-7,10-13] However, the results cannot be directly applied to the ophthalmic solution used in the authors' institution, as the concentrations of ticarcillin were higher, the containers were different, and the solutions used for dilution were different. Most previous authors[4,7,10,11] studied stability only over 24 h, as this period corresponds to conditions of normal use for IV solutions. All of those studies showed that ticarcillin is stable for at least 24 h, in concentrations ranging from 25 to 250 mg/mL.[4,7,10] Kamen and others[12] reported that ticarcillin is stable for 6 h when diluted in total parenteral solution. Anthony and Rubin[13] reported that a 0.5 mg/mL ticarcillin solution in sterile water (combined with heparin) retained its bioactivity at room temperature for up to 10 days. However, they used a bioassay to test stability, no analytical test results were reported, and the specificity of the method is unknown.

Zhang and Trissel[6] have reported the longest period of stability: 3 days of storage at room temperature for a 30-mg/mL solution diluted in 0.9% sodium chloride. Zhang and Trissel[6] also reported that ticarcillin solutions can be stored at 4°C for 21 days. Although their room temperature results are very similar to those reported here, Zhang and others[6] reported considerably less degradation at 4°C. Concentration-dependent stability may be the explanation.

Previous studies have shown that the stability of fortified vancomycin ophthalmic solutions was reduced by repeated opening of the bottles.[14] In this study the bottles were opened twice daily to simulate as closely as possible the conditions of practice after dispensing. Fortified ophthalmic solutions are administered in emergencies, and the dosage prescribed does not change from one patient to another or over the treatment course. Hence, solutions can be made up in advance in the pharmacy and stored frozen without affecting the expiry date. After thawing, these solutions can be used over 3 days if stored at room temperature or 6 days if stored at 4°C. Freezing also allows chemical and microbiological testing to be completed before use, if necessary.

The authors conclude, with 95% confidence, that ticarcillin diluted in 0.9% sodium chloride retains more than 90% of the initial concentration for 3 days if stored at room temperature or for 7 days if stored at 4°C. Prior freezing for 9 weeks at –20°C and protection from light for solutions stored at room temperature had no effect on the expiration period at room temperature.

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