

# Stability of Ceftrizoxime in 5 Percent Dextrose and 0.9 Percent Sodium Chloride

David C. Knoppert, David Freeman and Diane Webb

## ABSTRACT

The chemical stability of ceftizoxime, 1g/50mL minibag, was examined under room temperature, refrigerated and frozen conditions. Solutions of ceftizoxime were prepared in 0.9% NaCl (NS) and 5% Dextrose (D5W) and concentrations were determined for up to 90 days by high performance liquid chromatography. Ceftizoxime solutions (in either NS or D5W) of 1g/50mL minibag retained greater than 90% of their original concentration for 30 days when stored in the refrigerator. When solutions were stored at room temperature, more than 90% of the initial concentration remained for up to 4 days. When frozen, these solutions retained greater than 90% of their original concentration for up to 90 days. Subsequent thawed solutions retained chemical stability for 30 days when kept in the refrigerator.

**Key Words:** ceftizoxime, stability, IV admixture  
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## RÉSUMÉ

On a évalué la stabilité chimique des solutions de ceftizoxime (1 g/50 mL en mini-sac) à la température ambiante, au réfrigérateur et au congélateur. Pour cela, on a déterminé la concentration de solutions de ceftizoxime dans du NaCl à 0,9 % (NS) et du dextrose à 5 % (D5W) par chromatographie en phase liquide à haute résolution pendant une période allant jusqu'à 90 jours. Entreposés au réfrigérateur, les solutions de ceftizoxime (1 g/50 mL, en mini-sac, dans le NS ou le D5W) retiennent plus de 90 % de leur concentration initiale pendant 30 jours. À température ambiante, ces solutions conservent 90 % de leur concentration initiale jusqu'à 4 jours. Congelées, elles retiennent plus de 90 % de leur concentration initiale jusqu'à 90 jours. Après décongélation, elles peuvent conserver leur stabilité chimique pour 30 jours lorsqu'on les place au réfrigérateur.  
**Mots clés:** ceftizoxime, mélange de solutions intraveineuses, stabilité

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## INTRODUCTION

Ceftizoxime is a third generation cephalosporin which possesses activity against gram negative and anaerobic bacteria. The chemical stability of ceftizoxime, especially in minibags, is important for hospital pharmacies which provide an IV admixture service and minibags for dispensing at a later time.

There are at least four reports of ceftizoxime stability in the literature.<sup>1,2,3,4</sup> At room temperature ceftizoxime is reported to be stable in 5% Dextrose (D5W) or 0.9% NaCl (NS) for 24 to 48 h. Under refrigerated conditions (5°C) ceftizoxime is reported to be stable in NS for two to seven days (five

days for D5W). When frozen at -10°C, ceftizoxime is reported to be stable for 27 days in D5W and 90 days in NS. When frozen mixtures of ceftizoxime are thawed at room temperature, the drug is reported to be stable in D5W or NS for 24 h at room temperature or ten days under refrigeration.

The objective of this study was to examine the stability of 1 g of ceftizoxime added to a 50 mL minibag over 90 days in both D5W or NS under storage conditions of room temperature (22°C) refrigeration (5°C) and freezing (-20°C). We also examined the effect of microwaving on the stability of frozen solutions.

## METHODS

### Preparation of IV Bags

Under aseptic conditions, ceftizoxime (Cefizox, (L) 16890, SmithKline Beecham, Oakville, Ontario) 2 g vials were reconstituted with 20 mL sterile water for injection ((L)40-432-NA, Abbott Laboratories, Montreal, Quebec) on day 0. One gram of ceftizoxime was added to each 50 mL minibag of D5W ((L)41-587-NA, Abbott Laboratories) or NS ((L)40-388-NA, Abbott Laboratories). The bags were shaken, labelled and the concentration of ceftizoxime was determined in each bag on day 0. After analysis on day 0 the minibags were left at room temperature

(22°C, in the dark), refrigerated (5°C) or frozen (-20°C).

Bags of ceftizoxime stored frozen were thawed using a microwave oven (Frigidaire, model #FM892-1, 120V, 60HZ, 1300W) or allowed to stand at room temperature until thawed. Five frozen bags were placed in the microwave; the bags were rotated and turned over every two to three minutes. The microwave setting was "Auto Defrost"; the setting was 0.5. The samples were removed individually from the microwave as soon as all of the ice had thawed; the bags were not allowed to become warm in the microwave. The average length of time required for the frozen samples to thaw in the microwave was approximately ten minutes. Once thawed the solution was assayed for ceftizoxime by HPLC. Ceftizoxime bags (previously frozen for 90 days) were kept under refrigeration and were also assayed four, 14 and 30 days after thawing.

### Chromatography

All ceftizoxime concentrations were determined by high performance liquid chromatography (HPLC) using a Hewlett Packard 1090 HPLC system with a Hewlett Packard 3393A Integrator and a UV photometric detector set at 254 nm. The column, 10 cm x 3.2 mm I.D., packed with Spherisorb (C8, 5 µm Phase Sep; Deeside Ind. Est., UK) was maintained at 40°C. The mobile phase was a mixture of 12% methanol (BDH, Toronto, Ontario), 88% sodium dihydrogen phosphate buffer (5 mM) and 0.25% dibutylamine (DBA) adjusted to a final pH of 5.0 with orthophosphoric acid. The flow rate was maintained at 0.5 mL/min.

### Sample Preparation

Aliquots of ceftizoxime solution were withdrawn from the IV bags and diluted 1:200 with Milli-Q

water (Millipore, Toronto, Ontario). One hundred µL of diluted sample was then mixed with 100 µL of internal standard (enprophylline, 100 µg/mL) and 10 µL injected onto the column using an autoinjector (Hewlett Packard 1090).

Ceftizoxime standards were prepared in methanol: water (1:1). A standard curve was prepared and the standards were then frozen at -20°C. These samples were thawed at room temperature, diluted and assayed daily along with the samples from the minibags.

A minibag of ceftizoxime in NS

was left at room temperature in the dark for 90 days. The solution was analyzed chromatographically for breakdown products and potential interference with ceftizoxime and internal standard.

### Data Analysis

The reported ceftizoxime concentrations (expressed as a percentage of the concentration on day 0) represent the mean (± standard deviation) determinations of five separate minibags.

Ceftizoxime concentrations were considered within acceptable limits if the measured concentration was

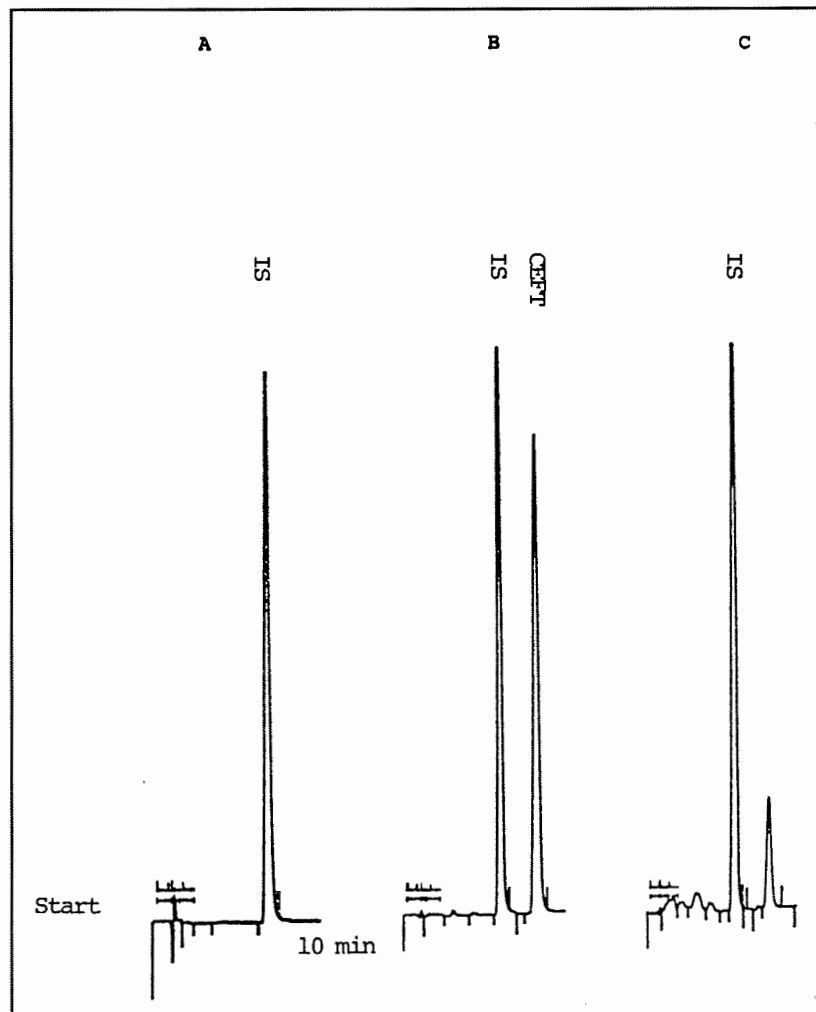


Figure 1. Chromatograms of (A) Internal Standard alone, (B) freshly prepared ceftizoxime solution; and (C) ceftizoxime solution after 90 days in the dark at room temperature. IS indicates Internal Standard (enprophylline) and CEFT indicates ceftizoxime.

**Table I.** Mean<sup>a</sup> Ceftriaxone concentration expressed as a percentage of the concentration on day zero

Day	RT (22°C)		Refrigeration (5°C)		Freezing			
					Microwave Thaw		RT Thaw	
	NS	D5W	NS	D5W	NS	D5W	NS	D5W
0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0
1	100.9±5.6	104.7±5.0	103.5±2.7	106.6±4.5	101.9±4.2	104.4±3.6	89.6±5.7	89.2±3.9
2	95.9±3.6	100.2±7.5	94.0±4.4	99.6±5.4	95.6±4.1	91.3±7.0	107.0±4.1	101.0±2.7
3	94.0±3.7	100.4±4.4	99.5±2.0	104.5±3.4	101.6±4.9	100.9±3.9	101.8±10.4	100.7±4.8
4	91.8±3.2	95.1±4.1	100.3±2.9	104.3±4.2	104.1±1.6	99.2±4.6	96.2±5.3	100.4±2.9
7	89.8±4.1	94.3±4.4	98.7±3.0	103.7±4.7	101.3±2.4	97.8±6.4	102.9±3.3	106.4±2.5
14	65.6±4.7	70.6±4.3	97.8±5.5	101.0±4.0	102.5±5.1	98.7±7.3	101.8±5.9	101.2±7.1
21			98.5±6.5	102.0±0.9				
30	44.9±4.0	39.8±1.7	90.7±4.6	91.8±3.8	97.4±6.2	92.1±6.5	96.1±4.2	93.0±5.6
60	23.9±1.6	20.7±1.0	80.6±3.2	80.8±4.9	96.0±1.7	93.2±3.0	101.5±6.4	100.4±4.0
90	13.7±0.5	9.9±0.7	84.9±0.9	85.0±5.8	103.1±2.7	102.3±2.2	101.7±7.0	100.2±7.0
T90 (days) <sup>c</sup>	4.6	3.9	45.0	37.6	90 <sup>b</sup>	90 <sup>b</sup>	90 <sup>b</sup>	90 <sup>b</sup>

<sup>a</sup> Mean of 5 determinations each day except for microwave thaw, in which only 4 replicates on day 2 and 4.

<sup>b</sup> An accurate estimate can not be made of the time to achieve 10% loss, since more than 90% of the initial concentration remained on day 90.

<sup>c</sup> Time to reach 90% of initial concentration.

not less than 90% of the concentration determined on day 0.

**RESULTS**

**Chromatography**

A chromatogram showing the peaks produced by the internal standard alone, a freshly prepared ceftriaxone solution and a ceftriaxone solution which had been left at room temperature for 90 days is shown in Figure 1. There is no evidence of interference by degradation products with ceftriaxone or the internal standard, enprofylline. The inter-assay coefficient of variation of control samples was 4.7%.

**Room Temperature**

The concentration of ceftriaxone remained greater than 90% of the day 0 concentration for seven and four days, in D5W and NS, respectively. (Table I) The decay curves were first order and were similar for both NS and D5W, resulting in approximately 10% loss by day four (Table I).

**Refrigerator**

The concentration of ceftriaxone remained greater than 90% of the day 0 concentration for 30 days in both D5W and NS. (Table I) First order degradation rates also

**Table II.** Ceftriaxone concentrations expressed as a percentage of the concentration on day 0. Conditions, frozen (-20°C) until day 90, then thawed, and stored in the refrigerator (5°C)

	Assay Day (after thaw)		
	4	14	30
<b>5% Dextrose</b>			
Microwave Thaw			
Mean*	102.2	92.1	95.4
S.D.	3.5	2.1	2.3
Room Temp. Thaw			
Mean*	99.2	94.7	89.7
S.D.	7.7	6.1	5.1
<b>0.9% NaCl</b>			
Microwave Thaw			
Mean*	101.3	94.1	102.3
S.D.	4.7	4.3	8.9
Room Temp. Thaw			
Mean*	104.0	96.4	96.8
S.D.	3.9	5.9	6.6

\* Mean of 5 determinations each day.

indicated that 90% of the initial concentration will be retained for 30 days.

**Frozen**

Ceftriaxone concentrations were essentially unchanged over a 90 day period when frozen in D5W or NS. (Table I) There is no apparent difference whether the frozen solution of ceftriaxone was thawed at room temperature or in

a microwave oven. When the frozen solution of ceftriaxone was thawed at day 90 (either at room temperature or by microwave) and then refrigerated, the concentration remained greater than 90% of the day 0 concentration after an additional 30 days storage. (Table II) (Under room temperature thaw conditions, the ceftriaxone concentration at day 30 in D5W was 89.7 ± 5.1%).

## DISCUSSION

This study was designed to examine the chemical stability of ceftizoxime solutions at room temperature (22°C), and under refrigerated (5°C) and frozen (-20°C) conditions as a function of time. No attempt was made to determine biological activity in any of these samples. Therefore, no correlation can be made between the degree of chemical degradation and loss of antibacterial activity.

A solution of ceftizoxime was kept at room temperature in the dark for 90 days. Approximately 10 to 14% of the parent compound remained after this time. Ceftizoxime breakdown products were shown not to interfere with the parent compound, ceftizoxime, or the internal standard, enpropyl-line, using the chromatographic conditions described.

Under the conditions of this study, solutions of ceftizoxime stored at 22°C have been shown to retain greater than 90% of their initial concentration for approximately 4 days. This extends the 24 to 48 h time period which had been previously reported.<sup>1,2</sup> The sterility of these solutions was not examined. Even though we have demonstrated a longer stability period for ceftizoxime solutions which are kept at room temperature, standard practice is to store all admixed solutions in the refrigerator.

Under refrigerator conditions, ceftizoxime has been shown to retain greater than 90% of the initial concentration for 30 days in both D5W and NS. This extends the previously reported stability of five days in D5W and seven days in NS.<sup>1,2</sup>

Ceftizoxime can be kept frozen for up to 90 days with essentially no change in concentration. The reason for the difference between our results and the 27 day expiration recommended by Lesko et al<sup>2</sup> is unclear. Our data indicate that it is likely that ceftizoxime stability (under frozen conditions of storage) extends beyond the 90 day period of this study.

Microwaves have no apparent effect on ceftizoxime stability. It would be useful to determine if the antimicrobial activity of ceftizoxime was affected by microwaves.

After frozen solutions of ceftizoxime are thawed, they retain greater than 90% of the day 0 concentration for 30 days. It does not matter whether the frozen solutions are thawed at room temperature or are microwaved. The ceftizoxime concentration in the D5W minibag which was thawed at room temperature was just below 90% at 30 days. We know of no reason for this apparent discrepancy.

The stability of ceftizoxime at room temperature, after it was

thawed, was not determined in the present study. However, because of the standard practice of storing admixtures in the refrigerator, stability data beyond 24 h<sup>1</sup> may not be necessary from a practical point of view. We did not examine situations where the minibag is frequently in and out of the refrigerator.

We conclude that ceftizoxime, 1 g/50 mL minibag, in either NS or D5W, retains greater than 90% of the original concentration following refrigeration of freshly prepared solutions for up to 30 days. The concentration of solutions, in either NS or D5W, remain essentially unchanged over 90 days when frozen. Frozen solutions which are thawed (either by microwave or at room temperature) retain greater than 90% of their original concentration for up to 30 days when stored in a refrigerator.

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