Chemical stability of diphenhydramine hydrochloride in minibags and polypropylene syringes

Ronald F. Donnelly

ABSTRACT

Solutions of diphenhydramine hydrochloride (12.5, 25, and 50 mg/50 mL) were prepared, in duplicate, in minibags containing dextrose 5% in water (DSW) or 0.9% sodium chloride (NS) and stored at either 22°C or 4°C, protected from light, for 91 days. Samples were taken from each minibag on days 0, 1, 3, 7, 14, 30, 59, and 91 and frozen at -72°C. Solutions of diphenhydramine hydrochloride (12.5, 25, and 50 mg/10 mL) were prepared in NS and packaged in polypropylene syringes, in triplicate, and sealed with friction caps. The syringes were stored at either 22°C or 4°C, protected from light, for 28 days. Samples were collected from each syringe on days 0, 1, 3, 7, 14, 22, and 28 and frozen at -72°C. All samples were analyzed in duplicate with a stability-indicating high-pressure liquid chromatography assay.

All chemical stability samples remained colourless and free of precipitate throughout the course of the study. The concentration of all diphenhydramine solutions was greater than 90% of the initial concentration over the entire study period for all diluents and storage temperatures studied. Diphenhydramine hydrochloride solutions diluted to concentrations of 12.5, 25, and 50 mg/50 mL with DSW or NS were considered chemically stable for at least 91 days when stored at either 22°C or 4°C and protected from light. Solutions of diphenhydramine diluted to 12.5, 25, and 50 mg/10 mL with NS, packaged in polypropylene syringes, and sealed with friction caps were considered stable for at least 28 days when stored at either 22°C or 4°C and protected from light.

Key Words: diphenhydramine, stability, dextrose, normal saline, high-pressure liquid chromatography

RÉSUMÉ

Des solutions de chlorhydrate de diphenhydramine (12,5, 25, et 50 mg/50 mL) ont été préparées, en deux exemplaires, dans des minisacs contenant du dextrose à 5 % dans l’eau (DSW) ou du chlorure de sodium à 0,9 % (NS), puis entreposées à des températures de 22°C ou de 4°C, à l’abri de la lumière, et ce pendant 91 jours. Des échantillons ont été prélevés de chaque minisac aux jours 0, 1, 3, 7, 14, 30, 59, et 91 et congelés à une température de -72°C. Les solutions de chlorhydrate de diphenhydramine (12.5, 25, et 50 mg/16 mL) ont été préparées dans le NS et conditionnées dans des seringues de polypropylène, en trois exemplaires, puis scellées avec des capuchons à friction. Les seringues ont été entreposées à des températures de 22°C ou de 4°C, à l’abri de la lumière, et ce pendant 28 jours. Des échantillons ont été prélevés de chaque seringue aux jours 0, 1, 3, 7, 14, 22, et 28, puis congelées à une température de -72°C. Tous les échantillons ont été analysés en double à l’aide d’une épreuve de stabilité par chromatographie liquide à haute pression.

Tous les échantillons de stabilité chimique ont été conservés à 22°C ou 4°C pendant toute la durée de l’étude. La concentration de toutes les solutions de chlorhydrate de diphenhydramine était supérieure à 90 % des concentrations initiales pendant toute la durée de l’étude, et ce pour tous les diluants et à toutes les températures d’entreposage. Les solutions de chlorhydrate de diphenhydramine diluées à des concentrations de 12.5, 25, et 50 mg/50 mL avec du DSW ou du NS ont été considérées comme étant chimiquement stables pendant une période d’au moins 91 jours lorsqu’entreposées à des températures de 22°C ou de 4°C et protégées de la lumière. Les solutions de chlorhydrate de diphenhydramine diluées à 12,5, 25, et 50 mg/10 mL avec du NS ou du DSW ont été considérées comme étant chimiquement stables pendant au moins 28 jours lorsqu’entreposées à des températures de 22°C ou de 4°C et protégées de la lumière.

Mots clés : diphenhydramine, stabilité, dextrose, solution saline, chromatographie liquide à haute pression

Can J Hosp Pharm 1999;52:150–155
INTRODUCTION

The acute pain service at our institution uses diphenhydramine for the management of nausea and vomiting in the postoperative patient-controlled analgesia program. The oncology service also uses diphenhydramine routinely as an antiemetic medication for chemotherapy-induced nausea and vomiting. For the surgery floors, diphenhydramine is prepared in minibags at concentrations of 12.5, 25, and 50 mg/50 mL of 5% dextrose in water (D5W) or 0.9% sodium chloride (NS). For the oncology patients, prefilled diphenhydramine syringes are made up on an as-needed basis by dilution with NS to concentrations of 12.5, 25, and 50 mg/10 mL. All minibags and syringes are given an arbitrary 48-h expiry date by our Pharmacy Department. This short expiry date results in considerable wastage of both time and materials.

The instability of diphenhydramine hydrochloride is related to the cleavage of the ether linkage under acidic conditions. This ether linkage is quite stable to both alkaline and oxidative conditions. Oxidation of diphenhydramine is possible, the amine group being the most likely site of oxidation; the compound is probably converted to the N-oxide.

The literature was reviewed to determine whether the stability of diphenhydramine alone had been investigated. Although the stability of diphenhydramine in combination with other drugs has been evaluated, no studies have reported the chemical stability of this drug alone when diluted with D5W or NS and packaged in minibags or polypropylene syringes.

Because no published studies concerning the chemical stability of diphenhydramine were available, a stability study of diphenhydramine hydrochloride was undertaken. The study simulated current practice conditions and evaluated the stability of various concentrations of diphenhydramine hydrochloride when prepared in minibags or polypropylene syringes and stored, protected from light, at either 22°C or 4°C.

METHODS

Validation of the High-Pressure Liquid Chromatography Assay

The stability-indicating nature of the high-pressure liquid chromatography (HPLC) assay was confirmed by forcibly degrading diphenhydramine samples and then monitoring the chromatograms for any interfering peaks. A 125-mg aliquot of diphenhydramine hydrochloride USP (A&C American Chemical Ltd., Montreal, Que., lot X51692M16/64822/09A20) was added to each of two 50-mL volumetric flasks. Alkaline-catalyzed hydrolysis of diphenhydramine was attempted by adjusting the pH of one solution to approximately 12.0 with 1.0 N sodium hydroxide (BDH Inc., Toronto, Ont., lot 9304066). Acid-catalyzed hydrolysis was attempted by adjusting the pH of the other solution to approximately 1.0 with concentrated hydrochloric acid (BDH Inc., lot 109521/11031). Solutions were diluted to volume after addition of acid or base. Each solution was analyzed by HPLC after a further 1:10 dilution to determine if the peaks from any degradation products interfered with the diphenhydramine peak. Beginning at time 0, a total of 9 samples were removed from each solution and subjected to chromatography over an 80-h period. Both stock solutions were heated, to 80°C, on a hot plate (Fisher Scientific Ltd., Nepean, Ont., model 210T) to accelerate degradation after the initial (time 0) sample was drawn. The purity of the diphenhydramine peaks was determined by multichannel (230 and 254 nm) and ultraviolet (UV) spectral analysis (200 to 350 nm) with EZChrom software (Version 2.15). The UV spectra of diphenhydramine hydrochloride USP were overlaid on the UV spectra of the diphenhydramine peaks from the degraded samples and the peaks of the degradation products, and similarity indexes were determined. A similarity index of 1 indicated a perfect match, and an index of 0.990 or greater indicated that the 2 spectra were virtually identical and that the eluting peaks likely represented similar compounds and were not contaminated by a co-eluting, interfering substance.

The linearity of the response curve plotting peak area ratio as a function of concentration was assessed over the concentration range 0.1 to 2.0 mg/mL. The accuracy of the method was assessed on 6 separate days and expressed as percentage recovery. Within-day variation was also assessed by injecting 5 replicate samples of diphenhydramine (0.5 mg/mL) at time 0 and then 8 and 24 h later. Between-day variation was determined by comparing the slopes and $r^2$ values from standard curves and area ratios for the injections of diphenhydramine on the 6 different days. The sensitivity of the assay was determined by measuring the smallest concentration of drug capable of producing a detectable peak and maintaining the linearity of the concentration response curve.

HPLC Assay

The HPLC system consisted of an isocratic solvent delivery pump (Shimadzu Corp., Kyoto, Japan, model LC-10AS) and a photodiode array detector (Shimadzu...
Stability Study

Diphenhydramine hydrochloride (Parke Davis, Scarborough, Ont., 50 mg/mL, lot 5Y116, 5N135) was diluted with D5W (Abbott Laboratories, Montreal, Que., lot 01-632-NA) or preservative-free NS (Abbott Laboratories, lot 16-169-NA) to either 12.5, 25, or 50 mg/mL and stored at either 22°C or 4°C for 91 days. All solutions were prepared in duplicate and protected from light during storage.

Samples were collected from each of the bags immediately after preparation and on days 1, 3, 7, 14, 36, 59, and 91 thereafter. These samples were placed in 10-mL clear glass sterile vials, visually inspected for colour change and particulate matter, and then frozen at -72°C in a scientific freezer (Forma Scientific Inc., Ohio, model 8433).

Diphenhydramine hydrochloride was diluted with preservative-free NS to either 12.5, 25, or 50 mg/mL and packaged in polypropylene syringes (Becton-Dickinson and Company, Franklin Lakes, NJ), which were sealed with friction caps (Sherwood Medical, St. Louis, Mo.). Syringes were prepared in triplicate, stored at either 22°C or 4°C, and protected from light.

Samples were collected from each of the syringes immediately after preparation and on days 1, 3, 7, 14, 22, and 28 thereafter. These samples were placed in 5-mL clear glass sterile vials, visually inspected for colour change and particulate matter, and then frozen at -72°C in a scientific freezer.

On the day of the analysis the sample vials were allowed to thaw, internal standard was added, and the sample was further diluted with mobile phase. Each sample was then analyzed in duplicate. The diphenhydramine concentration in each sample was determined by interpolation, with linear regression, from a standard curve of the diphenhydramine peak area ratio as a function of concentration. The percentage remaining was calculated as the observed mean concentration on each study day divided by the initial concentration, as determined by linear regression, expressed as a percentage. Solutions were considered stable if they retained 90% or more of the initial concentration.

The pH of each solution was measured with a calibrated pH meter with a silver/silver chloride electrode (Fisher Scientific Ltd., model Accumet 25).

RESULTS

Validation of the HPLC Assay

Chromatography indicated that acid-catalyzed hydrolysis caused the most significant deterioration of the diphenhydramine (Figure 1, Panel 2); however, there was adequate separation of the degradation products from the diphenhydramine peak. The base-catalyzed hydrolysis sample (Figure 1, Panel 3) showed limited degradation, even after 80 h of heating. The purity of the diphenhydramine peaks was confirmed by multichannel and UV spectral analysis. These analyses indicated a similarity index for all diphenhydramine peaks of greater than 0.990. UV spectral comparison of the peaks for diphenhydramine and the degradation products showed lower similarity (similarity index < 0.820). All diphenhydramine peaks were compared with an authentic diphenhydramine standard by superimposition of UV spectra. These spectra were very similar (similarity index > 0.990). The combination of spectral analysis and retention times showed that degradation products were distinct from diphenhydramine. The retention times for diphenhydramine, the internal standard, and the primary degradation product were 3.4, 4.7, and 5.5 min, respectively (Figure 1).

The response curve of peak area ratio as a function of concentration was linear (r² = 0.9994) over the diphenhydramine concentration range of 0.1 to 2.0 mg/mL. The correlation coefficients of the 6 standard curves for diphenhydramine ranged from 0.9998 to 1.0000. The average recovery of diphenhydramine over the study period was 99.5%, with a coefficient of variation of 0.98%.

The coefficients of variation for within-day and between-day analysis were 2.78% and 1.77%, respectively, when peak area ratios of samples were compared. For between-day variation, the slopes and r² values of the 6 standard curves were also compared.
regression, the amine peak percentage solved mean was considered considered of the initial 
were measured with a chlorid chloride (Eullet 25).

acid-catalyzed teration of (2); however, degradation erior. The base­
showed heating. The tes analysis confirmed by xed that degra­
A comparison of the base­
were compared standard by that degra­
diphenhydramine. 
the internal standard product were 3.4, 
as a function of 0.1 to 2.0 standard to 0.9998 to diphenhydramine chlorid a coefficient 
within-day and 1.77%. 
amples were slopes and also compared.

Figure 1. Sample chromatograms of diphenhydramine hydrochloride.
Panel 1 represents a sample containing the internal standard, propyl hydroxybenzoate (peak B), and diphenhydramine hydrochloride, 25 mg/50 mL in dextrose 5% in water after storage at 4°C for 91 days (peak A). mA = milliabsorbance units.
Panel 2 represents diphenhydramine hydrochloride after exposure to acid. Peak C is a diphenhydramine degradation product.
Panel 3 represents diphenhydramine hydrochloride after exposure to alkali.

The coefficients of variation between slopes and \( r^2 \) values were 1.52% and 0.001%, respectively. The results of sensitivity testing indicated that the assay could detect at least 125 ng of diphenhydramine hydrochloride.

Stability Study

All of the diphenhydramine samples remained clear and free of precipitate over the course of the study. No significant changes were noted in the pH of the diphenhydramine solutions. The concentrations of diphenhydramine solutions prepared in minibags and diluted with either D5W or NS did not change over the course of the study (Table I), and no additional peaks were detected on chromatographs of samples produced by HPLC analysis. The maximum change in the mean observed concentration on any day never exceeded 5.6%, and the regression-determined percentage remaining on day 91 was always greater than 96%. Because these changes were less than 10%, they are not of practical importance. Solutions of diphenhydramine prepared in polypropylene syringes with friction caps underwent similar changes in mean concentration over the study period (Table II). The maximum change in the mean observed concentration on any day never exceeded 4.3%, and the regression-determined percentage remaining on day 28 was always greater than 97%. These differences are not of practical importance and are within assay error.

DISCUSSION

The freezing and thawing of diphenhydramine hydrochloride samples appeared to have no detrimental effect on the sample solutions, as indicated by the lack of new peaks. Vials of diphenhydramine frozen for up to 91 days did not appear to degrade (Figure 1, Panel 1). Multichannel and UV spectral analysis showed that all diphenhydramine peaks were pure.

The chromatograms produced for degradation samples of diphenhydramine showed that the assay allowed for separation between the peaks for diphenhydramine, the internal standard, and the degradation products. The solution exposed to acid degraded almost completely with no emergence of interfering peaks. The solution exposed to alkali showed limited degradation even after being heated for 80 h. Multichannel and UV spectral analysis indicated that all diphenhydramine peaks from the validation study were pure. The UV spectra of the degradation product had a low similarity index relative to diphenhydramine. However, the UV spectra of the diphenhydramine chromatographic peak
Table I. Summary Table for Diphenhydramine Hydrochloride Stability in Minibags

<table>
<thead>
<tr>
<th>Initial Conc’n (mg/50 mL)</th>
<th>Diluent</th>
<th>Storage Temp. (°C)</th>
<th>Day 1 (%)</th>
<th>Day 3 (%)</th>
<th>Day 7 (%)</th>
<th>Day 14 (%)</th>
<th>Day 30 (%)</th>
<th>Day 59 (%)</th>
<th>Day 91 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>12.5 ± 0.37</td>
<td>NS</td>
<td>22</td>
<td>97.2 ± 1.49</td>
<td>98.5 ± 1.71</td>
<td>99.0 ± 1.24</td>
<td>94.4 ± 0.55</td>
<td>98.4 ± 1.42</td>
<td>97.3 ± 0.65</td>
<td>98.0 ± 1.48</td>
</tr>
<tr>
<td>11.0 ± 0.24</td>
<td>NS</td>
<td>4</td>
<td>98.4 ± 1.65</td>
<td>97.6 ± 0.56</td>
<td>96.8 ± 0.62</td>
<td>97.6 ± 1.49</td>
<td>97.8 ± 0.68</td>
<td>97.1 ± 0.71</td>
<td>98.3 ± 0.86</td>
</tr>
<tr>
<td>10.7 ± 0.18</td>
<td>DSW</td>
<td>22</td>
<td>98.3 ± 1.03</td>
<td>97.6 ± 1.85</td>
<td>95.2 ± 1.44</td>
<td>98.3 ± 1.24</td>
<td>97.0 ± 0.98</td>
<td>97.1 ± 1.55</td>
<td>96.7 ± 0.76</td>
</tr>
<tr>
<td>10.4 ± 0.18</td>
<td>DSW</td>
<td>4</td>
<td>106.4 ± 0.76</td>
<td>100.4 ± 1.10</td>
<td>98.9 ± 1.50</td>
<td>100.6 ± 2.25</td>
<td>99.4 ± 0.78</td>
<td>99.7 ± 2.10</td>
<td>102.2 ± 0.17</td>
</tr>
<tr>
<td>20.3 ± 0.41</td>
<td>NS</td>
<td>22</td>
<td>100.9 ± 0.80</td>
<td>100.7 ± 1.23</td>
<td>99.8 ± 0.51</td>
<td>99.5 ± 0.65</td>
<td>100.3 ± 0.05</td>
<td>100.2 ± 1.09</td>
<td>102.7 ± 1.50</td>
</tr>
<tr>
<td>22.1 ± 0.20</td>
<td>NS</td>
<td>4</td>
<td>99.7 ± 1.23</td>
<td>98.6 ± 0.26</td>
<td>99.4 ± 1.00</td>
<td>99.3 ± 0.78</td>
<td>99.6 ± 1.72</td>
<td>100.8 ± 0.96</td>
<td>108.0 ± 1.15</td>
</tr>
<tr>
<td>22.5 ± 0.14</td>
<td>DSW</td>
<td>22</td>
<td>98.4 ± 0.79</td>
<td>99.2 ± 0.51</td>
<td>98.1 ± 0.03</td>
<td>99.4 ± 0.07</td>
<td>100.2 ± 0.69</td>
<td>100.9 ± 0.71</td>
<td>100.4 ± 0.18</td>
</tr>
<tr>
<td>19.3 ± 0.13</td>
<td>DSW</td>
<td>4</td>
<td>99.9 ± 1.11</td>
<td>99.6 ± 2.17</td>
<td>102.5 ± 2.33</td>
<td>100.8 ± 0.50</td>
<td>100.8 ± 0.49</td>
<td>100.7 ± 0.40</td>
<td>100.1 ± 0.95</td>
</tr>
<tr>
<td>42.6 ± 0.36</td>
<td>NS</td>
<td>22</td>
<td>99.3 ± 0.86</td>
<td>99.4 ± 1.44</td>
<td>99.3 ± 1.40</td>
<td>97.8 ± 1.44</td>
<td>99.4 ± 1.31</td>
<td>100.8 ± 1.12</td>
<td>103.1 ± 1.39</td>
</tr>
<tr>
<td>43.3 ± 0.31</td>
<td>NS</td>
<td>4</td>
<td>100.0 ± 0.30</td>
<td>97.4 ± 1.09</td>
<td>98.6 ± 0.38</td>
<td>98.4 ± 0.67</td>
<td>99.3 ± 0.21</td>
<td>98.3 ± 0.93</td>
<td>98.5 ± 1.44</td>
</tr>
<tr>
<td>44.4 ± 0.24</td>
<td>DSW</td>
<td>22</td>
<td>100.5 ± 2.13</td>
<td>98.8 ± 1.02</td>
<td>99.7 ± 0.65</td>
<td>99.9 ± 2.36</td>
<td>100.6 ± 1.04</td>
<td>100.3 ± 0.45</td>
<td>99.5 ± 0.39</td>
</tr>
<tr>
<td>43.8 ± 0.33</td>
<td>DSW</td>
<td>4</td>
<td>102.4 ± 1.62</td>
<td>100.4 ± 1.90</td>
<td>101.1 ± 0.74</td>
<td>99.2 ± 0.17</td>
<td>101.6 ± 0.78</td>
<td>98.8 ± 0.99</td>
<td>99.7 ± 1.28</td>
</tr>
</tbody>
</table>

DSW = 5% dextrose in water, NS = 0.9% sodium chloride.
* Mean ± standard deviation of 4 determinations.

Table II. Summary Table for Diphenhydramine Hydrochloride Stability in Polypropylene Syringes with Friction Caps

<table>
<thead>
<tr>
<th>Initial Conc’n (mg/10 mL)</th>
<th>Diluent</th>
<th>Storage Temp. (°C)</th>
<th>Day 1 (%)</th>
<th>Day 3 (%)</th>
<th>Day 7 (%)</th>
<th>Day 14 (%)</th>
<th>Day 22 (%)</th>
<th>Day 28 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>13.4 ± 0.09</td>
<td>NS</td>
<td>22</td>
<td>98.4 ± 1.24</td>
<td>99.2 ± 0.71</td>
<td>99.1 ± 0.60</td>
<td>98.2 ± 0.59</td>
<td>95.7 ± 1.00</td>
<td>97.5 ± 0.64</td>
</tr>
<tr>
<td>13.0 ± 0.27</td>
<td>NS</td>
<td>4</td>
<td>99.7 ± 1.92</td>
<td>102.0 ± 0.70</td>
<td>101.1 ± 0.45</td>
<td>101.1 ± 1.08</td>
<td>101.5 ± 0.91</td>
<td>102.8 ± 1.05</td>
</tr>
<tr>
<td>25.3 ± 0.28</td>
<td>NS</td>
<td>22</td>
<td>99.9 ± 0.61</td>
<td>98.9 ± 0.66</td>
<td>99.6 ± 0.84</td>
<td>99.8 ± 0.42</td>
<td>99.3 ± 0.31</td>
<td>100.0 ± 0.21</td>
</tr>
<tr>
<td>25.1 ± 0.14</td>
<td>NS</td>
<td>4</td>
<td>99.8 ± 0.28</td>
<td>99.8 ± 0.72</td>
<td>99.9 ± 0.40</td>
<td>100.2 ± 0.73</td>
<td>99.4 ± 0.52</td>
<td>100.0 ± 1.06</td>
</tr>
<tr>
<td>49.5 ± 0.75</td>
<td>NS</td>
<td>22</td>
<td>99.9 ± 2.09</td>
<td>100.4 ± 2.54</td>
<td>99.4 ± 1.80</td>
<td>101.1 ± 0.56</td>
<td>101.2 ± 1.04</td>
<td>100.7 ± 0.99</td>
</tr>
<tr>
<td>49.2 ± 2.81</td>
<td>NS</td>
<td>4</td>
<td>100.7 ± 1.57</td>
<td>100.9 ± 0.80</td>
<td>99.7 ± 1.49</td>
<td>100.9 ± 0.97</td>
<td>98.9 ± 0.77</td>
<td>101.1 ± 0.30</td>
</tr>
</tbody>
</table>

DSW = 5% dextrose in water, NS = 0.9% sodium chloride.
* Mean ± standard deviation of 4 determinations.

and those of an authentic reference standard had a high similarity index, which indicated that the peak represented pure diphenhydramine.

The percentage of the initial concentration remaining varied only slightly, which indicates that no diphenhydramine degradation occurred over the 91-day period for solutions packaged in minibags of either D5W or NS and stored at either 22°C or 4°C and protected from light. The slight difference in pH between the D5W and NS did not appear to have any effect on the stability of the solution. Solutions packaged in syringes were stable for at least 28 days when stored at either 22°C or 4°C and protected from light. In addition, no degradation peaks were observed in the samples at any time, and the percentage of initial concentration remaining did not fall below 90%.

Although this study demonstrated that the chemical stability of diphenhydramine packaged in polypropylene syringes and sealed with friction caps is retained over a 28-day period, the expiry date cannot be extended until sterility data are collected. These data must be individually determined by each institution because of the high variability in conditions of preparation and storage.

**CONCLUSION**

A stability-indicating HPLC assay was developed for analysis of diphenhydramine hydrochloride. Solutions of this compound at 12.5, 25, and 50 mg/50 mL, prepared in minibags containing either D5W or NS, were chemically stable for 91 days when stored at either 22°C or 4°C. Diphenhydramine packaged in polyethylene syringes at institutions, this product has been chemically stable for 91 days when stored at 22°C or 4°C.

**Acknowledgements**

This study was funded by Parke-Davis, a division of Warner-Lambert Company.

Ronald F. Donnelly, PharmD, FAPhA, received the 1995 Research Award in the Basic Sciences from the American College of Hospital Pharmacists and the 1994 Young Investigator Award from the Canadian Society of Hospital Pharmacists.

**References**

2. Tissot IA, ed, Allyn and Bacon, New York.
4. Kirkland WD, A.C.S., American Chemical Society.
5. Chaudry IA, A.C.S., American Chemical Society.
7. Sules ML, A.C.S., American Chemical Society.

**Address correspondence to Ronald Donnelly.**
The expiry date of diphenhydramine hydrochloride packaged in polypropylene syringes may be extended to 28 days at institutions where the sterile integrity of the final product has been determined.

**Acknowledgement**

This study was partially funded by a grant from Parke-Davis. This paper is part of the submission that won the 1997 CSHP Baxter Award for Intravenous Therapy, Health Care Settings.

**References**


