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# A Pilot Chemical and Physical Stability Study of Extemporaneously Compounded Levetiracetam Intravenous Solution

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## Abstract

Levetiracetam is a commonly used antiepileptic medication for tumor-related epilepsy. However, the 100 mL intravenous (IV) infusion volume can be burdensome to imminently dying hospice patients. A reduced infusion volume would improve patient tolerability. The purpose of this study was to evaluate the stability of 1000 mg/25 mL (40 mg/mL) levetiracetam IV solution in sodium chloride 0.9%. We prepared levetiracetam 40 mg/mL IV solution and added it to polyvinyl chloride (PVC) bags, polyolefin bags, and polypropylene syringes. Triplicate samples of each product were stored at refrigeration (2–8°C) and analyzed on days 0, 1, 4, 7, and 14. Samples were subjected to visual inspection, pH measurement, and stability-indicating high-performance liquid chromatography (HPLC) analysis. Over the 2-week storage period, there was no significant change in visual appearance or pH for any of the stability samples. The HPLC results confirmed that all stability samples retained 94.2–101.3% of initial drug concentration and no degradation products or leachable material from the packaging materials were observed. We conclude that levetiracetam 1000 mg/25 mL IV solution in sodium chloride 0.9% is physically and chemically stable for up to 14 days under refrigeration in polypropylene syringes, PVC bags, and polyolefin bags.

## Keywords

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## Disciplines

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## Comments

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## **REPORT**

### **A Pilot Chemical and Physical Stability Study of Extemporaneously Compounded Levetiracetam Intravenous Solution**

Chenzira D. Raphael, Fang Zhao, Susan E. Hughes, and Katherine M. Juba

#### **ABSTRACT**

Levetiracetam is a commonly used antiepileptic medication for tumor-related epilepsy. However the 100 mL intravenous (IV) infusion volume can be burdensome to imminently dying hospice patients. A reduced infusion volume would improve patient tolerability. The purpose of this study was to evaluate the stability of 1000 mg/25 mL (40 mg/mL) levetiracetam IV solution in sodium chloride 0.9%. We prepared levetiracetam 40 mg/mL IV solution and added it to polyvinyl chloride (PVC) bags, polyolefin bags, and polypropylene syringes. Triplicate samples of each product were stored at refrigeration (2-8°C) and analyzed on days 0, 1, 4, 7, and 14. Samples were subjected to visual inspection, pH measurement, and stability-indicating high performance liquid chromatography (HPLC) analysis. Over the two-week storage period, there was no significant change in visual

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appearance or pH for any of the stability samples. The HPLC results confirmed that all stability samples retained 94.2-101.3% of initial drug concentration and no degradation products or leachables from the packaging materials were observed. We conclude that levetiracetam 1000 mg/25 mL IV solution in sodium chloride 0.9% is physically and chemically stable for up to 14 days under refrigeration in polypropylene syringes, PVC bags, and polyolefin bags.

**KEYWORDS:** intravenous, levetiracetam, concentrated, stability, epilepsy, seizures, pain, neuropathic

## **INTRODUCTION**

Seizures are a common symptom of patients suffering from brain tumors. Approximately 20-40% of all brain tumor patients have a seizure during the course of their disease.<sup>1</sup> Tumoral epilepsy has an adverse impact on quality of life due to the unpredictable nature and psychological effects of the disease.<sup>2</sup> Imminently dying patients frequently experience dysphagia and often require a switch from oral to parenteral antiepileptic drugs to prevent additional tumor-associated seizures.

Levetiracetam is an antiepileptic drug indicated as adjunct therapy for partial onset and myoclonic seizures in adults. It is effective at decreasing seizure frequency in tumor-related epilepsy and has a favorable pharmacokinetic profile with few drug interactions.<sup>2-4</sup> Levetiracetam is also used to treat neuropathic pain.<sup>5-8</sup> It is commercially available as an injectable solution for patients with dysphagia.<sup>9,10</sup> The levetiracetam 500 mg/5 mL vials are typically diluted in 100 mL of compatible diluent to achieve a 500 mg, 1000 mg or 1500 mg

dose.<sup>9</sup> The dose is administered as a 15-minute intravenous infusion. For ease of preparation ready-to-administer levetiracetam bags in 500 mg/100 mL, 1000 mg/100 mL, or 1500 mg/100 mL in sodium chloride 0.9% became available in recent years.<sup>10</sup>

Administration of 100 mL of fluid multiple times a day can be burdensome to imminently dying hospice patients by potentially worsening edema, nausea/vomiting, and respiratory secretions resulting in patient discomfort. Weighing the clinical risks and benefits of continuing IV levetiracetam versus switching to an alternate parenteral antiepileptic drug (AED) with less administration volume can be challenging for providers. If the same IV levetiracetam dose could be administered in a smaller volume, it may improve patient tolerability. Unfortunately, there is no published levetiracetam stability data beyond the maximum commercially available 15 mg/mL strength. The stability of 40 mg/mL levetiracetam was mentioned in a reference handbook for 24 hours at controlled room temperature, but it was based on unpublished personal communication.<sup>11</sup> The purpose of this pilot study was to evaluate the stability of levetiracetam 1000 mg/25 mL (40 mg/mL) in sodium chloride 0.9% packaged in polypropylene syringes, polyvinyl chloride (PVC) and polyolefin bags under refrigeration for up to 14 days.

## **MATERIALS AND METHODS**

### **Materials**

Levetiracetam injection 500 mg/5 mL vials were purchased from Hospira, Lake Forest, IL, NDC#0409-1886-02. The diluent, sodium chloride 0.9% injection was purchased from Baxter, Deerfield, IL, NDC#0338-0049-02. The empty 50 mL sterile polyolefin bags were purchased from Baxter, Deerfield, IL, product code 2B8019, and the 30 mL polypropylene syringes were purchased from BD, Franklin Lakes, NJ, product code 302832. Empty sterile PVC bags were not available commercially. Therefore, the 25 mL sodium chloride 0.9% injection

PVC bags were used (Hospira, Lake Forest, IL, NDC#0409-7984-20). The fluid in these bags was completely removed prior to the addition of the 40 mg/mL levetiracetam solution. HPLC standards were prepared using levetiracetam powder, 99.79% purity, purchased from PCCA, Houston, TX, lot C159856. Phosphoric acid and acetonitrile used for the HPLC analysis were purchased from Fisher Scientific, Fairlawn, NJ, lot# 068114 and 110762, respectively.

### **Stability Samples**

Under aseptic conditions, a 250 mL batch of 40 mg/ml levetiracetam was prepared by mixing 100 mL (20 vials) of commercially available levetiracetam 500 mg/5 mL injection with 150 mL of sodium chloride 0.9% in a 250 mL beaker. The 40 mg/mL levetiracetam solution was aseptically transferred into PVC bags, polyolefin bags, and polypropylene syringes, each containing 25 mL. Three replicates of each packaging were prepared, yielding a total of nine stability samples. All samples were sealed properly after the addition of the levetiracetam solution. All stability samples were stored at refrigeration (2 – 8°C). The batch preparation approach was used to ensure the uniformity of the initial concentration for all stability samples. Appropriate compounding procedures for actual dispensing are recommended in the discussion section.

Stability assessment was performed immediately after preparation (time zero), and at days 1, 4, 7 and 14. The bags and syringes were visually inspected at each time point for color, clarity, microbial growth, and particulates. A 1 mL sample was then withdrawn aseptically from each stability sample. A 200 µL aliquot from each sample was diluted with purified water in a 50 mL volumetric flask and analyzed by a stability-indicating high performance liquid chromatography (HPLC) method; three injections were performed for each of the triplicate samples. The remainder of the 1 mL sample was used for pH measurement (SevenEasy pH

meter, Mettler-Toledo Inc., Columbus, OH). The stability samples were re-sealed and immediately returned to the refrigerator. Since the study focus was physical and chemical stability, sterility was not required or tested.

### **Stability-indicating HPLC Analysis**

The stability-indicating HPLC analysis was performed using a Shimadzu model LC-2010AHT instrument (Shimadzu Scientific Instruments, Marlborough, MA). The chromatographic variables used were from a previous stability-indicating assay established in the same lab.<sup>13</sup> The HPLC column (ODS AQ, 5  $\mu$ m, 250  $\times$  4.6 mm, YMC America, Inc., Allentown, PA) was maintained at 30°C throughout the analysis. The mobile phase consisted of 0.1% aqueous phosphoric acid and acetonitrile at a volume-to-volume ratio of 85:15 with a flow rate of 1.0 mL/min. Each injection volume was 10  $\mu$ L, and the UV detection wavelength was set at 205 nm. Under these conditions, the levetiracetam retention time was approximately 5.2 minutes (Figure 1).

Standards of levetiracetam solutions were prepared for each time point for calibration purposes. A 10 mg/mL stock solution was prepared by dissolving the calculated amount of levetiracetam powder in purified water and standard solutions of 0.08, 0.12, 0.16, 0.20, 0.24 mg/mL were made by further dilutions into 100 mL volumetric flasks. A calibration curve was constructed at each time point by linear regression of the peak area of levetiracetam against levetiracetam concentration. The curves were found to be linear over the concentration range of the standards ( $r^2 = 0.996$  or better). Intraday and interday coefficients of variation were within 1.00%.

## **RESULTS**

At study initiation, the physical appearance of the compounded levetiracetam solution was clear, colorless, and free of particulate matter. Results of the chemical stability tests of pH and drug concentration are reported in Table 1 and 2 respectively. The pH values were consistent with the pH of the source levetiracetam product which was buffered at approximately pH 5.5 with acetic acid and sodium acetate.<sup>10</sup> The HPLC results indicated that the drug concentration were 4 – 8% higher than the nominal value of 40 mg/mL. This could be ascribed to the approximate nature of the compounding procedures (e.g. syringe accuracy) and potency range of the source products acceptable by the manufacturer. The drug concentration in the PVC bags was also slightly lower than that in the polyolefin bags or polypropylene syringes, which was most likely due to the residual sodium chloride 0.9% injection in the PVC bags. Nevertheless, all initial concentration values were within the  $\pm 10\%$  of the nominal value and were therefore considered acceptable for the study. For the remaining time points, the HPLC data were reported as percent initial concentration remaining. Levetiracetam was considered stable if the solution retained 90-110% initial drug concentration with no significant new peaks observed.

Over the two-week study period, all samples remained clear, colorless, and free of visible precipitation or microbial growth. No significant changes in the pH of any of the samples were observed (Table 1). The stability-indicating HPLC analysis also confirmed that all samples retained 94.2-101.3% of the initial drug concentration (Table 2). No new peaks, due to degradation products or leachables, were observed in the HPLC chromatograms.

## **DISCUSSION**

USP General Chapter <1191> discusses the general stability considerations in dispensing practice.<sup>13</sup> Levetiracetam is a simple organic molecule with relatively stable functional

groups.<sup>9,12,14</sup> The main concern with the compounded levetiracetam 40 mg/mL parenteral solution was potential drug adsorption to packaging materials and leachables from the same. This study evaluated three packaging materials for the following reasons. The PVC bags are the most commonly used IV bags in health systems and they are recommended by the manufacturer.<sup>9</sup> However, the use of PVC bags is becoming unfavorable in recent years due to environmental concerns of PVC incineration byproducts and potential health risks associated with the plasticizers.<sup>15,16</sup> Polyolefin bags are an alternative that hospitals can use if PVC-free bags are preferred. In addition, empty 50-mL polyolefin IV are available commercially, while empty 50-mL (or below) PVC bags are not readily available. Polypropylene syringes were included in this study in case the use of an infusion pump is desired. Based on the study results, levetiracetam 40 mg/mL parenteral solution is stable and compatible in all three packaging materials evaluated.

A 250 mL batch of 40 mg/mL levetiracetam solution was initially prepared in this pilot study to achieve a consistent starting drug concentration across all stability samples. To reduce contamination and eliminate the need for sterilization, the actual IV admixture products for patient use should be prepared as individual doses directly in the IV bags or syringes. Since this is a compounded sterile preparation, the pharmacy must follow all pertinent requirements specified in USP <797>, and assign Beyond Use Dating accordingly.<sup>17</sup>

## **CONCLUSIONS**

It is of great importance to provide comfort and symptom management to terminally ill patients in their final days. A 1000 mg/25 mL levetiracetam IV solution would be beneficial to hospice patients with tumoral epilepsy who cannot tolerate the commercially available 100 mL volume. These pilot study results confirm that levetiracetam 1000 mg/25 mL IV solution in

sodium chloride 0.9% injection is physically and chemically stable for up to 14 days under refrigeration (2-8°C) in polypropylene syringes, PVC bags, and polyolefin bags. Proper sterile compounding practice as per USP <797> must be followed when making the actual IV admixture preparations to be used in patients.

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**Table 1.** pH Results of Levetiracetam Solution Stability Samples (n = 3)

<b>Packaging</b>	<b>pH (Mean ± SD)</b>				
	<b>Time 0</b>	<b>1 day</b>	<b>4 days</b>	<b>7 days</b>	<b>14 days</b>
<b>PVC bag</b>	5.45 ± 0.42	5.41 ± 0.64	5.42 ± 0.11	5.38 ± 1.11	5.51 ± 0.74
<b>Polyolefin bag</b>	5.43 ± 0.53	5.37 ± 0.87	5.42 ± 0.11	5.30 ± 0.11	5.39 ± 0.32
<b>Polypropylene Syringe</b>	5.44 ± 0.38	5.36 ± 0.74	5.40 ± 0.53	5.29 ± 0.11	5.41 ± 0.00

**Table 2.** HPLC Results of Levetiracetam Solution Stability Samples (n = 3)

<b>Packaging</b>	<b>Initial Drug Concentration (mg/mL)</b>	<b>% Initial concentration remaining (Mean ± SD)</b>			
		<b>1 day</b>	<b>4 days</b>	<b>7 days</b>	<b>14 days</b>
<b>PVC bag</b>	41.7 ± 0.8	98.2 ± 0.7	97.5 ± 1.2	95.8 ± 0.7	94.2 ± 0.9
<b>Polyolefin bag</b>	43.2 ± 1.2	99.7 ± 1.6	98.3 ± 0.5	96.8 ± 5.4	95.8 ± 2.4
<b>Polypropylene Syringe</b>	42.9 ± 0.2	101.3 ± 2.2	100.7 ± 0.7	96.0 ± 0.9	94.6 ± 1.3

**Figure 1.** A representative chromatogram of levetiracetam showing the active peak at 5.2 minutes.

