

Stability of Levothyroxine in Sodium Chloride for IV Administration

Dawn K Strong, Diane Decarie, and Mary H H Ensom

ABSTRACT

Background: Levothyroxine by IV administration is often prescribed in the intensive care unit for the management of potential solid organ donors, following declaration of brain death and provision of consent for organ donation. Published data on the stability of levothyroxine in IV solutions are limited.

Objective: To evaluate the physical compatibility and chemical stability, over a 24-h period, of 2 concentrations of levothyroxine in 0.9% sodium chloride with storage at room temperature and with exposure to or protection from light.

Methods: Levothyroxine solutions (0.4 µg/mL and 2.0 µg/mL) were prepared in 50-mL minibags of 0.9% NaCl and stored at room temperature (25°C) with exposure to or protection from light. Samples were collected from each minibag at time 0 and after 0.5, 1.0, 1.5, 2.0, 3.0, 4.0, 8.0, 12.0, and 24.0 h. The samples were analyzed in triplicate with a validated stability-indicating high-performance liquid chromatography method using ultraviolet detection. A solution was considered stable if it maintained 90% of its initial concentration of levothyroxine. Changes in colour, clarity, and pH were assessed to determine the physical compatibility of the solutions.

Results: All samples remained clear, colourless, and free of precipitate throughout the study, and there were no significant changes in pH. Based on the 95% confidence interval of the slope of the curve relating concentration to time determined by linear regression, solutions of levothyroxine with concentration 0.4 µg/mL would maintain at least 90% of the initial concentration for 16.9 h with exposure to light and for 18.0 h if kept in the dark. Solutions of levothyroxine with concentration 2.0 µg/mL would maintain at least 90% of the initial concentration for 6.5 h with exposure to light and for 12.0 h if kept in the dark, with 95% confidence.

Conclusions: Extemporaneously prepared solutions of levothyroxine in 0.9% NaCl can be expected to remain stable for at least 6.5 h if stored without protection from light and at least 12 h if stored in the dark. Stability is related to concentration, with more dilute solutions having greater stability.

Key words: levothyroxine, IV administration, stability, organ donation

RÉSUMÉ

Contexte : La lévothyroxine administrée par injection i.v. est souvent prescrite dans les unités de soins intensifs lors de la prise en charge des donneurs potentiels d'organe, après avoir déclaré la mort cérébrale et avoir obtenu le consentement pour le don d'organe. Les données publiées sur la stabilité de la lévothyroxine dans des solutions intraveineuses sont toutefois limitées.

Objectif : Évaluer la compatibilité physique et la stabilité chimique, sur une période de 24 heures, de solutions de lévothyroxine préparées en deux concentrations dans du chlorure de sodium à 0,9 %, entreposées à la température ambiante à l'abri ou non de la lumière.

Méthodes : Les solutions de lévothyroxine (0,4 µg/mL et 2,0 µg/mL) ont été préparées dans des minisacs de 50 mL de chlorure de sodium à 0,9 % qui ont été entreposés à la température ambiante (25 °C) et exposés ou non à la lumière. Des échantillons ont été recueillis de chaque minisac à 0, 0,5, 1, 1,5, 2, 3, 4, 8, 12 et 24 heures. Les échantillons ont été analysés en triple à l'aide d'une épreuve validée mesurant la stabilité par chromatographie liquide haute performance avec détection ultraviolette. Les solutions étaient considérées comme stables si elles conservaient 90 % de la concentration initiale de lévothyroxine. La compatibilité physique a été évaluée en contrôlant tout changement dans la couleur, la limpidité et le pH des solutions de lévothyroxine.

Résultats : Tous les échantillons sont demeurés limpides, incolores et sans précipité tout au long de l'étude, et n'ont présenté aucun changement significatif du pH. D'après l'intervalle de confiance à 95 % de la pente de la courbe de la concentration en fonction du temps déterminée par régression linéaire, les solutions de lévothyroxine à 0,4 µg/mL conservaient au moins 90 % de la concentration initiale pendant 16,9 heures lorsqu'elles étaient exposées à la lumière et pendant 18,0 heures lorsqu'elles étaient à l'abri de la lumière. Les solutions de lévothyroxine à 2,0 µg/mL conservaient au moins 90 % de la concentration initiale pendant 6,5 heures lorsqu'elles étaient exposées à la lumière et pendant 12,0 heures lorsqu'elles étaient à l'abri de la lumière, avec un niveau de confiance de 95 %.

Conclusions : Les solutions extemporanées de lévothyroxine préparées dans du chlorure de sodium à 0,9 % devraient demeurer stables pendant au moins 6,5 heures si elles sont entreposées à la lumière et pendant au moins 12 heures si elles sont entreposées à l'abri de la lumière. La stabilité est liée à la concentration, les solutions plus diluées étant plus stables.

Mots clés : lévothyroxine, administration i.v., stabilité, don d'organe

INTRODUCTION

Organ transplantation is a life-saving treatment for patients with end-stage renal, hepatic, cardiac, lung, or pancreas failure.^{1,2} The majority of transplanted organs come from patients who have died in the intensive care unit (ICU) after declaration of brain death.³ During and after brain death, electrocardiographic, hemodynamic, and histopathologic changes occur, with subsequent depletion of circulating hormones and deterioration of organ function, all of which affect the quality of the donor organ and the success of the transplant. Aggressive donor management strategies are required to preserve the function of the donor's organs.³⁻⁶ One strategy that may improve the viability and function of organs after transplantation is the use in potential donors of combined hormonal therapy consisting of IV administration of levothyroxine, vasopressin, and corticosteroids.³⁻¹⁰ The Canadian guidelines on solid organ donor management¹¹ endorse the IV administration of levothyroxine.

Pharmacy staff and ICU nurses are reluctant to prepare and administer IV levothyroxine solutions for use in potential solid organ donors because information about their stability is lacking. In a recent study, Stadalman and others¹² reported that when levothyroxine sodium 40 µg/mL was admixed with 0.9% sodium chloride to a final concentration of 0.4 µg/mL, it was stable for 24 h at room temperature when protected from light. However, as discussed in more detail later in this article, the authors did not demonstrate that their testing procedure was a stability-indicating method.

The purpose of the study reported here was to examine the physical characteristics and chemical stability (defined as maintenance of more than 90% of original concentration, as determined by high-performance liquid chromatography [HPLC]) of levothyroxine 0.4 µg/mL and 2.0 µg/mL prepared in 50-mL minibags of 0.9% NaCl and stored under both light and dark conditions. These concentrations were chosen because they can be easily prepared and used when following the levothyroxine doses recommended by the Canadian guidelines on solid organ donor management: 20 µg IV bolus followed by 10 µg/h IV infusion or 100 µg IV bolus followed by 50 µg IV every 12 h.¹¹

METHODS

Preparation of Levothyroxine and Experimental Setup

Two sets of 6 bags of levothyroxine solution were prepared from commercially available levothyroxine (levothyroxine sodium for injection, 500 µg per vial; Pharmaceutical Partners of Canada, Richmond Hill, Ontario; lot 203463, expiry November 2009 [all experiments were completed before the expiry date]). Solutions of levothyroxine 0.4 µg/mL and

2.0 µg/mL were prepared by diluting the levothyroxine sodium 20 µg/mL and 100 µg/mL, respectively, in 0.9% NaCl and transferring the solutions to latex-free polyvinylchloride (PVC)-containing 50-mL minibags (Baxter Corporation, Toronto, Ontario; lot JB1301). Three bags of each concentration were exposed to ambient (fluorescent) light, and the remaining bags were stored in the dark (in opaque brown resealable bags). All samples were stored at room temperature (25°C; range 23.5°C to 26.5°C).

Physical Compatibility

The physical characteristics of the solutions were evaluated qualitatively at the time of preparation and at 0.5, 1.0, 1.5, 2.0, 3.0, 4.0, 8.0, 12.0, and 24.0 h. As samples were collected for analysis, each solution was tested by the same individual (D.D.) and was visually examined for changes in colour (against a white background) and for formation of precipitate (against a black background). A 2-mL aliquot was collected from each minibag at each time point for determination of pH. At every time point, the pH meter (model 8000, VWR International, Mississauga, Ontario) was calibrated with Sigma pH 7.00 and pH 4.00 reference solutions (Sigma-Aldrich, Oakville, Ontario; lots 038K0073 and 088K0735, respectively).

Chemical Stability

Preparation of Stocks and Standards

Stock solutions of levothyroxine were prepared daily from levothyroxine 1 mg/mL (Sigma-Aldrich, Oakville, Ontario; lot 097K0753) in 0.9% NaCl (Baxter Corporation, Toronto, Ontario; lot WD27MO). The internal standard was propranolol (Sigma Aldrich, Oakville, Ontario; lot 97H0311), diluted to a concentration of 0.5 µg/mL in HPLC-grade methanol (Fisher Scientific, Richmond, British Columbia; lot 08969535). To prepare stock solutions for constructing the calibration curve, levothyroxine 10 µg/mL was diluted in 0.9% NaCl to concentrations of 0.1, 0.2, 1.0, 2.0, 4.0, and 8.0 µg/mL. The standards were prepared by combining 0.5 mL of each stock solution and 0.5 mL of the internal standard (propranolol 0.5 µg/mL). The final concentrations of levothyroxine in the standard samples injected onto the chromatograph were 0.05, 0.1, 0.5, 1.0, 2.0, and 4.0 µg/mL, and the final concentration of propranolol in each standard was 0.25 µg/mL. Before injection onto the chromatograph, all standards were passed through a 0.45-µm microfilter to remove impurities.

A 6-point calibration curve was prepared with a blank (water) at the beginning of each run, to ensure that there was no carry-over from one run to the next. The range of this calibration curve (0.05 to 4.0 µg/mL) encompassed the diluted (0.2 and 1.0 µg/mL) test concentrations of levothyroxine 0.4

and 2.0 µg/mL. The daily calibration curve was generated by least-squares regression of the peak area ratio of levothyroxine to propranolol (the internal standard) versus the concentration of each levothyroxine standard. The accuracy of the assay was calculated as the mean deviation between nominal and observed concentrations. Precision (reproducibility) of the assay was evaluated by intraday and interday validation methods. The intraday variability was determined by running the standards' lowest limit of quantitation and low, medium, and high concentrations of levothyroxine (0.1, 0.75, 1.5, and 3 µg/mL, respectively) in quadruplicate throughout a single day. Interday variability was determined by running samples with the same concentrations (as in the testing for intraday variability) in quadruplicate daily for 4 days. The mean, standard deviation, coefficient of variation, and accuracy were calculated. Acceptable limits for coefficients of variation were defined a priori as less than 10% and acceptable limits for accuracy were defined a priori as more than 90%.

Preparation of Samples

Immediately after the physical observations were recorded, 1-mL samples were transferred to 12 × 75 mm glass dilution tubes (VWR International, Edmonton, Alberta) and stored at -85°C until analysis by stability-indicating HPLC with ultraviolet detection.

A 0.5-mL aliquot of each study sample was diluted with 0.5 mL of propranolol (internal standard) 5 µg/mL. The final theoretical levothyroxine concentrations were 0.2 and 1.0 µg/mL. Each sample was passed through a 0.45-µm microfilter before an 80-µL sample was withdrawn and injected onto the column.

HPLC Instrumentation

The HPLC instrumentation (model 2690, Waters Alliance System, Waters Ltd, Mississauga, Ontario) consisted of a delivery pump, an automatic injector equipped with a 200-µL injector, an Atlantis dC18 4.6 × 250 mm (5-µm unbounded silica-based) column (Waters Ltd; lot 013138176136), an Atlantis dC18 3.9 × 20 mm guard column (Waters Ltd; lot 0131383031), and an ultraviolet detector (dual absorbance detector, model 2487; Waters Alliance System) set at 232 nm. The mobile phase consisted of a 28%–32%–40% (v/v/v) mixture of methanol, acetonitrile (VWR International, Edmonton, Alberta; lot 49027), and 0.01 mol/L solution of KH₂PO₄ (Sigma-Aldrich, Oakville, Ontario; lot 107K0100) at pH 3.0. All solvents were HPLC-grade and were filtered before use. Samples were eluted at room temperature (25°C), and the flow rate was set at 1.4–1.75 mL/min to achieve optimal chromatographic characteristics. Specifically, for each sample, the flow rate at time 0 was 1.4 mL/min; between 3.5 and 5.0 min, the flow rate was gradually increased from 1.4 to 1.75 mL/min; and between 5.0

and 8.0 min, the rate was kept constant at 1.75 mL/min. The assay, developed in the authors' laboratory, was based on previous work of other researchers.¹³⁻¹⁵

Degradation of Levothyroxine

Levothyroxine 10 µg/mL was prepared from a 1 mg/mL stock solution. The pH was first adjusted to 12.4 with sodium hydroxide 1N and then returned to 6.0 with sodium hydroxide 1N. The pH was then adjusted to 2.1 with hydrochloric acid 1N and again returned to 6.0 with sodium hydroxide 1N. The sample was diluted with water to a final concentration of 4.0 µg/mL, combined with an equal volume of the internal standard, filtered, and injected onto the column. A second preparation of levothyroxine 4 µg/mL in 0.9% NaCl was exposed to light for a period of 36 h, combined with an equal volume of the internal standard, filtered, and injected onto the column. The chromatograms obtained for these degraded preparations were compared with chromatograms obtained from the standard curve to determine any changes in concentration, retention time, and shape of the peak.

Statistical Analysis

Mean, standard deviation, coefficient of variation, and accuracy were calculated for samples analyzed in triplicate (experimental samples) and quadruplicate (validation standards). The percentage of initial levothyroxine concentration remaining was calculated for each sample, and stability was defined as maintenance of at least 90% of the initial levothyroxine concentration. The percentage of levothyroxine remaining at 24 h was calculated from the concentration at 24 h, as determined by linear regression and concentration at time 0, according to the following formula: concentration at 24 h ÷ concentration at time 0 × 100%. The 95% confidence interval (CI) of the amount remaining at 24 h was calculated from the lower limit of the 95% CI of the slope of the curve relating concentration to time, determined by linear regression, via computer analysis, according to the following formula: lower limit of the 95% CI of the concentration at 24 h ÷ concentration at time 0 × 100%. If the percentage remaining at 24 h was not at least 90% of the initial concentration, then the time during which the solution would maintain at least 90% of its initial concentration was calculated, according to the following formula: 10 ÷ lower limit of the 95% CI of the slope of the curve relating concentration to time (determined by linear regression).

RESULTS

The regression analysis of the peak area ratio of levothyroxine to propranolol (the internal standard) versus the concentration of each levothyroxine standard demonstrated linearity over the range of the concentrations, with coefficient

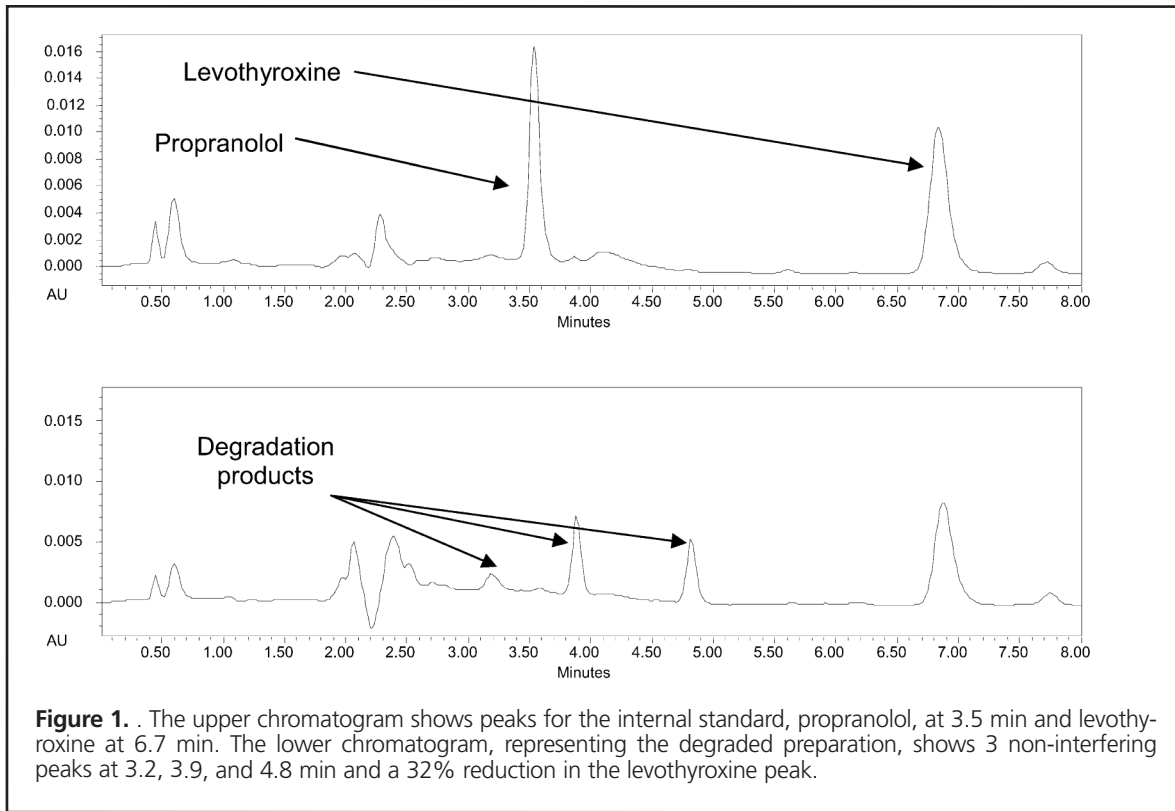


Table 1. Percentage of Initial Concentration of Levothyroxine 0.4 µg/mL* Remaining after Storage at 25°C in Minibags Exposed to or Protected from Light

Sampling Time (h)	Storage Conditions; % Remaining (Mean ± SD)	
	Light	Dark
Initial concentration (µg/mL)	0.40 ± 0.021	0.37 ± 0.004
0.5	92.5 ± 5.5	97.3 ± 1.3
1.0	97.5 ± 2.8	94.6 ± 4.5
1.5	95.0 ± 1.5	94.6 ± 6.5
2.0	90.0 ± 2.3	91.9 ± 2.3
3.0	92.5 ± 7.0	97.3 ± 1.5
4.0	95.0 ± 3.5	100.0 ± 5.0
8.0	90.0 ± 3.3	91.9 ± 6.8
12.0	90.0 ± 2.8	91.9 ± 0.8
24.0	90.0 ± 1.3	91.9 ± 2.0
% remaining at 24 h by linear regression†	93.4	94.1
Lower limit of 95% CI for % remaining‡	85.8	86.9
Time predicted to maintain at least 90% of initial concentration§	16.9 h	18.3 h

CI = confidence interval, SD = standard deviation.

*Nominal concentration.

†Calculated from concentration at 24 h as determined by linear regression and concentration at time zero, according to the following formula: concentration at 24 h ÷ concentration at time zero x 100.

‡Calculated from lower limit of 95% CI of the slope of the curve relating concentration to time, determined by linear regression, according to the following formula: lower limit of 95% confidence interval of concentration at 24 h ÷ concentration at time zero x 100.

§Calculated according to the following formula: 10 ÷ lower limit of the 95% CI of the slope of the curve relating concentration to time (determined by linear regression).

Table 2. Percentage of Initial Concentration of Levothyroxine 2.0 µg/mL* Remaining after Storage at 25°C in Minibags Exposed to or Protected from Light

Sampling Time (h)	Storage Conditions; % Remaining (Mean ± SD)	
	Light	Dark
Initial concentration (µg/mL)	1.91 ± 0.013	1.94 ± 0.038
0.5	103.1 ± 1.0	99.0 ± 6.4
1.0	103.1 ± 7.7	99.0 ± 9.1
1.5	100.0 ± 15.6	104.1 ± 0.3
2.0	103.1 ± 3.0	102.6 ± 0.9
3.0	100.5 ± 2.1	96.4 ± 0.8
4.0	102.6 ± 5.6	105.7 ± 4.9
8.0	104.7 ± 4.1	97.4 ± 1.4
12.0	96.9 ± 3.3	104.6 ± 4.2
24.0	73.8 ± 4.1	89.2 ± 12.3
% remaining at 24 h by linear regression†	74.3	90.9
Lower limit of 95% CI for % remaining‡	63.1	80.4
Time predicted to maintain at least 90% of initial concentration§	6.5 h	12.3 h

CI = confidence interval, SD = standard deviation.

*Nominal concentration.

†Calculated from concentration at 24 h as determined by linear regression and concentration at time zero, according to the following formula: concentration at 24 h ÷ concentration at time zero x 100.

‡Calculated from lower limit of 95% CI of the slope of the curve relating concentration to time, determined by linear regression, according to the following formula: lower limit of 95% confidence interval of concentration at 24 h ÷ concentration at time zero x 100.

§Calculated according to the following formula: 10 ÷ lower limit of the 95% CI of the slope of the curve relating concentration to time (determined by linear regression).

of determination (r^2) greater than 0.999 ($n = 4$). The intraday and interday coefficients of variation were within acceptable limits (<10%): 5.30% and 2.39% at 0.1 µg/mL, 5.55% and 6.15% at 0.75 µg/mL, 3.55% and 8.50% at 1.5 µg/mL, and 3.68% and 3.94% at 3 µg/mL, respectively. Intraday and interday accuracy was also within acceptable limits (>90%): 95.7% ± 2.7% and 95.5% ± 6.4% at 0.1 µg/mL, 91.5% ± 6.1% and 91.5% ± 7.8% at 0.75 µg/mL, 93.5% ± 3.7% and 98.1% ± 8.5% at 1.5 µg/mL, and 97.0% ± 2.6% and 99.0% ± 5.7% at 3.0 µg/mL, respectively. The lower limit of detection was 0.025 µg/mL. The retention times were 6.7 min for levothyroxine and 3.5 min for propranolol (Figure 1).

In the degradation studies (at room temperature), small non-interfering peaks formed and the area of the peak was reduced when the pH was adjusted to 12.4, and further degradation occurred when the pH was adjusted to 2.1: the levothyroxine peak was reduced by 32% and 3 degradation peaks were detected at 3.2, 3.9, and 4.8 min. No interfering peaks were detected (Figure 1). When exposed to light for a period of 36 h, the concentration of levothyroxine decreased by 67.5%, but no degradation peaks were observed on the chromatogram. Thus, the HPLC method was deemed capable of indicating stability.

No notable changes in pH or colour were observed, and no precipitation occurred in any of the solutions. The mean pH values (± standard deviation) were 6.10 ± 0.38 and 6.12 ± 0.41, for levothyroxine 0.4 µg/mL exposed to ambient light and stored in the dark, respectively, and 6.96 ± 0.10 and 6.98 ± 0.11 for levothyroxine 2.0 µg/mL exposed to ambient light and stored in the dark, respectively.

The HPLC analysis showed that none of the levothyroxine solutions exposed to light or kept in the dark was stable for 24 h (Tables 1 and 2). However, based on the 95% confidence interval of the slope determined by linear regression, levothyroxine 0.4 µg/mL can be expected to maintain at least 90% of the initial concentration for 16.9 h (storage in the light) or 18.3 h (storage in the dark), with 95% confidence (Table 1). Levothyroxine 2.0 µg/mL can be expected to maintain at least 90% of the initial concentration for 6.5 h (storage in the light) and 12.3 h (storage in the dark), with 95% confidence (Table 2).

DISCUSSION

Data on the stability of levothyroxine for IV use are very limited. The product monograph for levothyroxine sodium for injection (Pharmaceutical Partners of Canada Inc) recommends that 5 mL of 0.9% NaCl for injection, USP, be added

to the lyophilized drug for reconstitution, that the product be used immediately after reconstitution, that the solution be protected from light, and that the solution not be combined with other IV fluids.¹⁶ The Micromedex database states that levothyroxine for IV use should be reconstituted with normal saline, shaken, used immediately, and not added to other IV fluids.¹⁷ However, a study examining the stability of levothyroxine 100 µg/mL in 0.9% NaCl in polypropylene syringes found no change in clarity, pH, or potency after 7 days of storage at 5°C.¹⁸ Stadalman and others¹² recently reported that levothyroxine sodium (Bedford Laboratories, Bedford, Ohio) 40 µg/mL admixed with 500 mL 0.9% NaCl to a final concentration of 0.4 µg/mL was stable for 24 h at room temperature when protected from light. However, the assay was not deemed to be stability-indicating.¹⁹ In addition, the investigators used the ADVIA Centaur T4 assay (Siemens Healthcare Diagnostics Inc, Deerfield, Illinois), a competitive immunoassay that uses direct chemiluminescent technology and quantifies the amount of thyroxine in serum. It is possible that the assay did not distinguish between levothyroxine and its degradation products, which would explain the significant increase in measured levothyroxine concentrations over time.¹²

In the current study, we used a stability-indicating HPLC method to assay levothyroxine, testing 2 concentrations of the drug that are recommended by the Canadian guidelines on solid organ donor management (i.e., 0.4 µg/mL for infusion and 2 µg/mL for bolus infusion) under both light and dark conditions.

We noted an interesting finding during the assay validation of the study. When levothyroxine samples were stored at -85°C following preparation and then thawed for analysis, the levothyroxine peak was reduced by up to 60% after 2 freeze-thaw cycles. For levothyroxine 2 µg/mL, the percentage of the initial concentration decreased steadily, by 26.0% at 24 h and by 44.1% at 48 h for the solutions exposed to light and by 11.4% at 24 h and by 21.9% at 48 h for the solutions kept in the dark. The impact of freezing the samples before analysis may be what has contributed to the controversy about levothyroxine stability in IV fluids in previous studies.

CONCLUSIONS

Levothyroxine solutions (0.4 µg/mL and 2.0 µg/mL), prepared extemporaneously in 0.9% NaCl 50-mL minibags and stored at room temperature, can be expected to be stable (defined as maintenance of more than 90% of original concentration) for 16.9 h and 6.5 h, respectively, when stored in the light and for 18.3 h and 12.3 h when stored in the dark. Pharmacists can be confident that preparations of levothyroxine in 0.9% NaCl at these 2 concentrations prepared for IV administration to potential organ donors will be stable for up to 12 h if stored under dark conditions.

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