Original Article

Stability of Hydrocortisone Sodium Succinate in Intensive Care Units: Focus on Practical Points

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Background: Although single daily 24 hours preparation of hydrocortisone solution infusion is widely used in intensive care clinical practice, most manufacturers limit its infusion time to only four hours. The data on efficacy of this practice are scarce.

Objective: To determine the physical and chemical stability of hydrocortisone solution used in intensive care units (ICU).

Materials and Methods: Powder form of 100 mg hydrocortisone was reconstituted first with sterile water for injection (SWI) and then added to normal saline solution (NSS) to obtain 1 and 2 mg/mL solutions, or first reconstituted with NSS then added to bag of NSS to obtain 1 mg/mL solution. The solutions were then stored in three different conditions, refrigerator (4±2°C), ICU (25±3°C), and hospital room (30±2°C) temperatures for 48 hours. The physical and chemical stabilities were assessed at an initial time, 4, 8, 12, 24, and 48 hours.

Results: Hydrocortisone reconstituted in SWI showed an acceptable labeled amount range (100.28±3.83%), similar to reconstitution in NSS (96.05±1.00%). Hydrocortisone solutions of 1 and 2 mg/mL stored at 4±2°C, 25±3°C, and 30±2°C showed similar percent label amount, and the statistical tests were not significantly different among the three ranges of temperatures (p>0.05).

Conclusion: Hydrocortisone reconstituted using SWI followed by NSS to obtain final concentrations of 1 to 2 mg/mL or using only NSS to obtain a final concentration of 1 mg/mL, provided an acceptable range of % hydrocortisone remaining up to 48 hours when stored at 4±2°C, 25±3°C, and 30±2°C.

Keywords: Hydrocortisone; Intensive care units; Normal saline solution; Stability; Sterile water for injection

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The use of hydrocortisone sodium succinate is increasing as an adjunctive therapy in critically ill patients. Studies of hydrocortisone have shown an earlier reversal of shock and decreased mortality[1]. Surviving sepsis campaign guidelines recommend intravenous hydrocortisone at a dose of 200 mg per day in patients who still have ongoing shock, even when adequate fluid resuscitation and vasopressors were given[2]. Moreover, 24-hour continuous infusion of 200-mg hydrocortisone is suggested over bolus injections of 50-mg hydrocortisone every six hours to avoid the side effects, which are hyperglycemia and hypernatremia[3]. Hyperglycemia is usually found at the peak of repetitive boluses of hydrocortisone; therefore, continuous infusion of hydrocortisone is preferable[4]. Preventing adverse effects from selected medication is not the only factor to consider for clinical pharmacy services in critical care settings[5]. Minimizing dilution volumes of medications is another factor to be thought of in critically ill patients undergoing fluid restriction therapy[6,7]. To summarize, information on medication stability and minimization of dilution volume for hydrocortisone are necessary for intensive care unit (ICU) patients.

Currently in Thailand, hydrocortisone injection was found in the form of hydrocortisone sodium succinate, as power for injection, under a brand-

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name Solu-Cortef® by Pfizer and a generic name called hydrocortisone sodium succinate for injection BP 100 mg by Troikaa Pharmaceuticals Ltd., at the amount of 100 mg per vial. During the preparation process, the manufacturer recommended to dissolve the 100 mg hydrocortisone powder in not more than 2 mL of sterile water for injection (SWI) and further diluted to 100 to 1,000 mL, but not less than 100 mL, with normal saline solution (NSS) or 5% dextrose in water (D5W) to achieve the final concentration of not more than 1 mg/mL[8]. After being reconstituted, the resulting solutions should be used within four hours[9].

Although the manufacturer recommends dissolving hydrocortisone in SWI prior dilute with NSS or D5W[8,10], the direct reconstitution of 100 mg hydrocortisone in NSS 50 mL at 2 mg/mL for final concentration, or 100 mL at 1 mg/mL for final concentration, is considered as a simple method that fits with the high nursing workload and limited clinical pharmacy services in ICU of university hospitals in Thailand[11,12]. Moreover, this reconstituted hydrocortisone solution is usually administered to the patients via continuous infusion over 24 hours. This period is beyond the manufacturer's recommendation, which states that the reconstituted hydrocortisone solution should be used within four hours. Even though this is the method used in Thailand, there is no published data regarding the stability of the direct dilution in NSS. Likewise, there has not been any stability studies regarding hydrocortisone preparation of concentration higher than 1 mg/mL and the solutions used beyond four hours. Therefore, the purposes of the present study were 1) to evaluate the possibility of the direct dilution of hydrocortisone sodium succinate for injection BP (generic drug) in NSS without prior reconstituting in SWI, 2) to determine the stability of the concentrated hydrocortisone sodium succinate for injection BP at 2 mg/mL, and 3) to determine the stability of the solutions prepared from hydrocortisone sodium succinate for injection BP over 48 hours period in various environments.

Materials and Methods

The hydrocortisone powder for injection (Solu-Cortef®, Lot No. M43228, Pfizer, Belgium) used as a reference substance was from the Pharmacy Department, Ramathibodi Hospital, Bangkok, Thailand. The generic brand of the present study powder namely hydrocortisone sodium succinate for injection BP 100 mg (Lot No. H06971, H061049, and H061048, Troikaa Pharmaceuticals Ltd., Gujarat, India) were sponsored from the local commercial sources, Pinyo Pharmacy. Polyethylene (PE) 100 mL bags containing 0.9% (w/v) sodium chloride (NSS) were kindly supplied by Thai Otsuka Pharmaceutical Co., Ltd. (Samut Sakhon, Thailand). SWI 10 mL (Pharma Innova Co., Ltd, Pathum Thani, Thailand) was used throughout the study. The present study was approved by the Department of Pharmacy, Faculty of Pharmacy, Mahidol University, Bangkok, Thailand (78.084/167).

Preparation of standard stock solution

A standard stock solution was prepared by dissolving 100 mg of hydrocortisone (Solu-Cortef®) in 2 mL of SWI then measured 0.1 mL of hydrocortisone solution at 50 mg/mL diluted with 4.9 mL of SWI to obtain a standard stock solution of 1 mg/mL. The standard stock solution was used to 1) determine the maximum absorbance wavelength (λmax) for the detection of hydrocortisone, and 2) validate the ultraviolet (UV) spectrophotometric method for hydrocortisone analysis.

Spectrophotometric method

An UV spectroscopic scanning run (200 to 400 nm) was conducted with the reference solution to select the best UV wavelength (λmax) for the detection of hydrocortisone in NSS (UV-2600 UV-Visible spectrophotometer, Shimadzu, Kyoto, Japan). The analyses were carried out using NSS as blank.

UV spectrophotometric method validation

The UV spectrophotometric method was validated by determination of the following parameters, specificity, linearity, limit of detection (LOD) and limit of quantitation (LOQ), precision, accuracy, and robustness following the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) guideline[13].

Specificity: Specificity was evaluated by analyzing solutions containing all the components of the hydrocortisone powder of injection without the drug as placebo. The system response was examined for the presence of interference or overlaps with hydrocortisone responses at 247 nm.

Linearity: Three series using analytical curves, of hydrocortisone standard solutions in five different concentrations of 2.5, 5, 10, 20, and 30 µg/mL, were prepared by the dilution of the stock standard solution in NSS. Absorbance values were measured, in triplicate, at 247 nm. The linearity was evaluated using linear regression analysis by the least-square regression method, which was used to calculate the

correlation coefficient, y-intercept, and slope of the regression line.

LOD and LOQ: LOD and LOQ values were obtained from the calibration curve as 3.3σ/S, and 10σ/S, respectively, where σ is the standard deviation of intercept, and S is the slope of the calibration plot.

Accuracy: The accuracy test was conducted by three replications of three different spiked concentrations. The three hydrocortisone concentrations of 3.5, 10, and 25 μg/mL, were chosen. The recovery percentage (% recovery) was calculated according to equation 1.

$$\% \text{ Recovery} = \frac{\text{Measured concentration}}{\text{Theoretical concentration}} \times 100 \quad (1)$$

Precision: The precision was determined by repeatability (intra-day) and intermediate precision (inter-day). Repeatability was evaluated by assaying three determinations at the three concentrations of 3.5, 10, and 25 μg/mL, within the same day, under the same operating conditions. Intermediate precision was analyzed by comparing the assays using the three different concentrations of 3.5, 10, and 25 μg/mL, during three different days. Precision or repeatability and intermediate precision was expressed as the relative standard deviation (RSD).

Effect of the reconstitution solution type for hydrocortisone preparation

To study the effect of the reconstitution solution type, SWI and NSS were used as solvents. A hydrocortisone vial or hydrocortisone sodium succinate for injection BP 100 mg, was reconstituted with 2 mL of SWI or NSS. Then, it was added to 98 mL bag containing 0.9% (w/v) sodium chloride to give a nominal hydrocortisone concentration of 1 mg/mL.

Preparation of admixtures and stability study protocol

For using SWI as the reconstitution solution, a hydrocortisone vial, hydrocortisone sodium succinate for injection BP 100 mg, was reconstituted with 2 mL of SWI. Then, it was added to 48 mL and 98 mL bags containing solution of isotonic sodium chloride to give a nominal concentration of 2 and 1 mg/mL of hydrocortisone, respectively. In case of using NSS as the reconstitution solution, a hydrocortisone vial was reconstituted with 2 mL of NSS. Then, it was added to 98 mL bag containing 0.9% (w/v) sodium chloride to give a nominal concentration of 1 mg/mL of hydrocortisone. PE bags were stored in three different conditions, which were refrigerator temperature (4±2°C), at ICU temperature (25±3°C), and at hospital room temperature (30±2°C) for 48 hours. Four degrees Celsius was chosen to reflect the temperature of the bags that were likely to be exposed in a hospital refrigerator. ICU (25±3°C) and room temperature (30±2°C) represented the conditions that the bags might be exposed to an environment in ICU and hospital ward, respectively. The physical and chemical stability of all admixtures were evaluated initially and at 4, 8, 12, 24, and 48 hours. The physical stability of admixtures was evaluated regarding color change and the presence of particulate matter. The chemical stability was evaluated in terms of the percentage of remaining hydrocortisone content, which was calculated by equation 2. The acceptance value of % remaining hydrocortisone content of admixture in the range of 90% to 110% was accepted and considered as a chemically stable formulation[14].

$$\% \text{ Remaining hydrocortisone content} = \frac{\text{Analyzed amount of hydrocortisone at each time point}}{\text{Analyzed amount of hydrocortisone at initial time}} \times 100 \quad (2)$$

Statistical analysis

All values were expressed as mean ± standard deviation (SD), and statistically significant differences were evaluated by one-way analysis of variance (ANOVA) followed by a Tukey's honestly significant difference (HSD) test for multiple comparisons using the SPSS Statistics, version 17.0 (SPSS Inc., Chicago, IL, USA). Differences with p-values of less than 0.05 were considered statistically significant.

Results

The present study aimed to assess the stabilities of the hydrocortisone solutions in various reconstituted solutions, concentrations, and temperatures. The UV spectrophotometry is a simple and rapid method to assay hydrocortisone in admixtures. The authors chose SWI as the first dissolving solvent and NSS for the subsequent dilutions as precisely recommended by the Solu-Cortef® package insert[8]. Initially, an UV spectroscopic scanning run allowed selecting the wavelength of 247 nm as the best for the detection of hydrocortisone in both the standard and sample solutions.

Hydrocortisone powder of injection (Solu-Cortef®) contains hydrocortisone equivalent to 100 mg hydrocortisone, 0.8 mg monobasic sodium phosphate anhydrous, and 8.73 mg dibasic sodium phosphate dried. To verify the absence of peak interference from other excipients on the analysis of hydrocortisone in admixtures, the authors conducted the analyses of samples prepared with all the

Table 1. Accuracy result of spectrophotometric method for hydrocortisone analysis

Spiked concentration (µg/mL)	Measured concentration[a] (µg/mL); mean±SD	Recovery[a] (%); mean±SD
3.5	3.46±0.02	99.43±0.60
10	10.03±0.04	100.97±0.36
25	24.92±0.22	100.38±0.87
Average		100.26±0.77

SD=standard deviation

a n=3

Table 2. Repeatability (intra-day) and intermediate precision (inter-day) results of spectrophotometric method for hydrocortisone analysis

Spiked concentration (µg/mL)	Intra-day precision (% RSD)	Inter-day precision (% RSD)
3.5	0.60	1.15
10	0.35	0.65
25	0.87	0.79

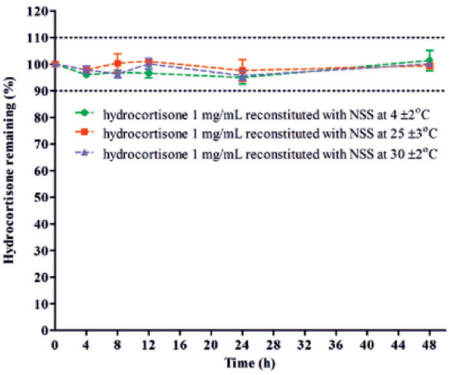

Figure 1. Percent hydrocortisone remaining stored in various temperatures for 48 hours (reconstituted and diluted in NSS) (n=3, mean±SD). The theoretical hydrocortisone concentration was equal to 1 mg/mL.

There was no significant difference (p>0.05) between % hydrocortisone remaining at each time point (at an initial time, 4, 8, 12, 24, and 48 hours) comparing the stability in three storage conditions.

excipients presented in the admixtures, but without the drug, as placebo. Absorption spectra did not show any potential interference of other excipients at 247 nm. A linear relationship was found using the absorbance at 247 nm and the concentration of hydrocortisone in the range of 2.5 to 30 µg/mL. The correlation coefficient was equal to 0.9997, indicating good linearity (r>0.999). The representative linear equation was y = 0.0407x – 0.0068. LOD and LOQ were found as 0.8 and 2.5 µg/mL, respectively. The accuracy was determined from three different concentrations at 3.5, 10, and 25 µg/mL. The % recovery is shown in Table 1. The result discovered that the % recovery was in the range of 99.43% to 100.97%. The intra-day and inter-day RSD values were found to be lower than 2% (Table 2). Therefore, the obtained UV spectroscopic method could be applied for the analyses of hydrocortisone from the admixtures used in the present study.

Since there was only one generic brand of hydrocortisone available in Thailand, the authors focused on the preparation method and the continuous infusion stability of the drug of generic hydrocortisone product, which is hydrocortisone sodium succinate for injection BP 100 mg. The authors found that hydrocortisone reconstituted in SWI, as recommended by Solu-Cortef® manufacturer[9], showed an acceptable labeled amount range (100.28±3.83%). In addition, hydrocortisone directly dissolved in NSS, as in routine clinical practice, showed the acceptable labeled amount range (96.05±1.00%). Therefore, the one-step preparation by directly dissolving hydrocortisone in NSS to a final concentration of 1 mg/mL, could still be recommended. Moreover, the hydrocortisone solutions stored at 4±2°C, 25±3°C, and 30±2°C, representing the temperature at the refrigerator, ICU, and hospital wards, respectively, showed similar percent label amount and the statistical tests were not different among the three ranges of temperatures (p>0.05), as shown in Figure 1 and 2.

Discussion

After the dilution of hydrocortisone solution, the final concentration of 1 mg/mL is the maximum concentration recommended in the package inserts[8,10]. However, a higher final concentration of hydrocortisone solution 2 mg/mL was also prepared in fluid-restricted patients[15]. Therefore, the authors assessed the stability of hydrocortisone admixtures in both concentrations, 1 and 2 mg/mL. Hydrocortisone solution, reconstituted in SWI, and further diluted in NSS to achieve final concentrations of 1 and 2 mg/mL were chemically stable for up to 48 hours in all conditions evaluated (Figure 2). To apply in the clinical practice, intensive care patients are usually faced with high severity of illness, therefore, to restrict fluid in these patients was also an important issue[16-18]. Hydrocortisone has been increasingly used during the early phase of septic shock[19]. A higher concentration of hydrocortisone to reduce fluid intake is also considered. From the stability test in the present study, the reconstitution of hydrocortisone in SWI and further dilution in NSS to achieve a final concentration of 2 mg/mL could be done[8,10].

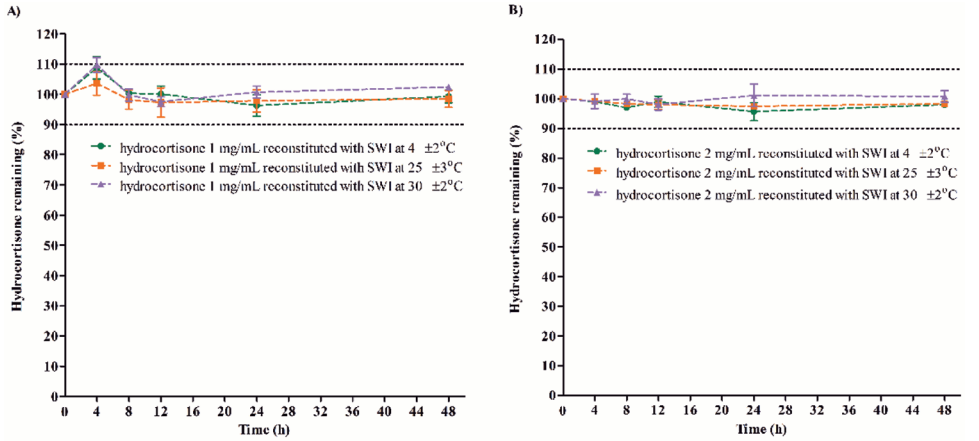

Figure 2. Percent hydrocortisone remaining stored in various temperatures for 48 hours (reconstituted in SWI and diluted in NSS) (n=3, mean±SD). The theoretical hydrocortisone concentration was equal to 1 mg/mL (A) and 2 mg/mL (B).

There was no significant difference (p>0.05) between % hydrocortisone remaining at each time point (at an initial time, 4, 8, 12, 24, and 48 hours) comparing the stability in three storage conditions.

According to Figure 1 and 2, the analyses at initiation and at 4, 8, 12, 24, and 48 hours showed the % hydrocortisone remaining results were within an acceptable range, which was 90% to 110%. In addition, there were no detectable changes of any hydrocortisone solutions from the initial color and odor, and no physical incompatibilities or precipitations being seen. However, there were limitations in the present study. Firstly, there was no stability test for the direct dilution of hydrocortisone in NSS to a final concentration of 2 mg/mL. Since the present study was performed in the period of Solu-Cortef® shortage due to limited import from Pfizer Company, the reference standard for another concentration of 2 mg/mL of one-step preparation of hydrocortisone solution in NSS could not be prepared. Consequently, the authors decided to evaluate only concentrations and temperatures often prepared and used in the authors settings. Secondly, the present study evaluated only one generic brand name of hydrocortisone. Future generic drugs of hydrocortisone should be evaluated if they became available.

Conclusion

Hydrocortisone reconstituted using SWI followed by NSS to obtain final concentrations of 1 and 2 mg/mL or using only NSS to have a final concentration of 1 mg/mL provided an acceptable range of percent hydrocortisone remaining over a period of 48 hours. Therefore, hydrocortisone powder for injection can be prepared by reconstituting in either SWI, as recommended by the original brand's label information, or NSS, as in the authors' routine practice, then further diluted with NSS. Hydrocortisone in 0.9% sodium chloride at a strength equivalent to 1 mg/mL was stable for up to 48 hours when stored in bags at refrigerator temperature (4±2°C), ICU temperature (25±3°C), and room temperature (30±2°C). In conclusion, for the ICU settings in Thailand, the one-time preparation of hydrocortisone 200 mg reconstituted in SWI followed by NSS to obtain 100 mL solution and used for 24 hours is safe to use.

What is already known on this topic?

Manufacturer's recommendation for hydrocortisone states that the reconstitute hydrocortisone solution should be used within four hours.

What this study adds?

In ICU settings, the practice of one-time preparation of hydrocortisone 200 mg in NSS 100 mL and used over 24 hours can be safely applied.

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Conflicts of interest

The authors declare no conflict of interest.

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