Long-term Physicochemical Stability of Concentrated Solutions of Sodium Valproate in Polypropylene Syringes for Administration in the Intensive Care Unit

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Abstract

In some situations, drug solutions in higher concentrations are used in intensive care units. The objective of this study was to evaluate the physicochemical stability of concentrated solutions of valproate sodium in polypropylene syringes during 30 days at 5°C ± 3°C. Five syringes of 40 mL containing 20 mg/mL of sodium valproate in 0.9% sodium chloride were prepared and stored at 5°C ± 3°C during 30 days. Immediately after preparation and periodically during the storage, valproate concentrations were measured by high-performance liquid chromatography. Spectrophotometric absorbance at different wavelengths, pH measurement, and microscopic observations were also performed. All solutions were physically stable during the study period storage at 5°C ± 3°C. No color change, turbidity, precipitation, or opacity at visual observation was noticed. No significant pH variations or optic densities were observed. No crystals were seen by microscopic analysis. Concentrations of valproate remained stable during the period of storage. Solutions of sodium valproate 20 mg/mL in syringes of 0.9 % sodium chloride were physically and chemically stable for at least 30 days when stored in syringes at 5°C ± 3°C. These solutions may be prepared in advance by a centralized intravenous additive service.

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Introduction

Sodium valproate is a broad-spectrum anticonvulsant drug used to control generalized, partial or myoclonic seizures, and other neurological conditions such as acute migraine and psychiatric illnesses.[1] Valproic acid is available in different forms,[2] and its intravenous (IV) formulation is used if the condition of the patient temporarily prevents oral administration of the drug.[3] It shows a great utility in the acute-care setting due to its therapeutic versatility and availability as a safe IV formulation. Given a relatively short half-life, IV valproic acid is ideally suited for continuous infusion administration.[1] In order to reduce the perfusion volume and prevent fluid overload, the intensivists and the obstetricians may prefer to administer a higher valproate IV concentration using an injection syringe.[4-6]

Chemical, in-use stability has been demonstrated for lower concentrations.[3,12,13] Closset et al have demonstrated a physical study during 48 hours,[7] but the chemical stability of high-concentrated injectable solutions remains unknown.

The aim of the study was to determine the physical and chemical stability of a higher concentration of sodium valproate (20 mg/mL) diluted in 0.9% sodium chloride (NaCl) in polypropylene syringes.

Materials and Methods

SOLUTION PREPARATION

Five polypropylene syringes of 40 mL (Lot 1701250P, Per. 12/2021; Becton

Dickinson, Erenbodegem, Belgium) containing 20 mg/mL of sodium valproate (Lot A5622, Per. 10/2020; Sanofi, Diegem, Belgium) in 0.9 % NaCl (Lot 165048131, Per. 11/2019; B Braun, Diegem, Belgium) were prepared under laminar airflow and stored at 5°C ± 3°C during 30 days with protection from light.

STANDARD AND QUALITY-CONTROL SOLUTIONS

A 100-mg/mL standard solution of sodium valproate (Depakine I.V. Sanofi) (Lot A5622, Per: 10/2020; Sanofi) was diluted in purified water to obtain five standard solutions (50 mg/mL, 25 mg/mL, 10 mg/mL, 5 mg/mL, 2.5 mg/mL) and two quality controls (12 mg/mL and 6 mg/mL).

CHROMATOGRAPHIC CONDITIONS

The chromatography was performed on an Alliance Waters high-performance liquid chromatographic (HPLC) system (Model 2695; Waters Association, Milford, Massachusetts) with a photodiode array detector (PDA) (Model 996; Waters Association) and a data acquisition and processing module (Empower 2 Software; Waters Association).

Separation was performed on a reversed-phase column (Lot 0103361961; CORTECS T3 2.7µm, 75 x 4.6mm; Waters Association).

The mobile phase consisted of 40% acetonitrile (Lot 1123601, Per. 07/2019; Biosolve BV, Valkenswaard, The Netherlands), 60% KH_2PO_4 buffer (pH 4) (Ref 1.04873.1000; Merck, Darmstadt, Germany), and H_3PO_4 (Ref 10G090501; VWR International, Fontenay-sous-Bois, France). The HPLC-grade solvent was then filtered through a 0.20-µm membrane filter (Lot R2BA85869; Durapore; Merck). The flow rate was set at 1 mL/min in isocratic mode, the column temperature at 30°C, and the wavelength at 210 nm (PDA detector).

PHYSICAL STABILITY

Physical compatibility was defined as the absence of particulate formation, haze, precipitation, color change, and gas evolution.[8] Throughout the study, particle contamination was searched by visual and microscopical inspection and by optical density and pH measurements.

The samples were visually inspected with the unaided eye in front of a black and white background, and the pellet obtained after centrifugation at 3000 rpm for 8 minutes was observed for crystals with a microscope 10 × (Carl Zeiss, Germany). The optical densities were measured by a spectrophotometer (Genesys 10 UV; Spectronic Unican, New York, New York) at 350 nm, 410 nm, and 550 nm to detect subvisible particles.[9]

The pH of the solutions were measured with a pH-meter (Inolab WTW, Weilhein, Germany) equipped with a glass electrode (Biotrode Hamilton Bonaduz, Switzerland) calibrated with two standard solutions at pH 4 (Lot HC68112575, CertiPur; Merck) and pH 7 (Lot HC68692277, CertiPur; Merck).

HIGH-PERFORMANCE LIQUID CHROMATOGRAPHIC ASSAY

The five standard solutions, the two quality controls, and the samples were all diluted 500-fold, and 50 µL of each were injected into the chromatograph. Results were automatically calculated by interpolation of a four-level calibration curve (linear through zero), performed by the Empower 2 software using peak areas versus standard concentrations.

VALIDATION OF THE METHOD

The within and between-day relative standard deviation (SD) values (n=10) were realized on two concentrations (12 mg/mL and 6 mg/mL). The determination coefficient r^2 was determined by a linear-regression analysis of peak area. Degraded samples of sodium valproate solutions were assayed to confirm separation of the parent drug from its degradation products. Valproate sodium solutions at natural, alkaline, and acidic pH were heated at 100°C during 15 minutes, 30 minutes, 45 minutes, and 60 minutes.

STABILITY STUDY

After preparation, the syringes were stored for 30 days at 5°C ± 3°C. The concentrations of sodium valproate were determined in triplicate for each syringe immediately after preparation and after 1 day, 2 days, 3 days, 4 days, 7 days, 9 days, 11 days, 14 days, 16 days, 18 days, 25 days, 28 days, and 30 days.

STATISTICAL ANALYSIS

As recommended by the U.S. Food and Drug Administration, solutions were considered stable if the lower limit of the 95% one-sided confidence interval of the mean remained superior to 90% of the initial concentration[10] or 95% of the initial concentration when any signs of physical instability existed.[11] The chemical stability of valproate was confirmed with the use of prediction interval in lieu of confidence interval.

Results

VALIDATION OF THE METHOD

The within and between-day relative SD values are shown in TABLE 1 and could be considered as acceptable. The linearity of the assay can be validated from 2.5 mg/mL to 50 mg/mL (determination coefficient r^2 >0.997). No additional peaks from decomposition products were observed (FIGURE 1).

PHYSICAL STABILITY

All solutions were physically stable during the entire storage period: no color

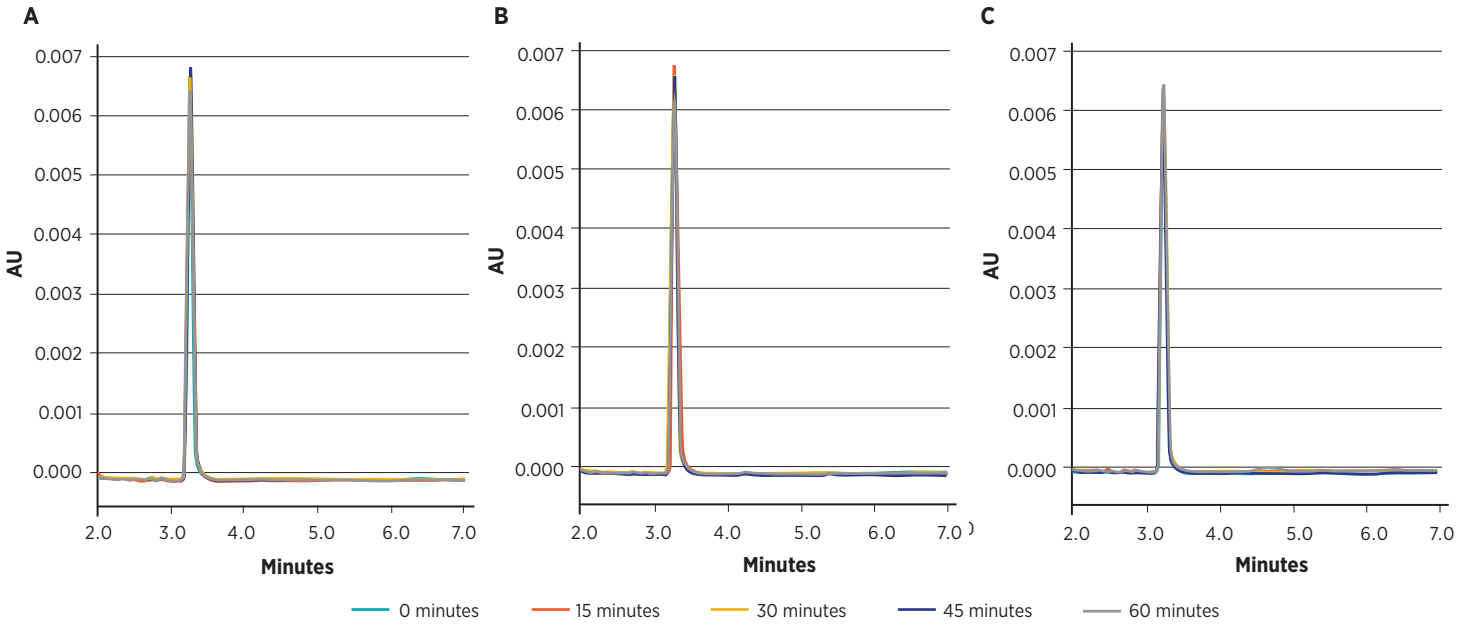
TABLE 1.

INTRA- AND INTER-REPRODUCIBILITY OF THE ASSAY.

CONCENTRATIONS	WITHIN-DAY CV (%) ± Standard Deviation n=10	BETWEEN-DAY CV(%) ± Standard Deviation n=10
6 mg/mL	0.7 ± 0.04	2.6 ± 0.16
12 mg/mL	0.3 ± 0.03	2.1 ± 0.25

FIGURE 1.

DEGRADATION CHROMATOGRAMS AT ALKALINE PH (A), NATURAL PH (B), AND ACIDIC PH (C).



Note: The chromatograms are superimposable for the different times of degradation.

change, turbidity, precipitation or opacity, significant variation in pH values in 0.9% NaCl (mean ± SD: 7.01 ± 0.28; minimum: 4.43 – maximum: 7.49), or optical densities were observed in the solutions. No crystals were seen by microscopic analysis.

CHEMICAL STABILITY

The sodium valproate content remained stable throughout the study (TABLE 2). These data support a chemical stability for at least 30 days. Any additional chromatographic peak did not appear over the entire study period.

Discussion

IV sodium valproate infusions are commonly used in intensive care units (ICUs) and as emergency medicine to treat seizures and other neurological conditions when oral administration is not possible.[1]

The total volume of infusion administered to patients admitted into ICUs is an important clinical parameter[4]; fluid balance and the prevention of fluid overload in many disease states remains a prevalent discussion in this unit.[5] One possible way to avoid such type of adverse effects is to reduce the global volume of infusion by using more concentrated drug solutions.[6]

Torres-Bondia have studied the stability about injectable solutions of lower concentrations of sodium valproate, and it showed

TABLE 2.

STABILITY OF VALPROATE HYDROCHLORIDE IN POLYPROPYLENE SYRINGES.

DAY	MEAN	SD	LL95% CI	LL95% PI
0	100.0	1.7	98.8	93.4
1	98.6	1.9	98.8	93.4
2	99.7	5.5	98.8	93.3
3	97.7	1.3	98.8	93.3
4	101.7	5.0	98.8	93.2
7	97.7	1.7	98.7	93.1
9	101.8	7.3	98.7	93.0
11	99.9	1.4	98.6	92.9
14	104.5	3.2	98.4	92.7
16	98.3	2.5	98.3	92.6
18	97.2	3.6	98.1	92.5
25	95.9	3.6	97.3	92.0
28	98.7	3.2	96.9	91.8
30	98.9	2.9	96.7	91.6

Evolution of mean concentration during storage for five syringes; Initial concentration: 19.6 ± 0.76 mg/mL. CI = confidence interval; LL= lower limits; PI = prediction interval; SD = standard deviation

no decomposition after 6 days of storage at room temperature.[12] However, the Depakine I.V. monograph mentions that in-use storage times would normally not be longer than 24 hours at 2°C to 8°C,[3] but a generic drug mentions that chemical and physical in-use stability after dilution has been demonstrated for seven days at 20°C to 22°C.[13]

The results of our study show that solutions of valproate sodium 20 mg/mL in 0.9 % NaCl are physically and chemically stable for at least 30 days when stored in syringes at 5°C ± 3°C with protection of light. These results allow us to add this solution to the list of our systematic studies of the chemical stability of ready-to-use long-term IV drug solutions[14] and the advance preparation by a centralized intravenous additive service (CIVAS) may be considered.[15]

Chemical stability was evaluated only, and the microbiological aspects were not investigated. However, according to Chapter <797> of the *United States Pharmacopeia*, our preparation can be assimilated to low-risk compounding.[16]

Conclusion

Solutions of valproate sodium 20 mg/mL in 0.9 % NaCl were physically and chemically stable for at least 30 days when stored in syringes at 5°C ± 3°C with protection from light and may be prepared in advance by a CIVAS. This concentration may be particularly useful in ICUs to treat patients and prevent fluid overload in patients.

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