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Study of Ketamine Infusions Extended Stability (SKIES)

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Abstract

Background: Structurally similar to phencyclidine (PCP), ketamine hydrochloride is widely used for treatment in patients with resistant depression, as an anesthetic for surgical procedures, and more. The usage of ketamine

if ketamine is safe to administer if diluted and stored for extended periods of time.

Objective: To evaluate the stability of ketamine hydrochloride infusion in 0.9% normal saline while in controlled ambient conditions.

Methods: A High-Pressure Liquid Chromatography (HPLC) analysis was performed after each time point to determine stability of Ketamine Hydrochloride 500mg diluted in 50ml of normal saline. An infusion was considered stable if the area under the curve was within the USP acceptable range of 95-105%.

Results: All samples remained physically unchanged over time. For all ketamine infusions, after each time point, the HPLC analysis was within 95-105%. Additionally, the analysis showed negative sterility samples and the pH remained stable throughout the study.

Conclusion: This study shows Ketamine HCL is stable in concentrations up to 10mg/ml in polyvinyl chloride (PVC) under ambient conditions for a maximum of 90 days.

Ke d : Ketamine; Ketamine HCL; Ketamine hydrochloride; Ketamine infusion; Extended stability; HPLC

fl d c i

With the spike in hospital admissions due to various indications, the country has seen an increase in the use of ketamine therapy. While sometimes used in severe cases for sedation, ketamine is a popular choice for pain management. Classi ed as a non-barbiturate dissociative anesthetic, the use of ketamine includes indications ranging from depression and pain control to sedation. Typical dosing for ketamine infusions can range with a maximum infusion dosing of up to 15mg/kg/hr in indications such as refractory status epilepticus. With these ranges, ketamine usage can reach elevated levels in a short period of time, and preparing this therapy can be time consuming.

At the time of this study, little information was known for the stability of the drug. Recent searches bring up information on the stability of vials stored in di erent areas, one being an emergency service unit. Other studies have stability information of ketamine with morphine sulfate [1]. However, it is di cult to extrapolate storage information from vials to polyvinyl chloride (PVC) or in combination with other therapies [2].

With new updates to USP <797> taking e ect November 2023, it calls for more robust information for using stability data. High Pressure Liquid Chromatography (HPLC) is becoming more of a standard analysis along with clear details on how the study was performed. Stability information consists of the drug concentration, the storage temperature and, the nal container. e purpose of this study was to provide extended stability information of Ketamine Hydrochloride diluted into a 50ml PVC container and stored at room temperature (22 - 25). An overview of studies that tested Ketamine to compare the di erent beyond use dates (BUD) [3-5] (Table 1).

Me h d

P e a a i fKe a i ea d f i Se -U

All ketamine hydrochloride infusions were prepared in a certi ed ISO-5 primary engineering control area within an ISO-7 clean room. e 50ml saline bags were supplied by ICU Medical [lot: 5639986 exp: 06/30/2023] and the ketamine hydrochloride 500mg/5ml vials from Hikma [lot 21052331/21052332 exp: 11/30/2024] and Hospira [lot: 39015CD/39290CD exp: 01/03/2024]. e 50ml saline bags have a range of over ll from 52 to 62mls. All ketamine vials did not require reconstitution.

A total of 121 samples with a total ll volume of 55 mls were compounded at the hospital in Lancaster, Pennsylvania and sent out to an analytical site in Oklahoma for testing. is was divided into two phases, the rst phase consisted of 44 bags which were compounded on July 22nd, 2022 for system suitable testing which was initiated on July 28th, 2022. In the second phase, 77 bags were compounded on October 27th, 2022, and stability testing was initiated on November 3rd, 2022.

To prepare the infusion, 5mls of the ketamine were drawn up using a 10ml Luer-lock BD syringe [lot: 2033223 exp: 01/31/2027] and injected into the 50ml ICU Medical 0.9% normal saline bag. e nal compounded items were then sent to the testing facility.

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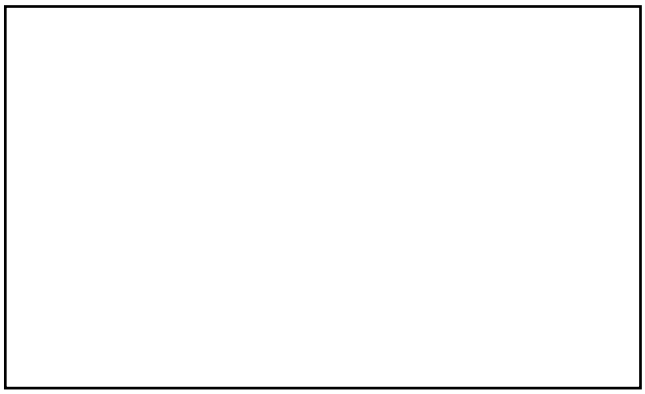
Testing consisted of particle counts, pH, assay, sterility, and endotoxin testing. Samples were evaluated at monthly intervals with time points consisting of 30, 60 and 90 days. Ketamine infusion bags were evaluated under ambient (25°C ± 2°C and 60% RH ± 5%) storage conditions. All testing was done under current good manufacturing practices (cGMP). e stability criteria were deemed acceptable for a range of 95.0-105.0%.

e pH was determined per USP <791> [6]. Endotoxin testing was performed per USP <85> with a speci cation of having no more than



no growth.

ere were no notable changes in appearance, pH, ll volume, or container closure. roughout the study, all 121 ketamine infusion bags conformed to the requirement of staying a clear, colorless solution that is free of visible particles. e pH was determined per USP <791> [6] and shows the di erent variables studied and the concluding results at each time point.

All tested samples depicted pH ranges of 4.0 to 4.4. is falls within the pH range (3.5-5.5) of ketamine which is found to be slightly acidic [2, 10] throughout the study, testing the container closure was vital as we needed to ensure an aseptic barrier was maintained. Testing was conducted via vacuum decay method and no anomalies were reported throughout the duration of the study.

USP<85> sets forth the requirement and limit for endotoxin testing [7] For our study, the infusion samples, when tested, were required to have no more than 1.67 EU/mg of endotoxin. As depicted in (Table 2), throughout the 90 days, the ketamine infusions samples tested below the detectable limits. To ensure no viable microorganisms are present, sterility testing was performed in accordance with USP <71> [8]. Sterility testing for the samples showed no growth. Furthermore, particulate counts were measured per USP <788> requirements [9]. Testing reports no anomalies throughout the duration of the study.

Other studies looked at the usage of ketamine in combination with other narcotics. is was referenced earlier in (Table 1). A er analyzing our data, we set out to illustrate the di erence in stability data of ketamine studies. It is important to note that prior to this study, the only viable data point was ketamine with no combination, and it was using a concentration of 0.6mg/ml [11]. All ketamine studies used PVC containers. From this graph, we can extrapolate how ketamine infusions may have the longest stability and the raw data from this study supports this idea.

Di c i

A er, obtaining the results we set out to compare our data against other studies that both looked at the usage of ketamine in PVC or syringes alone as well as studies that tested stability of ketamine in conjunction with other agents.

Ketamine therapy has grown in popularity in recent years; however, there is limited data on extended stability. With the increased usage of ketamine, the lack of data supporting safe administration of ketamine if diluted and stored for extended stability poses problems to both hospitals (due to shortages) as well as patients. Until the time of this study, ketamine infusions were prepared “on an as needed” basis by pharmacy sta of Lancaster General Health. Infusions were given an arbitrary beyond use date of 24 hours. To the authors’ knowledge and at the time this study was conducted, there are no published extended stability studies for ketamine hydrochloride infusions compounded in 50ml PVC bags.

Li i a i

A limitation to this study was accounting for the pre lled saline bags used during compounding. e 50ml pre lled 0.9% sodium chloride was used and 5 mls of ketamine 100mg/ml was injected ketam

into each container. ese saline bags contain approximation over ll amounts ranging from 52 to 62ml. is, in theory, could adjust the concentration from 10mg/ml to a range from 8.7-7.5 mg/ml.