Does an interaction exist between ketamine hydrochloride and Becton Dickinson syringes?

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ABSTRACT

Introduction An international alert from Becton Dickinson (BD) has noted the possibility of interaction between several molecules and some syringes. The Centralized IntraVenous Additives Service of the institution was using 3 mL BD syringes to store ketamine HCl. This study evaluated the interaction between ketamine and these syringes.

Method A batch of BD syringes produced in Europe and left in quarantine from the day of the international alert has been tested at 22, 29, 36, 43 and 50 days of storage at room temperature. At each time, the pH of the solutions was measured. The solutions were inspected visually and by microscope, and spectrophotometric measurements were performed. The concentrations were measured by a validated ultra-high-performance liquid chromatography-diode array detector.

Results Neither physical change nor pH modification was observed during the study. According to a lower limit of the 95% unilateral CI on the mean >90% of the theoretical concentration, the solutions remain stable for at least 50 days.

Conclusion In our study conditions, ketamine can be stored for at least 50 days without risk of sorption with syringes.

BD—the only vendor available—Plastipak 3 mL syringes were then used.

At that time, the pharmacy department of the institution faced another problem: the shortage of 10 mL phial of ketamine.^{6–9} The major data published in the literature do not mention stability studies of ketamine stored in BD syringes.^{5 10–12} Only one publication to our knowledge indicates stability of ketamine in BD syringes.¹³

The decision was therefore taken to test the possible interaction of ketamine with BD syringes in order to release quarantined batches without any risk for patients.

Aim of the study

The aim of the study is to detect a potential interaction between ketamine HCl and BD syringes.

MATERIALS AND METHODS

Solution preparation

Under aseptic conditions, 3 mL syringes (BD, lot 5143694) were previously prepared, containing 1 mL of non-diluted solution of Ketalar (Pfizer, lot 024093/023093) with a theoretical concentration of 50 mg/mL. This preparation occurred 22 days before the international alert from BD. The incriminated batch of syringes was then left in quarantine at room temperature.

From this batch, fifteen 3 mL syringes containing 1 mL of ketamine HCl were isolated to proceed to the stability test and to detect a possible interaction. The first day (T0) of the study was then day 22 after preparation because of the occurrence of the alert at that time.

In total, 3 of the 15 syringes were frost every seven days starting from day 22 (T0) after preparation, which means at days 22 (T0), 29 (T7), 36 (T14), 43 (T21) and 50 (T28). All frozen syringes were defrosted at the same moment and then tested. This procedure consists of freezing syringes at each time point and defreezing all of them at the time of analysis. This allows us to reduce the technical variability of the chromatographic measures, supported by previous studies.^{4 5}

Assay solutions were prepared using a 200-fold dilution in distilled water, and 200 µL of these solutions were injected into the ultra-high-performance chromatography (UPLC) system for analysis the same day.

Standard solution

Standard solutions were prepared using the commercial solution of ketamine HCl, diluted extemporaneously in distilled water.

Five levels of calibrator were prepared in triplicate using a 100-fold dilution to determine the

INTRODUCTION

The use of ketamine hydrochloride (Ketalar, Pfizer, Brussels, Belgium) is common in the medical department as a general anaesthetic agent and can also be used as an inducer of anaesthesia.¹ Moreover, it is increasingly used for its painkiller effects during anaesthesia.²

The US Food and Drug Administration published an international alert (19 August 2015 and 01 September 2015) to point out the potential interaction between a range of molecules with some batches of Becton Dickinson (BD) 3 mL and 5 mL syringes. This alert was relayed by BD itself. The problem was described as a possible loss of potency for a range of molecules compounded or repackaged and stored in those syringes.

The Centralized IntraVenous Additives Service (CIVAS) of our institution has developed a Terumo 3 mL syringe-filling process with 1 mL of ketamine, required by the intravenous compounding robot³ and validated as chemically stable for 180 days at room temperature.⁴ On the other hand, previous studies showed that frozen solutions of ketamine are stable during storage.^{4 5}

On the day of the international alert, there was a shortage of Terumo 3 mL syringes that forced the pharmacy department to choose another vendor.

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calibration curve (500, 400, 250, 100 and 50 µg/mL of ketamine HCl).

Quality control solution

Three quality control solutions were prepared containing 35, 25 and 15 mg/mL of ketamine HCl, respectively, and diluted 100-fold in distilled water.

Chromatographic analysis

An UPLC system connected to a photodiode array detector (Acquity H-Class, Waters Association, Milford, Massachusetts, USA) and a processing module (Empower 2 Software, Waters Association) were used.

The chromatographic separations were performed on a reversed-phase column charged surface hybrid C18 1.7 µm 2.1×100 mm (Waters Association) with a mobile phase containing 50% of ammonium acetate (Merck, Darmstadt, Germany) 10 mM and 50% of acetonitrile (The Biosolve Company, Lexington, Massachusetts, USA) at pH 5.5.^{4 14}

The flow rate was set at 0.6 mL/min, the column temperature at 40°C and the wavelength at 270 nm.

Validation of the UPLC method

A previous study has demonstrated the long-term stability of ketamine HCl in Terumo syringes at room temperature.⁴ Briefly, that study showed the physical and chemical stability of

ketamine for 180 days of storage at room temperature. The UPLC method was validated: the calibration was linear over the range 50–500 µg/mL with a calculated correlation coefficient (r^2) of 0.994. The limit of detection and quantification were respectively 0.001 and 0.004 mg/mL. The intra-assay and inter-assay precision for 15 and 25 mg/mL solutions were <10%.

The intentional degradation test consisting of heating samples at neutral, acidic and alkaline pH during 15, 30, 45 and 60 min (figure 1) proved the absence of interfering peak with ketamine.

pH determination, spectrophotometric analysis and microscope observation

At each time, solutions were visually inspected in front of black-and-white backgrounds and a centrifuged aliquot was examined by microscope. The pH of each solution was measured with glass electrode PH meter (inoLab, WTW GmbH, Weilheim, Germany) and spectrophotometric measurements were performed at three wavelengths (350, 410 and 550 nm) to exclude the apparition of turbidity.^{14–16} The turbidity is tested in order to detect the presence of subvisible particles.¹⁷

RESULTS

Chemical stability

The chemical analyses by UPLC did not detect any statistically significant decrease of the concentration over time during the

Figure 1 (A) Chromatograph showing degradation test before heating at natural, acidic and alkaline pH. (B) Chromatograph showing degradation test after 60 min heating at natural, acidic and alkaline pH.

study period. The results of mean concentrations and pH measurements are reported in [table 1](#).

The concentration of the solution can be considered stable for at least 50 days. In fact, the concentration can be first considered stable from the day of preparation to day 22 (T0 of the study) because it is close to the theoretical concentration recalculated on the day of preparation. On the other hand, it can be considered stable from T0 (day 22) to T28 (day 50) because the lower limit of the 95% unilateral CI on the mean remains >90% of the theoretical concentration (50 mg/mL) ([figures 2 and 3](#)).

The measurements of pH at each time point did not show any significant change in pH during storage (T0 to T28). Moreover, for the untestable period (day of preparation to day 22), we can rely on the data of a previous study⁴ starting the day of the preparation, which indicates mean pH values similar to ours (mean±SD: 5.17±0.02 vs 5.17±0.05).

Physical stability

There was no colour change, no turbidity or opacity and no precipitation observed in the solutions during the storage at room temperature for 50 days ([table 1](#)). No microaggregates were detected by microscope, neither were they revealed by a change of absorbance.

DISCUSSION

Due to the potential impact on health, US users of Plastipak syringes have reported a decrease in the concentration of certain drugs prepared and repackaged into BD Plastipak syringes.

The decrease in concentration reported for different drugs (atropine, cisatracurium, fentanyl, hydromorphone, methadone, midazolam, morphine, neostigmine, remifentanyl, rocuronium, etc) is caused by interaction with the piston seal used in some of the products and has been reported only after storage in these syringes. The potential risk associated with storage of drugs in syringes and eventual decrease in their concentration depends on the molecule and practice. BD published then an alert with the list of affected lots.

CIVAS is determining to ensure the global management of treatment. They commonly used such types of syringes to provide ready-to-use injectable drugs with acceptable physico-chemical and bacteriological quality.^{18 19}

Our CIVAS currently used a syringe-filling process of Terumo 3-mL syringes with 1 mL of ketamine until the shortage by Terumo, requiring the BD syringe use. Following the BD alert, we had to place our products in quarantine.

In the absence of major data, the decision was therefore taken to test the possible interaction of ketamine with BD syringe in order to release quarantined batches.

The BD alert mentions serial molecules of which only two are known to have a sorptive phenomenon (fentanyl and hydromorphone).²⁰ For others, no mention of sorption has been made to date.

The interactions between drug solutions and containers are of two types: sorption by the container and extraction of some components of the container.

The sorption phenomenon is well known, especially with bags of polyvinyl chloride. The sorption phenomenon is classified as physical incompatibility.²¹ In cases of sorption, the intact

Table 1 Results of UPLC, pH and spectrophotometric measurements over the time

	Ultra-high-performance chromatography concentrations (mg/mL) Mean±SD	pH	Wavelengths		
			350 nm	410 nm	550 nm
T0					
Syringe 1	52.92±0.09	5.07	0.01	0.002	0.001
Syringe 2	52.77±0.66	5.09	0.011	0	0
Syringe 3	51.96±0.13	5.09	0.013	0.001	0
Mean ± SD	52.55±0.52	5.08±0.01	–	–	–
T7					
Syringe 4	51.18±0.13	5.16	0.015	0.001	0
Syringe 5	53.92±1.44	5.16	0.015	0.001	0
Syringe 6	52.84±0.22	5.14	0.015	0.001	0
Mean±SD	52.65±1.38	5.15±0.1	–	–	–
T14					
Syringe 7	54.03±0.28	5.16	0.015	0.001	0
Syringe 8	52.58±0.14	5.2	0.014	0.001	0
Syringe 9	52.58±0.21	5.2	0.015	0.001	0
Mean±SD	53.06±0.84	5.19±0.2	–	–	–
T21					
Syringe 10	46.40±0.37	5.21	0.016	0.002	0
Syringe 11	46.68±0.29	5.18	0.016	0.001	0
Syringe 12	54.67±0.29	5.14	0.016	0.001	0
Mean±SD	49.25±4.70	5.18±0.04	–	–	–
T28					
Syringe 13	46.54±0.39	5.21	0.017	0.001	0
Syringe 14	53.55±0.50	5.24	0.015	0.001	0
Syringe 15	54.24±0.47	5.25	0.015	0.001	0
Mean±SD	51.44±4.26	5.23±0.2	–	–	–
Total mean±SD	51.79±2.86	5.17±0.05	0.01±0.0019	0.0011±0.0005	0.0001±0.0003

Figure 2 Evolution of the concentration of Ketamine over the time.

drug is lost from the solution to be administered by adsorption to the surface or absorption into the matrix of the container material, administration set or filter. As a result of the pioneering work by Moorhatch and Chiou²² and follow-up studies by other researchers, numerous drugs exhibiting sorption have been identified, including amiodarone, carmustine, diazepam dactinomycin, lorazepam, insulin, nitroglycerin, sufentanil, thiopental, vitamin A and warfarin.²⁰

Adsorption to surfaces commonly results from interactions of functional groups within the drug molecule to binding sites on the surfaces. Adsorption occurs on plastic surfaces of bags, administration sets and filters. The adsorption phenomenon becomes important to drug delivery for agents administered in small quantities or low concentration because a clinically relevant amount of the agent may be removed from solution. Drugs administered in larger quantities lose a smaller percentage of the total dose. This difference occurs because of the saturation of binding sites on the container surface. At higher drug concentrations, binding site saturation can occur with only an insignificantly small drug loss from a therapeutic standpoint.

Absorption into the matrix of plastic containers and administration sets, especially those made of polyvinylchloride (PVC), is a source of drug loss from solution for lipid-soluble drugs. The PVC is made pliable and flexible by incorporating substantial amounts of phthalate plasticisers. Lipid-soluble drugs diffuse

from the solution into the plasticiser in the plastic matrix. Plastics that contain little or no phthalate plasticisers, such as polyethylene and polypropylene, do not readily absorb lipid-soluble drugs into the polymer core.

The opposite effect, leaching of phthalate plasticisers into the solution, for example, may also occur. The presence of surface-active agents of large amounts of organic co-solvents in the formulation may enhance leaching of the plasticiser.²¹ The most notable example in recent years concerns the Eprex in pre-filled syringes.²³ The placing on the market of polyolefin infusion bags reduced the problem significantly.²⁴

Leachables may include a variety of chemicals or their derivatives used in the manufacture of single-use components. There is a potential that substances leached from the plastic may affect safety and/or efficacy.²⁵

Relevant incompatibilities between prefilled syringes and drug products include the safety of syringe-based leachables that accumulate in drug products and the ability of leachables to interact with the drug product's ingredients as such interactions can affect safety, efficacy, stability and physical viability.²⁶

The Cramer classification classifies organic chemicals into one of three classes (I, low; II, intermediate; and III, high), reflecting the probability of low, moderate and high toxicity in an explicit way.²⁷

Over 540 extractables were identified and classified following the Cramer decision tree.²⁸ Thirteen extractables had individual risk index values <0.1 mg/day, although four of these had additional risk indices, based on multiple different toxicological end points, >0.1 mg/day. Additionally, approximately 50% of the extractables were classified into Cramer class I (low risk of toxicity) and approximately 35% were in Cramer class III (no basis to assume safety). Lastly, roughly 20% of the extractables triggered either an in vitro or in silico alert for mutagenicity. When Cramer classifications and the mutagenicity alerts were compared with the risk indices, extractables with safety alerts generally had lower risk index values, although the differences in the risk index data distributions, extractables with or without alerts, were small and subtle.²⁸

The objective of our stability study was to exclude a possible interaction between ketamine and BD syringes because of the shortage of ketamine; meanwhile, the only syringes available were the BD ones. The results show that ketamine is not subjected to a sorption phenomenon and allow us to confirm the stability of ketamine in BD syringes for at least 50 days. We cannot extrapolate these results to other molecules.

This means that, for now, without further information from the pharmaceutical company, each molecule must be individually tested at every used concentration and in every used size syringe.^{29 30}

CONCLUSION

The international alert of BD pointing out the possible interaction between 3 mL syringes and a range of molecules occurred when the pharmacy department of the institution faced one problem of ketamine shortage. Yet, one part of the ketamine remaining was already repackaged in such syringes, which were the only available syringes at that time.

We proceeded to chemical and physical analyses in order to ensure the stability of ketamine into such syringes and to be able to release quarantined batches.

The chemical analyses allow us to consider that no loss of ketamine by sorption with the syringe was detected. Moreover, we did not observe any significant change in pH during the analyses.

Figure 3 Evolution of the relative concentration of Ketamine over the time.

The physical study does not show any change in spectrophotometric measurements neither visual nor microscopic inspection. This allows us to conclude the absence of visible or subvisible particles during storage.

Ketamine HCl can thus be stored for at least 50 days in BD syringes from this batch and all following batches as long as their components remain unmodified.

Key messages

What is already known on this subject?

- There is a possible interaction between Becton Dickinson (BD) 3 mL syringes and molecules stored in such syringes.
- One publication indicates stability of ketamine in BD syringes.
- We needed to do this study because we faced a shortage of ketamine; meanwhile, the molecule was already repackaged in 3 mL BD syringes.

What this study adds?

- This study confirms the stability of ketamine in BD 3 mL syringes for 50 days.

Contributors JDH: hospital pharmacy. EG: laboratory technician and medical laboratory. BB: biostatistician, Centre de Biostatistics and medical documentation. JJ: Centre de Biostatistics and medical documentation. LG: medical laboratory.

Competing interests None declared.

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