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Development of ready-to-use ketamine hydrochloride syringes for safe use in post-operative pain

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Abstract

Study objectives: To increase safety in use of ketamine. This would be achieved by introducing a ready-to-use (RTU) intravenous syringe of ketamine hydrochloride, which would be prepared under aseptic conditions in the hospital pharmacy, for post-operative pain.

Methods: The chemical stability of ketamine hydrochloride solution (1 mg/mL) in 0.9% sodium chloride was determined at 4°C, 25°C and 40°C by means of a stability-indicating capillary electrophoresis method. Changes in pH and the presence of non-visible particulate matter were measured throughout the study. Sterility testing was performed to check the integrity of the syringes.

Results: The loss in potency was less than 8% after 12 months at the three temperatures, and no degradation products were detected. The pH values did not change appreciably and the syringe contents remained sterile throughout the study. Each syringe fulfilled all *US Pharmacopeia* criteria in terms of non-visible particles.

Conclusion: RTU syringes of ketamine hydrochloride with a shelf life of one year can be manufactured and supplied by the hospital pharmacy for use in post-operative pain. This product will help reduce the risk of dilution errors and lead to significant economic advantages.

Keywords

Ketamine, drug stability, central intravenous additive service (CIVAS), RTU, analgesia, post-operative pain

Introduction

Ketamine is a general anaesthetic for human and veterinary use. It is often termed a dissociative anaesthetic because unlike with the conventional ones, patients appear detached from their surroundings, and their eyes remain open. The brand name of the hydrochloride salt is Ketalar. Pharmacologically, this drug is very similar to other dissociative anaesthetics, such as phencyclidine. However, ketamine suppresses respiration much less than most other available anaesthetics, and is therefore still used in human medicine as a first-choice anaesthetic for patients with an unknown medical history, e.g. traffic accident victims, in paediatrics and in other types of minor surgery.

Ketamine, like phencyclidine, acts primarily as a non-competitive antagonist of the NMDA receptor, which opens in response to binding of the neurotransmitter glutamate. The NMDA receptor mediates the analgesic effects of ketamine at low doses, which mainly take place in the hippocampal formation and in the prefrontal cortex. Ketamine can be used in small doses as an analgesic, particularly for the treatment of pain associated with movement, neuropathic pain, and to relieve acute pain. When used in small doses, the psychotropic side effects, e.g. hallucinations, are less apparent and more easily managed than those of benzodiazepines.

When used in sub-anaesthetic doses, ketamine causes analgesia without loss of consciousness and can thus be used for the treatment of pain [1-4]. This type of analgesia is

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used in recovery rooms and is usually reserved for patients who are resistant or allergic to opioids. Until recently, at the University Hospitals of Geneva (HUG) [5], ketamine syringes were prepared extemporaneously by anaesthetists or nursing staff. The preparation of a syringe of ketamine consists of a 10-fold dilution of Ketalar from the normal doses used in anaesthesia, i.e. 10 or 50 mg/mL, to a recommended analgesic dose of 1 mg/mL. Preparations under such conditions can introduce dilution errors [6] and/or increase the risk of infection [7-9].

In the past three years, three incidents have occurred in our hospital because of ketamine dilution errors. In December 2003, an anaesthetist forgot a dilution step, resulting in the administration of 60 mg of ketamine instead of the 7 mg prescribed. During the injection, the patient entered a state of deep drowsiness, causing the anaesthetist to realise the mistake and stop the procedure. Fortunately, the patient did not suffer any medical problems as a result of this error. In July 2005, a patient operated on for sigmoidectomy was administered morphine, paracetamol and ketorolac (all intravenously) for analgesia, but continued to experience pain. Ketamine was then prescribed to improve the analgesia: the 42-kg patient was given 45 mg of ketamine. Such a dose is appropriate for anaesthesia and was administered instead of the analgesic dosage, i.e. 4.5 mg. This caused immediate respiratory failure, myosis and an 84% saturation. Resuscitative measures were quickly applied and the patient fortunately recovered without notable consequences other than a prolonged stay in the recovery room. A third incident involving a similar dilution error took place more recently.

The aim of this study was to develop a RTU ketamine syringe for use in post-operative pain, with a long shelf-life and prepared under aseptic and good manufacturing practice (GMP) conditions to improve the safe administration of this drug. The analytical method selected for this work was a capillary electrophoresis coupled to UV detection (CE-UV) method. The choice of this technique was mainly based on its low organic solvent consumption, low capillary cost, the high efficiency and the faster method development compared with liquid chromatography. Moreover, CE-UV is particularly suitable for the analysis of small basic compounds with chromophore groups, such as ketamine.

Material and Methods

Material and chemical products:

Polypropylene syringes: KlerpackTM BD/3325382 Ref KSY15010 Shield Medicare tamper-evident caps: TEC 1000 B (B.Braun, Melsungen, Germany).
Ketamine hydrochloride Ph Eur: (Fagron GmbH Co, Germany), batch number 0505A432, expiry date: 09 2009.
Procaine hydrochloride Ph Eur: (Hänseler, Herisau, Switzerland), batch number 2001070326, expiry date: 04 2007.
Sodium chloride 0.9% solution: (Bischel, Switzerland).
Tris (trishydroxymethylaminomethane) for pH buffer: (Fluka AG, Switzerland).
Phosphorous acid concentrated: (Fluka AG, Switzerland).

Preparation of syringes for the stability study

An injection solution was prepared that contained 0.9% sodium chloride in water and 1 mg/mL of ketamine hydrochloride. The solution was sterilised by filtration (Millipore 20 Millipack Gamma Gold 0.22 μm) and 10 mL was transferred into 10 mL polypropylene syringes under a horizontal laminar-airflow hood in a GMP class B clean room. The syringes were closed using tamper-evident caps and stored at either 4 ± 2°C, 25 ± 2°C or 40 ± 2°C. The solutions were analysed at eight different time points: immediately after preparation (day 0), after day 2 and day 7, and after one, three, five, seven and 12 months.

Capillary electrophoresis (CE) analysis

CE instrumentation and conditions

Our method was adapted from those of Cherkaoui and Veuthey [10]. The CE system was an HP^{3D}-CE apparatus (Agilent, Waldbronn, Germany) equipped with a diode array detector. A CE Chemstation (Agilent Technologies) was used for CE control, data acquisition and handling. Separations were performed in a fused silica capillary (BGB Analytik AG, Böckten, Switzerland) with an inner diameter of 50 μm and a total length of 48.5 cm (distance to UV detector: 40 cm). Experiments were carried out in cationic mode, i.e. anode at the inlet and cathode at the outlet, by applying a constant voltage of 30 kV with an initial ramping of 1 kV/s. The capillary was maintained at 25°C, samples were injected by pressure (50 mbar for 10 s), and UV detection was recorded at 200 nm. The background electrolyte solution was a 50 mM tris-phosphate buffer set at pH 2.5. Before initial use, the capillary was sequentially washed with methanol, 1 M HCl, water and background electrolyte (BGE) for five minutes each. Between analyses, the capillary was flushed with BGE for two minutes.

Validation of the CE method

The capillary electrophoresis method was validated according to French Society of Pharmaceutical Science and Technology guidelines [11] before applying it to the stability study of the RTU ketamine hydrochloride solution. Standard (std) and reconstituted formulation (rf) solutions at five different ketamine hydrochloride concentrations

(60, 80, 100, 120, and 140 µg/mL) were prepared daily and used to test for linearity and accuracy. In addition, six replicate solutions, each one of 100 µg/mL (corresponding to the 10-fold dilution of 100% ketamine hydrochloride present in the formulation), were prepared daily and used to determine the precision of the dilution method. Validation results are summarised in Table 1. Slopes and intercepts were not significantly different between rf and std samples (t tests), and intercepts were not significantly different from 0 (t test). All statistical tests were positive, thus verifying the linearity and accuracy of the method. Furthermore, the tests yielded good determination coefficients (r^2), and adequate recovery and precision values (Table 1). Therefore, the method was accepted for determining ketamine hydrochloride concentrations in RTU intravenous polypropylene syringes.

Stability-indicating method

To rule out possible interference of degradation products during the ketamine hydrochloride determination, 1 mL of a 1 M sodium hydroxide solution and 1 mL of a 1 M hydrochloric acid solution were added to 1 mL of the ketamine hydrochloride mother solution (1 mg/mL). The solutions were heated at 100ºC in a water bath for two hours. In order to check the absence of decomposition products eluting under the analyte peak, the peak height/area ratio was compared at two different detection wavelengths (200 and 220 nm) with a pure ketamine hydrochloride standard.

Sample preparation during the stability study

Stock solutions containing 1 mg/mL of ketamine hydrochloride and 1 mg/mL of procaine hydrochloride (internal standard (IS)) were prepared in distilled water. Standard samples were prepared by diluting the stock solutions in distilled water to obtain a ketamine concentration ranging from 60-140 µg/mL and a procaine concentration of 100 µg/mL. The 1 mg/mL ketamine hydrochloride assay solution (syringe) was diluted in distilled water to obtain a final concentration of 100 µg/mL. As with the calibration samples, procaine hydrochloride was added to the assay solution as an internal standard (final concentration of IS = 100 µg/mL).

Table 1: Validation results for ketamine hydrochloride analysed by capillary electrophoresis coupled to UV detection

	Ketamine hydrochloride
Determination coefficients for std and rf (r^2)	0.997/0.998
Mean recovery and confidence interval*	99.40 ± 0.69%
Intra-day precision (CV)	0.60%
Day-to-day precision (CV)	1.97%

Key: std: standard, rf: reconstituted formulation, r^2: determination coefficients, CV: coefficient of variation, *(N = 15, $t_{(0.05; N-1)}$ = 2.145)

Sterility testing

The tests were performed using a method developed and validated by the quality control laboratory in the HUG pharmacy department [12]. This test is based on the use of standard disposable syringes and classic 0.22 µm membrane filters (fit for aseptic purposes) to retain hypothetical microbes on the membrane. Then a liquid CASO (casein-peptone soymeal-peptone) broth is introduced to the same syringe by the same filter but through the outside filter tip to allow microbe re-suspension and growth. One syringe at each of the three storage temperatures, i.e. 4 ± 2ºC, 25 ± 2ºC and 40 ± 2ºC, was tested for sterility on days 0, 2 and 7, and after one, three, five, seven and 12 months.

Endotoxin (LAL) detection

The tests were performed using the method in the *US Pharmacopeia* for endotoxin detection. One syringe at each of the three storage temperatures was tested for endotoxin at eight different time intervals (see Sterility testing).

pH determination

The pH of the solutions stored at the three different temperatures was measured at each time interval with a glass electrode pH meter (Metrohm model 691, Herisau, Switzerland). Before each measurement, the pH meter was calibrated at pH 4.01 and 7.00.

Non-visible particulate matter

A HIAC Royco counter (SKAN, Allschwil, Switzerland) with a HRLD-50 sensor module (serial number 95080045) was used for the particle count determination. Three runs were carried out, and particle counts were performed at each time interval on 10 mL samples obtained from syringes at the three storage temperatures.

Results

Only the ketamine hydrochloride peak was seen on the electropherograms of the acid and base degraded samples. The ratio values of the analyte peak after base decomposition of a fresh ketamine hydrochloride standard solution were 0.98 and 1.01 at 200 and 220 nm, respectively. For acid decomposition, ratio values were 0.98 and 1.01 at 200 and 220 nm, respectively. These results confirm the purity of the analyte peak. Figure 1 depicts a typical electropherogram of RTU ketamine hydrochloride solution in 0.9% NaCl after 12 months at 25°C. The solutions were considered stable if the drug levels remained higher than 90% of the original concentration at the time of preparation. The results confirmed the stability of these solutions as the ketamine concentration remained above 95% after 12 months at 4°C, 25°C and 40°C (Figure 2). The pH varied slightly during the study for all three temperature regimes by, on average, 0.5 pH units at 4°C, 0.5 pH units at 25°C and 0.4 pH units at 40°C. However, these changes had no effect on the assay results. Similar variations have already been observed during stability studies of several active ingredients in ampoules, and are therefore not expected to be related to leakage from the syringes. The sterility tests and endotoxin tests were found to be negative in all cases. Furthermore, the syringes fulfilled all *US Pharmacopeia* criteria in terms of non-visible particles in all cases: the admixture remained clear without visible particulate matter throughout the study period. The absence of significant

Figure 1: Typical electropherogram of ketamine HCl in NaCl 0.9% at 25°C after 12 months

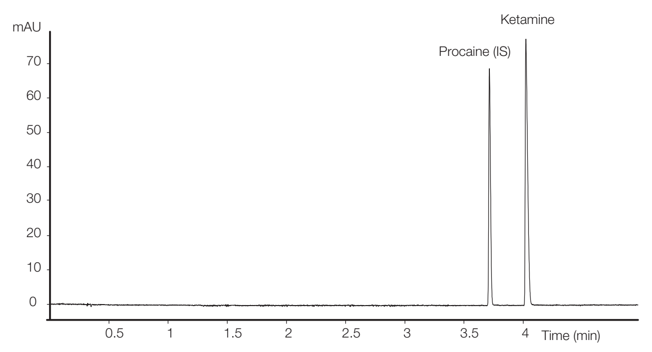
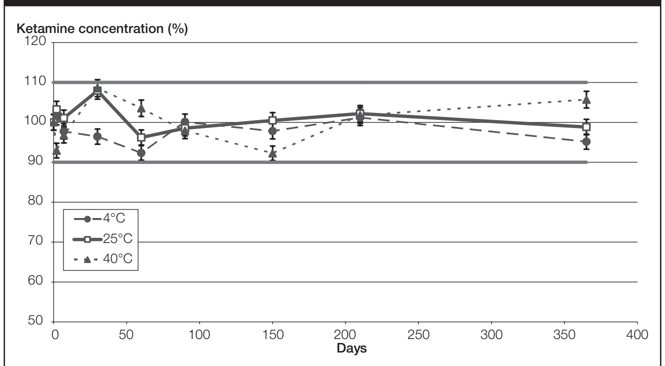


Figure 2: Stability of ketamine HCl 1 mg in 1 mL of a 0.9% sodium chloride solution in polypropylene syringes for a period of 12 months at 4°C, 25°C and 40°C



water loss through the syringe walls was visually verified, by controlling the volume of each tested sample. However, no gravimetric test was carried out.

Discussion

The objective in developing a RTU ketamine syringe was to ensure the best possible safety for the patient. There are two main reasons why RTU ketamine syringes contribute to the safety of the preparation of ketamine for administration in post-operative pain.

First, this method ensures proper aseptic conditions during the preparation of syringes, thereby reducing the risk of microbiological contamination. This contrasts with previous occasions when ketamine syringes were prepared in hospital wards or operating rooms, increasing the risk of contamination. A recent study (unpublished data) examining microbiological contamination in preparations prepared by anaesthetists showed that 0.5% of drugs prepared in the anaesthesiology unit of our hospital were contaminated by microbes, illustrating that asepsis is sometimes compromised. This can occur either during aseptic production and/or during storage, because of a loss of syringe integrity. Microbial contamination is a risk inherent to aseptic production, which must be minimised by strict application of GMPs. These include regular environmental controls, initial and continuing education of operators and process validation through media-fill simulations as shown in a recent study [13]. In our study, syringe integrity was demonstrated by the negative results of the sterility tests.

Second, RTU ketamine syringes prevent dilution errors during ketamine preparation, which was our primary motivation for designing these syringes. The global error rate for drug preparation in anaesthesia is 5% [14]. It has therefore been essential to improve patient safety by reducing errors in ketamine preparation. Our experience has shown that no incidents have been declared after the use of nearly 30,000 RTU syringes (containing atropine, phenylephrine, ephedrine, insulin, isoprenaline or vancomycin) over the past three years in our hospital. Furthermore, since RTU ketamine syringes are prepared by the hospital pharmacy staff, this allows for the production of standardised labels and packaging. A standardised coloured labelling scheme (in agreement with international standards) and a standardised packaging of sealed boxes can both increase the safe use and quality of this drug.

To the best of our knowledge, all previously published stability studies involving ketamine hydrochloride in syringes have been carried out only for periods of up to one month [15], which is too short to ensure suitable batch production and appropriate storage. If ketamine solutions are only stable for this short time period, syringes in both ward stocks and at the bedside can quickly expire, which means that numerous batches would be necessary, increasing the chances of contamination. For these reasons, we carried out a long-term study, and the results showed that the ketamine hydrochloride solution remains stable after 12 months, even under accelerated degradation conditions (40°C).

From an economic standpoint, RTU ketamine syringes are profitable for three main reasons. First, it costs Euros 7 to prepare a 1 mg/mL ketamine syringe using 1mL from a 10 mg/mL Ketalar ampoule, i.e. Euros 6 for the Ketalar ampoule, most of which is discarded, and Euros 2 for the syringe, cap, needle and some NaCl 0.9% solution for dilution. In contrast, a RTU ketamine syringe only costs Euros 3 to prepare. For 2,000 RTU ketamine syringes produced in a year, the savings would amount to Euros 8,000. Second, because RTU ketamine syringes increase safety and decrease the chance of error, their use can decrease the average duration of a patient's hospital stay. This can especially hold true for drugs like ketamine, because a potential overdose can strongly depress vital organs, which would require expensive procedures, such as resuscitation measures, in an intensive care unit. From this viewpoint, the savings are indirect. Third, unused RTU syringes in their original unopened carton boxes can be returned to stock and made available for other patients. This reduces costs because of waste.

Conclusion

Ready-to-use ketamine syringes supplied by the hospital pharmacy and stored in the anaesthesiology unit were found to be stable at room temperature and in accelerated degradation conditions for at least twelve months, with no significant loss in potency. Their long shelf-life allows for an optimised use of production batches. Furthermore, the availability of pre-filled syringes reduces the risks of errors and/or microbiological contamination. The preparation of RTU syringes of ketamine can also provide a means to decrease the overall cost of health care, and save time for hospital staff.

Disclosure

Nothing to disclose.

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