Physicochemical stability of oxycodone-ketamine solutions in polypropylene syringe and polyvinyl chloride bag for patient-controlled analgesia use

Mikaël Daouphars,¹ Charles-Henri Hervouët,² Pierre Bohn,³ Delphine Martin,⁴ Jean Rouvet,¹ Florence Basuyau,¹ Rémi Varin²

¹Department of Pharmacy, Cancer Centre Henri Becquerel, Rouen, France

²Department of Pharmacy, University Hospital Charles Nicolle, Rouen, France

³Nuclear Medicine Department, Cancer Centre Henri Becquerel, Rouen, France

⁴Palliative Care Unit, University Hospital Charles Nicolle, Rouen, France

Correspondence to

Dr Mikaël Daouphars, Department of Pharmacy, Cancer Centre Henri Becquerel, Rouen 76000, France; mikaël.daouphars@chb.unicancer.fr

MD and C-HH contributed equally.

Received 20 April 2016

Revised 31 August 2016

Accepted 19 September 2016

Published Online First

17 October 2016

EAHP Statement 3:
Production and Compounding

ABSTRACT

Objectives The study evaluated the stability of three combinations of oxycodone and ketamine diluted in normal saline (NS) after storage for 7 days at 23°C and exposed to light.

Methods The stability of three mixtures of oxycodone and ketamine (oxycodone 0.4 mg/mL+ketamine 40 mg/mL, oxycodone 10 mg/mL+ketamine 0.1 mg/mL and oxycodone 10 mg/mL+ketamine 40 mg/mL) in NS stored in a polypropylene syringe and a polyvinyl chloride (PVC) bag was studied. The physical characteristics, including pH, colour and precipitation, were evaluated. The samples were analysed in triplicate by a stability-indicating high-performance liquid chromatography method.

Results There was no significant change in the pH values of any solution. No precipitation or change in colour was observed. All formulations maintained more than 95% of the initial concentration of each drug on day 7. No trace of degradation products was detected.

Conclusions Ketamine (0.1–40 mg/mL) combined with oxycodone (0.4–10 mg/mL) is physically compatible and chemically stable for 7 days when diluted with NS, packaged in polypropylene syringe or PVC bag and stored at 23°C.

INTRODUCTION

For patients with cancer, adequate control of chronic pain may necessitate continuous subcutaneous or intravenous infusion of narcotics as morphine. Such a parenteral opioid therapy is often administered by patient-controlled analgesia (PCA).¹ However, high doses of morphine can cause side effects, such as sedation, in some patients facing serious pain.^{2–3} A strategy to manage these adverse effects may require a change to a different strong opioid, such as oxycodone and, should the oxycodone dose turn out to be important, may need an association with another narcotic such as ketamine. Ketamine, a non-competitive N-methyl-D-aspartate receptor antagonist, has been shown effective to relieve neuropathic pain, and to reduce opioid-driven side effects, which has increased its use in combination.⁴

Ketamine has been reported to be stable with morphine^{5–6} and with hydromorphone.^{7–8} Although the stability of oxycodone has been demonstrated,^{9–10} there is a lack of information related to its stability and compatibility in combination with ketamine.

Thus, the objective of this study was to evaluate the stability of oxycodone-ketamine mixed infusion solutions, prepared in 0.9% sodium chloride (NaCl)

and stored for a period of 7 days at room temperature and exposed to light in two different types of container (polypropylene (PP) syringe and polyvinyl chloride (PVC) bag). Three different concentration combinations were studied with ketamine at 0.1 and 40 mg/mL and oxycodone at 0.4 and 10 mg/mL, to cover concentration ranges encountered in clinical practice. The recommendations for stability studies from Bardin *et al* were applied.¹¹

METHODS

Assay validation

Forced degradation

Degradation products of both oxycodone and ketamine were generated by treatment with acid or base and heat, using methods adapted from Walker *et al*.⁷ An oxidative degradation (by hydrogen peroxide 20V) and light degradation (by Ultraviolet B (UVB) lamp) were performed too.

A 1.6 mg/mL solution of oxycodone was mixed with sodium hydroxide 1N and heated at 90°C in a glass vial for 11 hours, protected from light. Each sample neutralised with hydrochloric acid 1N and diluted with high-performance liquid chromatography (HPLC) water was subsequently analysed. The samples were drawn just before incubation and three other times over the 11-hour period. Chromatograms were checked for the appearance of additional peaks and for changes in retention time and peak shape. The ultraviolet (UV) spectral purity (200–365 nm) of the oxycodone peak in chromatograms of a degraded sample and the sample taken at 11 hours was retained to evaluate the final chromatographic system.

A 1.6 mg/mL ketamine solution was mixed with sodium hydroxide 1N and heated at 90°C in a glass vial for 30 hours, protected from light. This sample, neutralised with hydrochloric acid 1N and diluted with HPLC water, was subsequently analysed. Nine mL of 20V hydrogen peroxide was added to 1 mL of the ketamine-hydrochloride stock solution (10 mg/mL). The solution was heated at 100°C for 6 hours. A 1.6 mg/mL ketamine hydrochloride solution was contacted with UVB (312 nm) through a transilluminator TFX-20.MC (Vilber Lourmat, Torcy, France) for 6 hours. The UV spectral purity of the ketamine peak in chromatograms of a degraded sample and the sample taken at time zero was retained for evaluation of the final chromatographic system.

Chromatographic system and separation

Following the forced degradation phase, a chromatographic separation method was developed to

To cite: Daouphars M, Hervouët C-H, Bohn P, *et al*. *Eur J Hosp Pharm* 2018;**25**:214–217.

allow concurrent analysis of oxycodone and ketamine and to ensure the separation of ketamine and oxycodone from their degradation products, adapted from methods used by Walker *et al.*⁷ The mobile phase consisted of a concentration gradient of a mixture phosphate buffer (10 mM, pH 6) and acetonitrile (figure 1). Each sample was traced for 15 min. The mobile phase was pumped through a Discovery HS 25 cm×4.6 mm C18, 5 µm column (Supelco Analytical, Lesquin, France) with an Ultimate 3000 System Controller solvent delivery system (Dionex, Courtaboeuf, France). Oxycodone and ketamine were detected at 220 nm with a photodiode array detector (Thermo Fisher Scientific, Courtaboeuf, France) and chromatograms were recorded directly on a computer with Chromeleon software V6.8 (Dionex).

Validation of the liquid chromatographic method

The liquid chromatographic method was validated according to the guidelines of the French Society of Pharmaceutical Sciences and Techniques (SFSTP) before applying it to the stability study of the mixture of oxycodone and ketamine. The present method was fully validated using a total error approach.^{12–14} The e-nova software V3.0 (Arlenda) was used to compute all validation results and to build the accuracy profiles. On each day, fresh standards of oxycodone and ketamine were prepared and chromatographed to build standard curves, with naloxone 0.4 mg/mL as an internal standard.

Stability study

Sample preparation and storage

Triplicate test solutions of different concentrations of analytes were prepared in a PP syringe (BD Plastipak 60 mL) and in a PVC bag (Easyflex 500 mL, Macopharma) in an ISO Class 5 isolator.

For each test solution, some volume of OxyNorm (glass ampoules 10 mg/mL, 1 mL for injection, Mundipharma, Paris, France) and Ketamine Panpharma (glass ampoules 10 mg/mL,

5 mL for injection, Panpharma, Boulogne-Billancourt, France) were mixed with 0.9% NaCl solution. Concentrations (in mg/mL) of ketamine and oxycodone were respectively: 40/0.4 (test solution 1), 0.1/10 (test solution 2) and 40/10 (test solution 3). All test solutions were stored for 7 days at room temperature ($22.7^{\circ}\text{C} \pm 0.5^{\circ}\text{C}$) and under light exposure.

On the day of analysis, the samples of each test solution were diluted with HPLC water to obtain a concentration of each analyte of 50 µg/mL after addition of the internal standard.

Physical stability

A physicochemical study was conducted on the same test solutions for pH and turbidity evolution. A visual control of each sample against light was conducted every day to determine any change of aspect, colour or limpidity. The pH measurements were recorded on a pH meter (pHennomenal pH 1000L, VWR, Germany) calibrated on each day.

Statistical analysis

Means, SDs and coefficients of variation were calculated for the samples analysed in triplicate. For each study day, the percentage of the initial oxycodone and ketamine concentrations remaining was calculated for each sample. Stability was defined as maintenance of at least 95% of the initial oxycodone and ketamine concentrations. A beyond-use date was determined as the time taken for the concentration, estimated using the lower limit of the 95% CI of the degradation rate, to decline to 95% of the initial (day 0) concentration.

RESULTS

Assay validation

Forced degradation of oxycodone

Approximately 20% of the initial oxycodone concentration remained at the end of the 11-hour forced degradation period at 90°C and acid catalysis, and there was chromatographic evidence of at least three degradation products. These degradation products did not interfere with oxycodone quantification. The alkalisation, oxidation and UVB did not generate any measurable loss of oxycodone. The UV spectral purity of the oxycodone peak remained identical with that of an authentic oxycodone standard.

Forced degradation of ketamine

The acidification did not generate any measurable loss of ketamine over the 30-hour study period. However, with the hydrogen peroxide at 100°C, approximately 30% of the ketamine was lost over the 6-hour study period. The alkalisation generated one degradation product eluted after ketamine. Six degradation products were created by exposure to the UVB lamp for 8 hours. None of these degradation products did interfere with the parent compound. Moreover, the UV spectral purity of the ketamine peaks in the samples remained identical with that of a ketamine standard. The consistency of the UV spectra throughout the degradation phase, and their similarity to authentic standards, and the chromatographic separation of these degradation products from both parent compounds indicated that the stability of ketamine and oxycodone could be determined by this analytical method.

Assay validation for oxycodone and ketamine

The response function¹³ built from the calibration standards was a weighted quadratic regression for oxycodone and ketamine. Our method presents a good linearity for oxycodone and ketamine from 25 to 75 µg/mL. Accuracy¹³ was good for

Figure 1 Typical chromatogram for day 7. Oxycodone eluted at approximately 6.36 min, naloxone (internal standard) at approximately 7.94 min and ketamine at approximately 10.21 min. The degradation products seen in the accelerated degradation studies were not observed. The dotted line represents the percentage of phosphate buffer over time for the mobile phase concentration gradient phosphate buffer/acetonitrile.

each compound as the relative biases were always lower than 0.5%. The precision was obtained by computing the coefficient of variation for repeatability and intermediate precision at each concentration of the validation standards. The results did not exceed 0.7% for repeatability and 0.7% for intermediate precision. The accuracy profile¹⁴ was determined by joining the extremes of the 95% interval, that is, that will contain 95% of the future individual results. The acceptance limits were 2% for all the concentrations. The relative upper and lower b-expectation tolerance intervals did not exceed the acceptance limits for each compound in the dosing range. Detection and quantitation limits for oxycodone and ketamine were 9.3, 25 and 2.3, 25 µg/mL, respectively. These results indicate that oxycodone and ketamine concentrations were measured accurately and reproducibly with acceptable error rates.

Stability study

Over the 7-day period, no significant degradation was observed for oxycodone or ketamine. In all mixed infusion samples, the oxycodone concentration remaining on the last study day was greater than 99.3% of the initial concentration (range: 99.3–100.3%

(figure 2)). For oxycodone, linear regression based on the fastest degradation rate with 95% confidence showed that mixed solutions stored at room temperature would retain 95% of the initial concentration for at least 9.7 days in PP syringes, and at least 25.2 days in PVC bags.

In all mixed infusion samples, the ketamine concentration remaining on the last study day was at least 99.6% of the initial concentration (range: 99.6–101.0% (figure 3)). For ketamine, linear regression based on the fastest degradation rate with 95% confidence showed that mixed solutions stored at room temperature would retain 95% of the initial concentration for at least 13.4 days in PP syringes, and at least 9.8 days in PVC bags.

The degradation products observed in the forced degradation portion of the study were not seen in any chromatogram during the stability study (figure 1).

pH and physical inspection

All solutions were initially clear and colourless and remained so for the duration of the study. No visible particle was observed in any test solution. The initial pH of the solutions was dependent on both the concentration of the drugs and the packaging. The initial pH of test solution 1 in PP syringe and PVC bag was 4.3

Figure 2 Observed concentration of oxycodone (as mean percentage of initial concentration $\pm$ SD) in mixtures with ketamine. Test solutions identified as ketamine (K) mixed with oxycodone (O) concentrations in mg/mL, with blue bars for polypropylene syringes and green bars for polyvinyl chloride bags.

Figure 3 Observed concentration of ketamine (as mean percentage of initial concentration $\pm$ SD) in mixtures with oxycodone. Test solutions identified as ketamine (K) mixed with oxycodone (O) concentrations in mg/mL, with blue bars for polypropylene syringes and green bars for polyvinyl chloride bags.

and 4.0, respectively. The initial pH of test solution 2 in PP syringe and PVC bag was 5.0 and 4.9, respectively. Then, the initial pH of test solution 3 in PP syringe and PVC bag was 4.5 and 4.2, respectively. During storage at room temperature, the pH of all the solutions varied by less 0.5 pH unit.

DISCUSSION

For both ketamine and oxycodone, over the 7-day study period the concentration of all mixed infusion samples remained above 99%. In reports in which no significant change in the concentration of the studied drugs is noticed, it is important to prove that the analytical method is specific and capable of indicating the stability of the compounds of interest. This was demonstrated in the initial part of our work, in which the products from forced degradation could be separated from both ketamine and oxycodone.

Ketamine and oxycodone can be considered as stable drugs. Solutions provided by pharmaceutical companies (10 and 50 mg/mL) and stored at ambient temperature are stable over 1 year. During the forced degradation phase of our work, no measurable loss of ketamine over the 30-hour study period at 90°C was generated by hydrochloric acid 1N. The substantial degradation of ketamine arose in basic solution with heating at 90°C for 30 hours, in oxidative solution with heating at 100°C and by exposure to UVB for 8 hours. Oxycodone is more stable than ketamine because significant degradation of oxycodone occurred only in acidic solution with heating at 90°C for 11 hours.

A report has been published regarding the compatibility of ketamine with several drugs.¹⁵ The chemical compatibility and stability of ketamine with other drugs were studied over a period of at least 7 days with hydromorphone^{7–8} or 91 days with morphine.^{5–6} Similarly, we show the compatibility and stability of ketamine with another strong opioid, oxycodone, in infusion solutions. We studied a range of 0.1–40 mg/mL for ketamine and 0.4–10 mg/mL for oxycodone: therefore, our results are applicable to any mixed infusion solution of ketamine and oxycodone comprised in these ranges, as usually accepted in such stability studies.¹¹ Possible leaching of diethylhexyl phthalate from PVC bags was not assessed in our work. However, this leaching is unlikely to occur as both ketamine-injectable and oxycodone-injectable solutions lack any lipophilic excipient, and no leaching was shown in previous stability studies of ketamine or oxycodone infusion solutions.

In our study, mixed infusion solutions of oxycodone (0.4–10 mg/mL) and ketamine (0.1–40 mg/mL) were physically compatible and chemically stable in all assessed combinations of concentrations when prepared in normal saline, stored in a PP syringe or a PVC bag at 23°C and exposed to light. Consequently, a 7-day expiration date for these mixed infusion solutions can be suggested. Using the mixture of oxycodone and ketamine, PCA may improve pain management. Our study helps to secure the use of this interesting therapeutic alternative in the treatment of chronic pain of cancer origin. The verification of aseptic technique and testing of sterility of finished products should be performed before this extended expiry date is implemented in practice.

Key messages

- ▶ Oxycodone is regularly associated with ketamine for patients with cancer with neuropathic pain.
- ▶ Extended stability of oxycodone has been demonstrated, and ketamine has been reported to be stable with morphine and with hydromorphone.
- ▶ In our study, oxycodone and ketamine were physically compatible and chemically stable for 7 days in all combinations of concentrations and packaging that were tested. Therefore, an extended expiry date can be granted for the mixture of oxycodone and ketamine used in clinical practice, and especially for patient-controlled analgesia.

Contributors MD, C-HH and DM conceived the study. C-HH collected the study data. MD and C-HH analysed the data. MD and C-HH drafted the article. MD, C-HH, PB, DM and JR ensured a critical revision of the article. MD, C-HH, PB, DM, JR, FB and RV finally approved the version to be published.

Competing interests None declared.

Provenance and peer review Not commissioned; externally peer reviewed.

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