ARTICLE

Stability of Ketamine–Propofol Mixtures for Procedural Sedation and Analgesia in the Emergency Department

Ronald F Donnelly, Elaine Willman and Gary Andolfatto

ABSTRACT

Background: The mixture of ketamine and propofol administered together is reportedly an effective agent for procedural sedation and analgesia in the emergency department. However, the physical compatibility and chemical stability of extemporaneous solutions prepared from generic formulations of the drugs are not known.

Objective: To investigate the physical compatibility and chemical stability of 50:50 and 30:70 mixtures of generic ketamine and propofol packaged in polypropylene syringes and stored at room temperature (23°C) with exposure to light.

Methods: Mixtures of ketamine (10 mg/mL) and propofol emulsion (10 mg/mL) were prepared at 50:50 and 30:70 ratios, packaged in capped polypropylene syringes (3 syringes for each mixture), and stored at room temperature with exposure to light. One sample from each syringe was analyzed in duplicate at time 0 and after 1 and 3 h. Physical changes such as pH, separation or cracking of the emulsion, change in colour, and formation of gas were monitored. The chemical stability of each drug was assessed by high-performance liquid chromatography.

Results: Both mixtures of ketamine and propofol were physically compatible during storage for up to 3 h. There were no signs of change in any of the physical parameters during the 3-h study. Each drug retained at least 97% of its original concentration.

Conclusion: Mixtures of ketamine and propofol at 50:50 and 30:70 ratios were physically compatible and chemically stable for up to 3 h when stored in capped polypropylene syringes at room temperature with exposure to light.

Key words: ketamine, propofol emulsion, mixture, compatibility, stability, syringe

RÉSUMÉ

Contexte : L'association kétamine-propofol semble être efficace pour induire une sédation et une analgésie d'intervention aux urgences. Cependant, on ne connaît pas la compatibilité physique et la stabilité chimique des solutions extemporanées de cette association, préparées à partir des génériques de ces deux médicaments.

Objectif : Analyser la compatibilité physique et la stabilité chimique de mélanges 50:50 et 30:70 de kétamine et de propofol génériques conditionnés dans des seringues de polypropylène qui ont été conservées à la température ambiante (23°C) et exposées à la lumière.

Méthodes : Des mélanges de kétamine (10 mg/mL) et de propofol en émulsion (10 mg/mL) ont été préparés dans des rapports de 50:50 et 30:70, puis conditionnés dans des seringues de polypropylène munies d'un capuchon (3 seringues pour chaque mélange) qui ont été entreposées à la température ambiante et exposées à la lumière. Un échantillon de chaque seringue a subi une double analyse au temps 0, puis après 1 et 3 heures. Chaque échantillon a été examiné à la recherche de changements physiques, notamment les changements de pH, la séparation de l'émulsion, le changement de couleur et la formation de gaz. La stabilité chimique de chaque médicament a été déterminée par chromatographie liquide haute performance.

Résultats : Les deux mélanges de kétamine et de propofol étaient physiquement compatibles durant l'entreposage pendant une période allant jusqu'à 3 heures. Aucun signe de changement dans aucun des paramètres physiques n'a été observé pendant la période d'étude de 3 heures. Chaque médicament a conservé au moins 97 % de sa concentration initiale.

Conclusion : Les mélanges de kétamine et de propofol dans un rapport de 50:50 et de 30:70 étaient physiquement et chimiquement stables pendant une période allant jusqu'à 3 heures, lorsqu'ils étaient entreposés dans des seringues de polypropylène munies d'un capuchon, à la température ambiante, et exposées à la lumière.

Mots clés : kétamine, émulsion de propofol, mélange, compatibilité, stabilité, seringue

[Traduction par l'éditeur]

Can J Hosp Pharm 2008;61(6):426–430

INTRODUCTION

Procedural sedation and analgesia for painful procedures is the standard of care in emergency medicine.[1] The ideal agent for procedural sedation and analgesia should be safe and easy to administer, should provide analgesia and amnesia with rapid onset, and should allow quick recovery and cause a minimum of adverse effects. Common agents include propofol, ketamine, fentanyl–midazolam, and etomidate.[1]

Ketamine and generic propofol mixed in the same syringe (so-called "ketofol") has been described as an effective agent for procedural sedation and analgesia in the emergency department.[2] This combination has also been shown to be safe and effective in the operating room[3-5] and the office setting[6] and as an induction agent for rapid-sequence intubation in the emergency department.[7] The combination of ketamine and propofol appears to provide sedation and analgesia with fewer toxic effects than either drug alone and with fewer adverse effects than the combination of propofol and fentanyl.[8]

Future areas of research include the use of different ratios of ketamine and propofol (e.g., 30:70), which may provide greater relaxation while maintaining analgesia and cardiovascular support.

Propofol emulsions are milky white and opaque; when the clear, colourless ketamine solution is added, the admixture takes on the white appearance of the emulsion. Generic propofol emulsions contain soybean oil, glycerin, egg lecithin and water, in addition to 1% propofol. The proprietary brand contains purified egg phosphatide (instead of the egg lecithin) and ethylenediaminetetra-acetic acid (EDTA). The effect of the different formulations on the compatibility and stability of the mixture is not known.

Simulated Y-site administration showed that a 1:1 combination of ketamine and propofol was compatible for 1 h at room temperature.[9] At the time of the current study, there were no reports of the compatibility of ketamine and propofol mixed in a plastic syringe. Therefore, the purpose of the study was to determine the physical compatibility and chemical stability of an extemporaneous mixture of ketamine and propofol when combined in 50:50 and 30:70 proportions and stored in polypropylene syringes at room temperature. Because of the opaque nature of the mixture, precipitation of either compound could not be observed visually; therefore, the concentration changes of both drugs were monitored with high-performance liquid chromatography (HPLC) methods.

METHODS

Sample Preparation

Propofol 1% emulsion (10 mg/mL; Novopharm Ltd, Toronto, Canada, lot 06K325, expiry August 2008) was combined in a ratio of either 50:50 or 70:30 with ketamine solution (10 mg/mL; Sandoz Inc, Boucherville, Quebec, lot 132425). Ten-millilitre samples of the mixture were then transferred to each of three 20-mL polypropylene syringes (Becton Dickinson and Company, Franklin Lakes, New Jersey), which were sealed with syringe caps (Baxa Corporation, Markham, Ontario, reference number 66001). The syringes were stored at room temperature (23°C) with exposure to light.

Physical Evaluation

At each measurement time, the pH was measured, in duplicate, with a calibrated pH meter (Accumet model 25, Fisher Scientific Co, Ottawa, Ontario). Buffer 4 (Fisher Scientific, lot SC6236793, expiry September 30, 2008) and buffer 7 (Fisher Scientific, lot SC7134746, expiry May 12, 2009) were used to calibrate the pH meter initially. The emulsions were observed under illuminated 4 × magnification for signs of separation, cracking, gas production, and colour change against a black background. An unopened vial of propofol 1% emulsion was used as a colour control. Visual inspections were conducted by a single observer (R.F.D.).

HPLC Analysis

The components of the HPLC system consisted of an isocratic pump (model LC-10ATvip, Shimadzu Corp, Tokyo, Japan), a photodiode assay detector (model SPD-M6A, Shimadzu Corp), and an auto injector (model Sil-10AXL, Shimadzu Corp). Each drug was assayed separately.

A previously published method[10] was used for analyzing propofol. A mobile phase containing acetonitrile–methanol–water (55:10:35) was pumped first through a C_{18} guard column (Phenomenex Inc, Torrance, California, catalogue number AJO-4287) and subsequently through a C_{18} analytical column (Luna 5 µm 4.6 mm × 250 mm column; Phenomenex Inc, lot 365391-1) at 1 mL/min. Elution of 50-µL samples was monitored at 270 nm. Thymol (1 mg/mL in water; Sigma Aldrich Co, St Louis, Missouri) was used as an internal standard. The method was determined to be stability-indicating by following forced degradation samples over 146 h. The pH of a 10-mL sample of propofol 1% emulsion (Novopharm Ltd, lot 06K325, expiry August 2008) was adjusted to about 1.2 with concentrated hydrochloric acid (BDH Inc, Toronto, Ontario, lot 120834), while another 10-mL sample was adjusted to a pH of about 12.0 with sodium hydroxide 5N solution (Fisher Scientific, lot SC6135444, expiry May 31, 23008). These degradation solutions were heated to 50°C in a hot water bath, and multiple samples were tested over 146 h. Validation consisted of completion of a standard curve over the concentration range of 0.01 to 0.05 mg/mL, a recovery study, and determination of intraday variance at 0.03 mg/mL. A standard stock solution was prepared by diluting commercially available propofol 1%

emulsion (Novopharm Ltd, Toronto, Ontario, lot 06K326, expiry October 2008) with acetonitrile–methanol–water (55:10:35) to 0.1 mg/mL. The standard stock solution was further diluted to 0.01, 0.02, 0.03, 0.04, and 0.05 mg/mL with acetonitrile–methanol–water (55:10:35) after the addition of 50 µL of internal standard. The recovery solution was prepared in the same manner as the 0.03 mg/mL standard solution except that the initial propofol 1% emulsion was the same lot as that used for the test solutions. Intraday testing was based on 5 replicate injections completed at 3 separate time points (0, 4, and 14 h). Peak purity was assessed through multiple-wavelength (220 and 270 nm) and ultraviolet (UV) spectral analysis (206–350 nm) and visual monitoring of peaks for change in shape.

Analysis of the ketamine used a previously validated HPLC method,[11] which consisted of mobile phase containing 25% acetonitrile, 0.1% phosphoric acid, 85% sodium dodecyl sulfate 1.6 mmol/L, and 0.3% dibutylamine 0.5 mol/L, with final pH adjusted to 5.0. The mobile phase was pumped through a 5-µm, C_{18} 4.6 × 250 mm column (Luna ODS 18(2), Phenomenex Inc, lot 410754) at a rate of 1.0 mL/min. Peaks were monitored at 270 nm after injection of 50-µL samples. Phenol (0.3 mg/mL; Fischer Scientific, lot 026530) was used as the internal standard. The peak purity of ketamine peaks was determined through the use of multiple-wavelength (270 and 254 nm) and UV spectral analysis (200–350 nm). The UV spectral comparison of ketamine peaks from degraded samples with the ketamine reference material was completed, and correlation coefficients were calculated. Intraday variation was calculated from 5 replicate injections at 3 separate time points. Recovery samples were run concurrently on those days. The linearity of all standard curves was assessed by least-squares regression analysis. Samples containing ketamine–propofol were tested using this method to determine if there were any interfering peaks from the propofol or other excipients.

Immediately after preparation of the test mixtures, as described above, a 2-mL sample from each syringe was filtered through a 0.2-µm polytetrafluoroethylene filter (PTFE, Millipore, Carrigtwahill, Ireland, catalogue number SLLG025SS) into clean glass test tubes. The filtered samples were then diluted either 1:50 (for the 50:50 mixture) or 1:100 (for the 30:70 mixture) with 100% acetonitrile, and 300 µL of the resulting solution was combined with 50 µL of internal standard and 650 µL of the mobile phase. These samples were then assayed in duplicate (n = 6). The filtration and analysis steps were repeated at 1 and 3 h after preparation.

The rationale for filtering the solutions was to remove any precipitate that might have formed and that was not visible but that could be redissolved when diluted with 100% acetonitrile. The effect of filtering the mixture were also studied by assaying solutions of propofol both before and after filtration.

Solutions were considered stable if both drug concentrations remained above 90% of the original value.

RESULTS

There was no significant change in the pH of either solution after 1 or 3 h of storage at room temperature and exposure to light. The average pH of the 50:50 mixture was initially 4.98 and was nearly the same (4.99) 3 h later. For the 30:70 mixture, the average pH was 5.16 initially and 5.15 after 3 h of storage. There were no visible signs of separating or cracking of the emulsion after 3 h of storage in polypropylene syringes. Furthermore, there was no apparent change in the white milky colour and no evidence of gas formation after 3 h.

Chromatograms of acidic and alkaline forced-degradation samples showed no interfering peaks after 146 h. Purity testing confirmed that the parent peaks from the degraded samples remained pure. Analysis of the standard curve samples using the propofol method gave a linear correlation (r^2) value of 0.9944, with an accuracy of 102.5% ± 2.2%. Intraday variance was 1.13% over a 14-h period. Both propofol and internal standard peaks in the test samples were pure, as indicated by UV spectral and multiple-wavelength analysis. Peak shape did not change over the course of the study. There was an decrease of approximately 1.5% in concentration after filtering.

Linear correlation for analysis of the standard curve samples using the ketamine method yielded an r^2 value of 0.9999 with an accuracy of 99.7% ± 1.0%. Over a 30-h period, the intraday variance was 0.68%. None of the ketamine degradation peaks interfered with the parent compounds. Purity of the ketamine peak was confirmed by multichannel and UV spectral analysis, as well as peak shape and retention times. Spectra from the parent compounds were highly correlated with those from the reference material (> 0.990).

Chromatography results for samples of the 50:50 mixture with the ketamine method, to check for interfering peaks, are shown in Figure 1. Figure 2 illustrates a typical chromatogram for the 50:50 sample using the propofol assay method. There were no interfering peaks in either case.

Drug concentrations in both combinations remained above 97% after storage at room temperature with exposure to light for up to 3 h (Tables 1 and 2). No new peaks appeared in any of the chromatograms.

DISCUSSION

Previous work[9] describing the compatibility of a mixture of ketamine and propofol in a 50:50 ratio, using a reformulation of the original product containing EDTA, reported that the combination was stable for up to 1 h at room temperature. Another study,[12] which used the original formulation (without EDTA), reported the formation of globules after

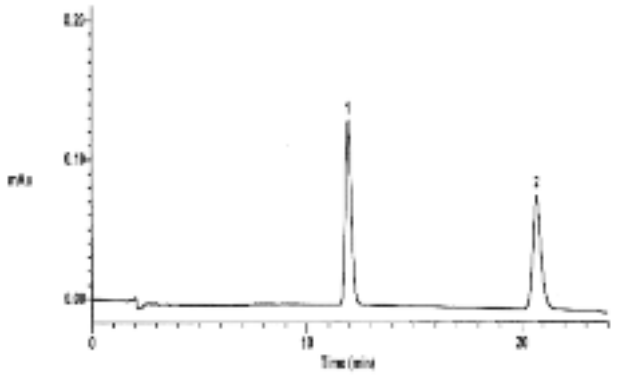

Figure 1. Chromatogram of ketamine in 50:50 mixture of ketamine and propofol. Peak 1 (10.8 min) represents the internal standard, and peak 2 (20.4 min) is the ketamine.

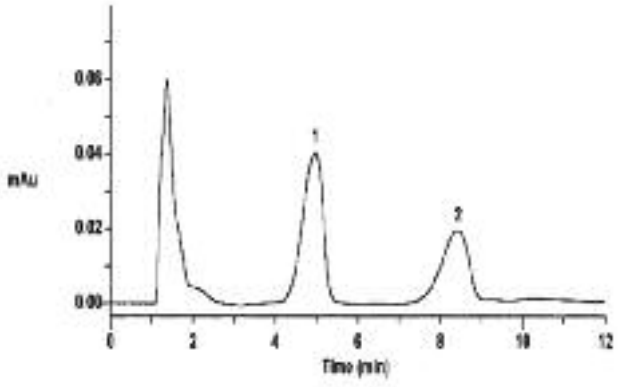

Figure 2. Chromatogram of propofol in 50:50 mixture of ketamine and propofol. Peak 1 (5.2 min) represents the internal standard, and peak 2 (8.4 min) is the propofol.

6 h. The reformulated original brand contains a purified egg phosphatide and EDTA, whereas generic brands contain egg lecithin and no EDTA. The EDTA was added to the formulation to address a problem with microbial contamination of the product; however, the effect of EDTA on stability is unknown. The impact of the difference in purity of the emulsifying agent is also unknown. No compatibility or stability data could be found for any other proportions.

The combination of ketamine and propofol remains a milky white opaque emulsion, which makes it difficult to see the formation of any precipitate. Because of the hydrophobicity of the propofol, a change in the solvent system could cause precipitation of the drug. The pH of the starting solutions differed from the pH of the individual drugs; such a pH shift might cause precipitation. To overcome this visibility problem, other authors have tried dilution,[9] centrifugation of the

Table 1. Stability of 50:50 Mixture of Ketamine (10 mg/mL) and Propofol (10 mg/mL)*

Drug	% of Initial Concentration Remaining		
	Initial concentration (mg/mL)	After 1 h	After 3 h
Ketamine	5.2 ± 0.06	99.5 ± 1.2	99.5 ± 0.7
Propofol	4.9 ± 0.27	97.3 ± 2.8	101.5 ± 1.3

*Stored in polypropylene syringes, at room temperature (23°C), with exposure to light.

Table 2. Stability of 30:70 Mixture of Ketamine (10 mg/mL) and Propofol (10 mg/mL)*

Drug	% of Initial Concentration Remaining		
	Initial concentration (mg/mL)	After 1 h	After 3 h
Ketamine	3.3 ± 0.06	97.8 ± 1.5	99.0 ± 0.9
Propofol	6.8 ± 0.11	101.3 ± 2.3	97.6 ± 1.1

*Stored in polypropylene syringes, at room temperature (23°C), with exposure to light.

emulsion,[9,12] and addition of a dye.[12] We chose to monitor the change in concentration by first filtering the prepared samples to remove any precipitate that might have been present initially and then assaying the resulting solution for a change in concentration. The concentration of the filtered solutions was 1.5% less than that of the unfiltered solutions; this difference is probably insignificant, given the intraday variation of 1.13%. To eliminate any possible filtration effect, all collected samples were filtered just before being assayed.

Combinations of ketamine 10 mg/mL and propofol emulsion 10 mg/mL, in either 50:50 or 30:70 proportions, packaged in polypropylene syringe, were physically and chemically stable for at least 3 h when stored at room temperature with exposure to light. These data indicate that ketamine and propofol can be combined and stored in the same syringe, to be readily available for use as a potent induction agent for rapid-sequence intubations. In particular, the stability data for the ketamine and propofol 30:70 mixture will allow it to be used to induce greater relaxation while maintaining analgesia and cardiovascular support.

References

1. Bahn EL, Holt KR. Procedural sedation and analgesia: a review and new concepts. *Emerg Med Clin North Am* 2005;23(2):503-517.
2. Willman E, Andolfatto G. A prospective evaluation of ketamine/propofol combination ("ketofol") for procedural sedation and analgesia in the emergency department. *Ann Emerg Med* 2007; 49(1):23-30.
3. Frizelle HP, Duranteau J, Samii K. A comparison of propofol with a propofol–ketamine combination for sedation during spinal anesthesia. *Anesth Analg* 1997;84(6):1318-1322.
4. Akin A, Guler G, Esmaoglu A, Bedirli N, Boyaci A. A comparison of fentanyl–propofol with a ketamine–propofol combination for sedation during endometrial biopsy. *J Clin Anesth* 2005;17:187-190.

5. Frey K, Sukhani R, Pawlowski J, Pappas AL, Mikat-Stevens AM, Slogoff S. Propofol versus propofol–ketamine for retrobulbar nerve block: comparison of sedation quality, intraocular pressure changes, and recovery profiles. *Anesth Analg* 1999;89(2):317-321.
6. Mourad M, El-Hamamsy M, Anwar M, Schwarz E. Low dose ketamine reduces sedative doses of propofol during ambulatory trans-oesophageal echocardiography. *Egypt J Anaesth* 2004;20:41-46.
7. Walls R, Murphy MF, Luten RC, Schneider RE. *Manual of emergency airway management*. Philadelphia (PA): Lippincott Williams & Wilkins; 2004.
8. Messenger DW, Murray HE, Dungey PE, VanVlymen J, Sivilotti MLA. Low-dose ketamine versus fentanyl as adjunct analgesic to procedural sedation with propofol: a randomized clinical trial [abstract]. *Can J Emerg Med* 2007;9(3):183.
9. Trissel LA, Gilbert DL, Martinez JF. Compatibility of propofol injectable emulsion with selected drugs during simulated Y-site administration. *Am J Health Syst Pharm* 1997;54(11):1287-1292.
10. Bhatt-Mehta V, Paglia RE, Rosen DA. Stability of propofol with parenteral nutrient solutions during simulated Y-site injection. *Am J Health Syst Pharm* 1995;52(2):192-196.
11. Donnelly RF. Physical compatibility and chemical stability of ketamine and morphine packaged in polypropylene syringes. *Can J Hosp Pharm* 2009. In press.
12. Michaels MR, Stauffer GL, Haas DP. Propofol compatibility with other intravenous drug products: two methods pf evaluating IV emulsion compatibility. *Ann Pharmacother* 1996;30(3):228-232.

Ronald F Donnelly, MSc(Chem), BSc(Pharm), is Product Development Pharmacist, Custom Compounding Area, Department of Pharmacy, The Ottawa Hospital, Ottawa, Ontario.

Elaine Willman, MD, is a resident with the Department of Pathology, University of British Columbia, Vancouver, British Columbia.

Gary Andolfatto, MD, is with the Emergency Department, Lions Gate Hospital, Vancouver, British Columbia.

Address correspondence to:
Ronald F Donnelly
Department of Pharmacy
The Ottawa Hospital
1053 Carling Avenue
Ottawa ON
K1Y 4E9

e-mail: rdonnelly@ottawahospital.on.ca

Acknowledgements
This study was supported by unrestricted grants from Sandoz Canada and Novopharm Canada.