Stability and Compatibility of Hydromorphone and Ketamine in Normal Saline

Scott E. Walker, Shirley Law, and Carlo DeAngelis

ABSTRACT

Objectives: This report presents the results of a 2-part study of hydromorphone and ketamine. The objective of the first part of the study was to assess the physical compatibility over a 24-h period of 12 combinations of hydromorphone and ketamine prepared in syringes by direct mixing of the manufacturers' solutions. The objective of the second part of the study was to evaluate the compatibility and chemical stability of 4 concentration combinations of hydromorphone and ketamine diluted in 0.9% sodium chloride (normal saline [NS]) after storage for 24 days at 4°C or 23°C.

Methods: For the 24-h study, physical compatibility was assessed visually for mixtures of hydromorphone and ketamine at concentrations ranging from 1.0 to 47.5 mg/mL and from 0.5 to 49.0 mg/L, respectively. For the 24-day compatibility and chemical stability study, the following mixtures were assessed: hydromorphone 1.0 mg/mL and ketamine 0.5 mg/mL, hydromorphone 20.0 mg/mL and ketamine 0.5 mg/mL, hydromorphone 1.0 mg/mL and ketamine 20.0 mg/mL, and hydromorphone 20.0 mg/mL and ketamine 20.0 mg/mL. The mixtures were inspected visually, pH was determined, and the concentration of the 2 drugs in each mixture was determined by a stability-indicating liquid chromatographic method.

Results: The concentrations of quality control samples and standards deviated less than 5% on average from known concentrations for both hydromorphone and ketamine. Mean analytical error for replicate samples between and within days was less than 5% for both drugs. For the 24-h physical compatibility study, the 12 mixtures of hydromorphone and ketamine were physically compatible for the duration of the study. For the 24-day chemical stability study, both hydromorphone and ketamine retained greater than 90% of their initial concentrations for the entire study period when stored at either 4°C or 23°C. The pH of all solutions changed by less than 0.2 pH unit over the study period.

Conclusions: A 24-day expiration date is recommended for the following mixtures of hydromorphone and ketamine, diluted in NS and stored in glass at 4°C or 23°C: hydromorphone 1.0 mg/mL and ketamine 0.5 mg/mL, hydromorphone 20.0 mg/mL and ketamine 0.5 mg/mL, hydromorphone 1.0 mg/mL and ketamine 20.0 mg/mL, and hydromorphone 20.0 mg/mL and ketamine 20.0 mg/mL. Mixtures with a wider range of concentrations of the 2 drugs were physically compatible for

RÉSUMÉ

Objectifs : Ce rapport présente les résultats d'une étude de deux parties sur l'hydromorphone et la kétamine. L'objectif de la première partie de l'étude était d'évaluer la compatibilité physique, sur une période de 24 heures, de 12 associations d'hydromorphone avec de la kétamine, préparées dans des seringues en mélangeant directement les solutions du fabricant. L'objectif de la seconde partie était d'évaluer la compatibilité et la stabilité chimique des associations hydromorphone–kétamine, à quatre concentrations différentes, diluées dans du chlorure de sodium à 0,9 % (solution salée [NS]) et entreposées pendant 24 jours à 4 °C ou à 23 °C.

Méthodes : Lors de l'étude de 24 heures, la compatibilité physique a été évaluée par inspection visuelle des mélanges hydromorphone–kétamine aux concentrations variant entre 1,0 et 47,5 mg/mL et entre 0,5 et 49,0 mg/L, respectivement. Lors de l'étude de compatibilité et de stabilité chimique sur 24 jours, les associations suivantes ont été évaluées: hydromorphone 1,0 mg/mL—kétamine 0,5 mg/mL, hydromorphone 20,0 mg/mL–kétamine 0,5 mg/mL, hydromorphone 1,0 mg/mL–kétamine 20,0 mg/mL, et hydromorphone 20,0 mg/mL–kétamine 20,0 mg/mL. Les mélanges ont été inspectés visuellement, le pH a été mesuré et les concentrations des deux médicaments dans chacun des mélanges ont été déterminées au moyen d'une épreuve de stabilité par chromatographie liquide.

Résultats : Les concentrations des étalons et des échantillons de contrôle de la qualité présentaient un écart moyen inférieur à 5 % des concentrations connues pour l'hydromorphone et la kétamine. L'erreur analytique moyenne pour les sous-échantillons entre chaque jour et d'un jour à l'autre était inférieure à 5 % pour les deux médicaments. Pour l'étude de compatibilité physique de 24 heures, les 12 associations hydromorphone–kétamine se sont révélées physiquement compatibles pendant toute la durée de l'étude. Quant à l'étude de stabilité chimique sur 24 jours, l'hydromorphone et la kétamine ont toutes deux, entreposées à des températures de 4 °C ou de 23 °C, conservé plus de 90 % de leurs concentrations initiales pendant toute la durée de l'étude. Le pH de toutes les solutions a varié de moins de 0,2 unités de pH au cours de l'étude.

Conclusions : Il est recommandé de ne pas conserver pendant plus de 24 jours les mélanges suivants d'hydromorphone et de kétamine, dilués dans du NS et entreposées dans des contenants de verre à 4 °C ou à 23 °C : hydromorphone 1,0 mg/mL–

24 h, but expiry dates for mixtures of these drugs at any specific institution should take into account the known contamination rate within the institution's IV additive program.

Key words: hydromorphone, ketamine, compatibility, stability, liquid chromatography

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kétamine 0,5 mg/mL, hydromorphone 20,0 mg/mL–kétamine 0,5 mg/mL, hydromorphone 1,0 mg/mL–kétamine 20,0 mg/mL, et hydromorphone 20,0 mg/mL–kétamine 20,0 mg/mL. Les mélanges des deux médicaments à des concentrations plus étendues étaient physiquement compatibles pendant 24 heures; les dates d'expiration des mélanges de ces deux médicaments doivent tenir compte du taux de contamination bactérienne relatif au programme d'additifs aux solutés intraveineux de chaque établissement.

Mots clés : hydromorphone, kétamine, compatibilité, stabilité, chromatographie liquide

INTRODUCTION

Continuous IV or SC infusion of narcotics to control chronic pain has become an acceptable and, in many centres, common method of treating patients with cancer.[1] In addition to improving the control of chronic pain, the use of portable infusion pumps allows patients to be managed at home.[1] However, in some patients with severe pain, high doses of morphine are associated with side effects, such as tremor. Management of these side effects often necessitates a switch to more potent narcotics, such as hydromorphone and, when the hydromorphone dose also becomes extremely high, addition of a second drug such as ketamine. Ketamine is a noncompetitive *N*-methyl-D-aspartate (NMDA) receptor antagonist introduced recently for analgesia in patients with chronic pain. The role of the NMDA receptor in processing nociceptive input and its ability to improve pain management and reduce opioid-related adverse effects have led to renewed clinical interest in ketamine.[2] Low-dose ketamine is defined as a single dose of less than 2 mg/kg IM or less than 1 mg/kg IV or by epidural. Low-dose ketamine may also be given by continuous IV infusion at a rate of approximately 20 µg/kg per minute.[2]

The stability of ketamine in IV solutions is not well documented. Although this drug is reportedly physically compatible with morphine over a 24-h period,[3] its manufacturer does not provide any information on compatibility or stability with commonly used IV solutions,[4] and no information has been published documenting stability determined with a stability-indicating analytical method. Conversely, the stability of hydromorphone is well documented, both alone[5,6] and in combination with other medications.[7-16] However, no information has been published related to the stability and compatibility of hydromorphone in combination with ketamine.

The objective of the first component of this study was to test the 24-h compatibility of various combinations of hydromorphone and ketamine prepared by direct mixing of the manufacturers' solutions. In the second part of the study, the stability and compatibility of 4 concentration combinations of hydromorphone and ketamine, prepared with 0.9% sodium chloride (normal saline [NS]) as a base solution, were evaluated over a 24-day period at 4°C and 23°C by means of a validated, stability-indicating liquid chromatographic method.

METHODS

Assay Validation

Accelerated Degradation

Degradation products of both hydromorphone and ketamine were generated by treatment with acid or base and heat. A 5.0 mg/mL solution of hydromorphone was adjusted to pH 8.2 with sodium hydroxide and heated at 91°C in a glass vial for 72 h, protected from light. Samples were drawn just before incubation and at 6 other times over the 72-h period. The mobile phase used initially to monitor the degradation of hydromorphone consisted of a mixture of 0.01 mol/L sodium dihydrogen phosphate buffer (65%) and acetonitrile (35%). The mobile phase was pumped at 1 mL/min through an Ultrasphere ODS (octadecylsilane) 25 cm x 4.2 mm C_{18}, 5-µm column (distributed in Canada by Beckman, Mississauga, Ontario) with a 600E System Controller solvent delivery system (Waters Corporation, Mississauga, Ontario). Hydromorphone was detected at 280 nm with a UV6000LP scanning variable-wavelength ultraviolet detector with a 6-nm bandwidth deuterium lamp (Thermo Separation Products, San Jose, California), and chromatograms were recorded directly on computer with ChromQuest software (ThermoQuest Inc., San Jose, California). Over the 72-h period, chromatograms were inspected for the appearance of additional peaks and for changes in retention time and

peak shape. The UV spectral purity (in the range of 200 to 365 nm, as detected with the UV6000LP detector) of the leading edge, middle, and tail of the hydromorphone peak in chromatograms of a degraded sample and the sample taken at time zero was also compared. The sample taken at 72 h was retained to assist in the evaluation of the final chromatographic system.

Two 1.0 mg/mL ketamine samples were adjusted to pH 1.5 and 12.7 with hydrochloric acid and sodium hydroxide, respectively. Each solution was placed in a glass vial and heated at 96°C for 45 h, protected from light. Samples were drawn just before incubation and at 11 other times over the 45-h period. Analytical procedures for processing the samples were the same as for the hydromorphone samples, except that ketamine was detected at 250 nm wavelength. Over the 45-h period chromatograms were inspected for the appearance of additional peaks and for changes in retention time and peak shape. The ultraviolet spectral purity of the leading edge, middle, and tail of the ketamine peak in chromatograms of a degraded sample and the sample taken at time zero was determined as for hydromorphone and compared. The sample taken at 45 h was retained to assist in the evaluation of the final chromatographic system.

Chromatographic System and Separation

After the formation of degradation products, a chromatographic separation method was developed to allow simultaneous analysis of hydromorphone and ketamine and to ensure the separation of ketamine and hydromorphone from their degradation products. The mobile phase consisted of a 50:50 mixture of a phosphate buffer and acetonitrile. The phosphate buffer (pH 9.4) was prepared by dissolving 10.7 g of sodium phosphate dibasic heptahydrate in 4 L of distilled water. The pH of the mixed solution was adjusted to 7.3 with 14.7 mol/L phosphoric acid. Each sample was traced for 12 min. The mobile phase was pumped at 1 mL/min through a 25 cm x 4.2 mm C_{18}, 5-µm column with a 600E System Controller solvent delivery system. Hydromorphone and ketamine were detected at 280 nm with the scanning variable-wavelength ultraviolet detector, and chromatograms were recorded directly on computer with ChromQuest software. The samples containing either hydromorphone and its degradation products or ketamine and its degradation products, as produced through the accelerated degradation (described above), were mixed, and the ultraviolet spectral purity of the 2 drugs relative to fresh, undegraded samples was determined.

Table 1. Final Concentrations of Hydromorphone (Stock Concentration 50 mg/mL) and Ketamine (Stock Concentration 50 or 10 mg/mL) for 24-h Compatibility Study*

Final Concentration (mg/mL)	
Hydromorphone	**Ketamine**
1.0	49.0
1.0	9.8
2.5	47.5
2.5	9.5
5.0	45.0
5.0	9.0
25.0	25.0
25.0	5.0
45.0	5.0
45.0	1.0
47.5	2.5
47.5	0.5

*All solutions remained clear and colourless, without evolution of gas and with no visible evidence of precipitate, at all observation times during the 24-h study period (immediately after mixing and at 2, 18, and 24 h).

Assay Validation, Accuracy, and Reproducibility

The accuracy and reproducibility of the method were tested over a 4-day period. During this period, system suitability criteria (theoretical plates, tailing, and retention time) were also established for each compound of interest to ensure consistency between study days. Each sample was chromatographed in duplicate. Inter- and intra-day reproducibility were assessed by means of the coefficient of variation of the peak area for samples determined in duplicate, and accuracy was determined on the basis of deviations from the known concentration with both standards and quality control samples.

Compatibility Study

In the first part of the study, the physical compatibility of hydromorphone and ketamine was evaluated visually over 24 h. Hydromorphone hydrochloride (Dilaudid-XP for injection, 50 mg/mL, Knoll Pharma Inc., lot 00650037C, expiry November 2000) was mixed directly with ketamine hydrochloride (Ketalar for injection, Parke Davis a division of Warner-Lambert Canada Inc., 10 mg/mL, lot 85147, expiry date January 2000, or 50 mg/mL, lot 79133, expiry date May 1999) to prepare 12 solutions. No saline or other diluent was used in these solutions. The final concentrations ranged from 1.0 to 47.5 mg/mL for hydromorphone and from 0.5 to 49.0 mg/mL for ketamine (Table 1). All samples were stored in glass test tubes and were inspected visually immediately after mixing and at 2, 18, and 24 h. Each sample was observed for the

presence of a precipitate, colour change, change in clarity, and evolution of gas. No chromatographic analysis to verify actual concentration was performed on any of these samples.

Stability Study

Sample Preparation and Storage

The stability and compatibility of combinations of sterile hydromorphone and sterile ketamine in NS, stored for up to 24 days, were determined in the second part of the study. The lot numbers and expiry dates of the drugs were identical with those of the drug samples used for the 24-h physical compatibility study (see previous section). Six 4-mL aliquots, diluted with NS, were prepared for each of 4 concentration combinations, for a total of 24 samples. After mixing, the initial nominal concentrations of hydromorphone and ketamine were as follows: hydromorphone 1.0 mg/mL and ketamine 0.5 mg/mL, hydromorphone 20.0 mg/mL and ketamine 0.5 mg/mL, hydromorphone 1.0 mg/mL and ketamine 20.0 mg/mL, and hydromorphone 20.0 mg/mL and ketamine 20.0 mg/mL. Three samples of each concentration combination were stored at room temperature (23°C), and three were stored in the refrigerator (4°C), all in glass test tubes. One container of each concentration–temperature combination was used for physical inspection and pH determination, and the other 2 were used to determine the concentration of hydromorphone and ketamine by liquid chromatographic analysis on days 0, 2, 3, 15, 17, 21, 22, and 24.

Liquid Chromatographic Analysis

On each study day, fresh standards of hydromorphone and ketamine were prepared and chromatographed to construct standard curves.

A stock solution of hydromorphone was prepared by dissolving an accurately weighed quantity of approximately 100 mg of sterile hydromorphone hydrochloride powder (Hydromorphone Non Sterile Powder, Knoll Pharma Inc., lot L50150094, expiry January 1999) in 2 mL of distilled water. This stock solution of approximately 50 mg/mL was then diluted to prepare 8 standards with concentration 0.5, 1.0, 2.0, 5.0, 10.0, 15.0, 20.0, and 25.0 mg/mL. These 8 standards plus a blank were used to construct a standard curve. Three quality control samples were also prepared, with final nominal concentrations of 3.5, 7.5, and 22.5 mg/mL. One microlitre of each standard, quality control sample, and a blank was directly chromatographed in duplicate on each study day.

A stock solution of ketamine was prepared by dissolving an accurately weighed quantity of approximately 500 mg of ketamine ketamine hydrochloride powder (Sigma Chemical Co., lot 40H0599) in 5 mL of distilled water. This stock solution of approximately 100 mg/mL was then diluted to prepare 9 standards with concentration 0.3, 1.3, 2.5, 5.0, 10.0, 15.0, 20.0, 25.0, and 50.0 mg/mL. These 9 standards plus a blank were used to construct a standard curve. Three quality control samples were also prepared, with final nominal concentrations of 3.1, 12.5, and 37.5 mg/mL. One microlitre of each standard, quality control sample, and a blank was directly chromatographed in duplicate on each study day.

Hydromorphone and ketamine were quantified simultaneously each day with the reverse-phase liquid chromatographic separation described under "Chromatographic System and Separation", above. The average peak area of the 2 replicates from each study sample containing hydromorphone and ketamine were subjected to least-squares linear regression, and the concentrations were interpolated from standard curves and recorded to the nearest 0.001 mg/mL.

pH and Physical Inspection

Physical inspection was performed at the same time as samples were drawn for the chemical analysis. On each of the study days, a 0.5-mL sample of each concentration–temperature combination was drawn and placed in a 10 x 75 mm glass test tube. Each sample was inspected visually for colour and clarity, and the pH was measured. The pH meter (Accumet, model 925, Fisher Scientific, Toronto, Ontario) was equipped with a microprobe glass-body electrode (catalogue no. 13-639-280, Fisher Scientific) and was standardized each day with 2 commercially available buffer solutions. The pH was recorded to the nearest 0.001 of a pH unit but is reported to 0.1 of pH unit.

Data Reduction and Statistical Analysis

Means (± standard deviation) were calculated for analyses completed in duplicate. Analytical error was assessed by the coefficient of variation (standard deviation divided by the mean). Log–linear and linear–linear fits for the data from the accelerated degradation studies (at 91°C and 96°C for hydromorphone and ketamine, respectively) were compared for goodness of fit by the maximum likelihood method of Box and Cox.[17,18]

Mean concentrations for each solution were analyzed by least-squares linear regression to determine the percentage of the initial concentration remaining on the last day of the study. The 95% confidence interval of the slope of concentration versus time was also calculated (SPSS for Windows, release 10.0.5, 1999) to determine the lower limit of the concentration remaining on the last day of the study. Multiple linear regression and analysis of variance (SPSS for Windows, release 10.0.5, 1999) were used to compare differences between temperatures and concentrations for similar analytical tests. The 5% level was used as the *a priori* level of significance, and all references to significance refer to this level.

The concentrations of hydromorphone and ketamine solutions were considered within acceptable limits if they were at least 90% of the initial concentration on any given day. On each study day or at each evaluation period, the samples were visually inspected for colour, clarity, presence of particles, and evolution of gas. If there was no change in colour or clarity and no precipitate was evident, the mixture was considered physically and visually compatible.

RESULTS

Assay Validation

Accelerated Degradation of Hydromorphone

At the end of the 72-h accelerated degradation period approximately 70% of the initial hydromorphone concentration remained, and there was chromatographic evidence of at least one degradation product in the solvent front (Figure 1, chromatogram A). This degradation product was not identified and did not interfere with hydromorphone quantification for either the initial isocratic or final gradient separations. This rate of degradation corresponds to a half-life of about 141 h under these conditions. A similar fit was obtained for both the first-order rate (r value = 0.9903) and the zero-order rate (r = 0.9946). The ultraviolet spectral purity of the hydromorphone peak remained identical with that of an authentic hydromorphone standard. The predictable degradation, the chromatographic separation of hydromorphone from ketamine and from the degradation products of both compounds (Figure 1, chromatogram A), and the ultraviolet spectral homogeneity of a degraded sample and its similarity to that of an authentic standard demonstrated that the stability of hydromorphone could be determined with this analytical method.[19,20]

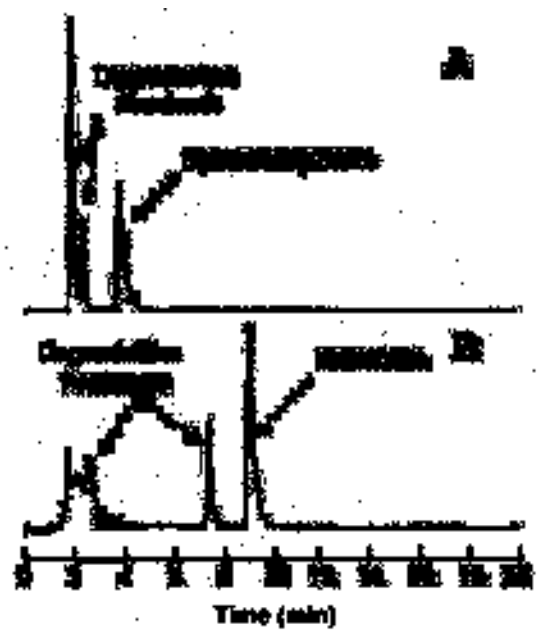

Figure 1. Chromatograms demonstrating the ability of the chromatographic system to completely separate hydromorphone and ketamine from their degradation products and from other sample contaminants. Chromatogram A shows hydromorphone after 72-h incubation at 91°C and pH 8.2. Degradation products eluted within the first 3 min. Chromatogram B shows ketamine after 26-h incubation at 96°C and pH 12.7, when approximately 40% of the original material remained. Degradation products eluted within the first 3 min.

Accelerated Degradation of Ketamine

At pH 1.5, there was no measurable loss of ketamine over the 45-h study period. However, at pH 12.7 and 96°C, approximately 73% of the ketamine was lost over the 45-h study period. This corresponds to a half-life of 24.6 h under these conditions, and these data were better described by a first-order rate (r = 0.9824) than by a zero-order rate (r = 0.9467). A number of degradation products appeared in the solvent front, and at least one other product eluted before ketamine (Figure 1, chromatogram B). None of these degradation products was identified nor did they interfere with ketamine quantification. Furthermore, the ultraviolet spectral purity of the ketamine peak in the sample from pH 12.70 remained identical with that of an authentic ketamine standard. The predictable degradation of ketamine over the first 45 h, the consistency of the ultraviolet spectra throughout the degradation period and their similarity to authentic standards, and the chromatographic separation of these degradation products from both ketamine and

Table 2. Observed Concentration of Hydromorphone (as Mean Percent of Initial Concentration ± Standard Deviation) in Mixtures with Ketamine (in Normal Saline)

	4°C				23°C			
Study Day	**1:0.5***	**20:0.5†**	**1:20‡**	**20:20§**	**1:0.5***	**20:0.5†**	**1:20‡**	**20:20§**
0	100.0 ± 1.1	100.0 ± 0.4	100.0 ± 0.7	100.0 ± 2.2	100.0 ± 0.3	100.0 ± 2.3	100.0 ± 1.2	100.0 ± 0.0
2	101.9 ± 1.3	96.6 ± 1.0	102.4 ± 0.7	97.9 ± 1.1	101.5 ± 0.5	99.0 ± 0.6	103.4 ± 2.8	97.9 ± 0.1
3	101.0 ± 3.6	95.7 ± 1.2	101.4 ± 1.6	95.9 ± 0.4	99.2 ± 0.1	96.4 ± 0.1	101.9 ± 0.8	95.9 ± 1.6
15	98.1 ± 0.3	96.4 ± 2.5	103.8 ± 1.2	99.1 ± 0.9	99.3 ± 2.0	98.7 ± 2.4	101.9 ± 3.3	99.1 ± 2.8
17	97.7 ± 0.1	102.7 ± 0.2	101.7 ± 4.8	104.9 ± 2.1	97.5 ± 2.2	102.7 ± 0.9	104.3 ± 0.2	104.9 ± 0.4
21	100.7 ± 1.5	103.7 ± 0.9	100.7 ± 0.7	101.6 ± 3.2	99.9 ± 2.7	103.6 ± 0.2	100.3 ± 1.7	101.6 ± 0.3
22	99.0 ± 6.1	102.4 ± 0.2	101.1 ± 5.8	103.5 ± 2.5	102.0 ± 0.5	102.3 ± 1.0	94.8 ± 1.3	103.5 ± 0.1
24	101.1 ± 3.7	104.8 ± 0.2	97.9 ± 1.3	103.9 ± 1.3	99.3 ± 3.3	105.1 ± 2.5	100.8 ± 3.1	103.9 ± 0.9
CV (%)¶	1.5	3.6	1.7	2.9	1.4	2.9	2.9	3.1
% remaining on day 24 by linear regression**	98.9	107.2	98.9	104.6	99.8	105.8	97.8	106.4
Lower limit of 95% CI for % remaining on day 24††	95.3	101.2	95.3	99.4	96.2	102.7	91.1	101.3

CV = coefficient of variation, CI = confidence interval.
*Nominal concentrations: hydromorphone 1.0 mg/mL and ketamine 0.5 mg/mL. Actual initial concentration of hydromorphone was 0.8 and 0.8 mg/mL in the samples stored at 4°C and 23°C, respectively.
†Nominal concentrations: hydromorphone 20.0 mg/mL and ketamine 0.5 mg/mL. Actual initial concentration of hydromorphone was 21.7 and 21.3 mg/mL in the samples stored at 4°C and 23°C, respectively.
‡Nominal concentrations: hydromorphone 1.0 mg/mL and ketamine 20.0 mg/mL. Actual initial concentration of hydromorphone was 0.8 and 0.8 mg/mL in the samples stored at 4°C and 23°C, respectively.
§Nominal concentrations: hydromorphone 20.0 mg/mL and ketamine 20.0 mg/mL. Actual initial concentration of hydromorphone was 21.3 and 21.0 mg/mL in the samples stored at 4°C and 23°C, respectively.
¶Variability of estimated concentrations over the study period, expressed as CV.
**Calculated from concentrations on day 0 and day 24 as determined by linear regression, according to the following formula: [100 x (concentration on day 24 / concentration on day 0)].
††Calculated from lower limit of 95% CI of the slope of the concentration–time relation, determined by linear regression, according to the following formula: 100 x [concentration on day 0 – (24 x 95% CI of slope)] / regression-determined intercept for day 0.

hydromorphone indicated that the stability of ketamine could be determined by this analytical method.[19,20]

Assay Validation for Hydromorphone

Analysis of duplicate hydromorphone quality control samples at concentrations of 3.5, 7.5, and 22.5 mg/mL demonstrated that concentrations were estimated with mean deviations of less than 10%, 6%, and 5%, respectively, between observed and known concentrations. The coefficient of variation on duplicate analysis was approximately 1.5% within days and less than 2.5% between days. Accuracy and reproducibility for standards were similar. Average deviations from the known concentrations were within 5.0%, and replicate error (as coefficient of variation) of duplicate analysis within days ranged from 0.1% to 4.3% and averaged less than 1.5% for all concentrations. These analyses indicated that the hydromorphone concentrations were measured accurately and reproducibly and that differences of 10% or more could be confidently detected with acceptable error rates.[21,22]

Assay Validation for Ketamine

Analysis of duplicate ketamine quality control samples at concentrations of 3.1, 12.5, and 37.5 mg/mL demonstrated that concentrations were estimated with mean deviations of 6.5%, 0.8% and 0.5%, respectively. The coefficient of variation on duplicate analysis averaged 2.1% within days and less than 5.7% between days. Accuracy and reproducibility for standards were similar. Average deviations from the known concentrations were within 2.8%, and replicate error (as coefficient of variation) of duplicate analysis within days ranged from 0.1% to 3.2% and averaged approximately 1% for all concentrations. These analyses indicated that the ketamine concentrations were measured accurately and reproducibly and that differences of 10% or more could be confidently detected with acceptable error rates.[21,22]

Compatibility and Stability Studies

At room temperature over a 24-h period, mixtures of hydromorphone (1.0 to 47.5 mg/mL) and ketamine

Table 3. Observed Concentration of Ketamine (as Mean Percent of Initial Concentration ± Standard Deviation) in Mixtures with Hydromorphone (in Normal Saline)

	4°C				23°C			
Study Day	**1:0.5***	**20:0.5†**	**1:20‡**	**20:20§**	**1:0.5***	**20:0.5†**	**1:20‡**	**20:20§**
0	100.0 ± 0.0	100.0 ± 0.0	100.0 ± 0.0	10.00 ± 0.0	100.0 ± 0.0	100.00 ± 0.0	100.0 ± 0.0	100.0 ± 0.0
2	99.5 ± 2.4	97.3 ± 0.3	98.6 ± 0.4	99.1 ± 1.0	98.1 ± 0.9	98.4 ± 2.7	99.4 ± 0.4	101.0 ± 0.2
3	102.7 ± 0.5	98.6 ± 5.0	102.3 ± 0.0	103.5 ± 2.1	100.7 ± 2.3	99.0 ± 1.0	101.0 ± 0.0	103.6 ± 1.7
15	102.2 ± 1.0	100.7 ± 1.9	99.8 ± 0.0	98.0 ± 0.9	99.4 ± 2.9	104.4 ± 0.0	98.6 ± 1.3	99.0 ± 3.1
17	104.4 ± 1.8	104.2 ± 1.4	96.3 ± 0.5	100.3 ± 4.1	103.9 ± 0.3	105.5 ± 0.2	95.4 ± 1.6	102.0 ± 0.4
21	101.0 ± 3.9	102.5 ± 1.9	98.2 ± 0.4	101.0 ± 1.8	105.1 ± 0.1	103.4 ± 0.4	97.3 ± 0.4	103.3 ± 0.0
22	103.6 ± 0.9	95.6 ± 1.5	95.5 ± 0.3	96.4 ± 0.9	104.8 ± 0.6	100.9 ± 4.7	95.7 ± 0.9	101.5 ± 0.6
24	102.2 ± 1.5	104.1 ± 0.4	96.2 ± 0.3	94.9 ± 2.5	103.7 ± 1.2	102.3 ± 4.0	95.9 ± 0.3	99.8 ± 1.2
CV (%)¶	1.5	3.6	1.7	2.9	1.4	2.9	2.9	3.1
% remaining on day 24 by linear regression**	96.8	99.5	97.8	96.3	95.8	98.4	94.2	97.4
Lower limit of 95% CI for % remaining on day 24††	99.0	101.6	96.2	99.5	92.1	93.0	90.9	95.9

CV = coefficient of variation, CI = confidence interval.
*Nominal concentrations: hydromorphone 1.0 mg/mL and ketamine 0.5 mg/mL. Actual initial concentration of ketamine was 0.4 and 0.4 mg/mL in the samples stored at 4°C and 23°C, respectively.
†Nominal concentrations: hydromorphone 20.0 mg/mL and ketamine 0.5 mg/mL. Actual initial concentration of ketamine was 0.4 and 0.3 mg/mL in the samples stored at 4°C and 23°C, respectively.
‡Nominal concentrations: hydromorphone 1.0 mg/mL and ketamine 20.0 mg/mL. Actual initial concentration of ketamine was 19.8 and 19.9 mg/mL in the samples stored at 4°C and 23°C, respectively.
§Nominal concentrations: hydromorphone 20.0 mg/mL and ketamine 20.0 mg/mL. Actual initial concentration of ketamine was 19.8 and 19.1 mg/mL in the samples stored at 4°C and 23°C, respectively.
¶Variability of estimated concentrations over the study period, expressed as CV.
**Calculated from concentrations on day 0 and day 24 as determined by linear regression, according to the following formula: [100 x (concentration on day 24 / concentration on day 0)].
††Calculated from lower limit of 95% CI of the slope of the concentration–time relation, as determined by linear regression, according to the following formula: 100 x [concentration on day 0 – (24 x 95% CI of slope)] / regression-determined intercept for day 0.

(0.5 to 49.0 mg/mL) were physically compatible. No precipitate was visible in any of the samples, no colour changes occurred, and no gas was produced on mixing.

During the 24-day stability study, neither hydromorphone nor ketamine degraded to a measurable extent. In all of the samples, the hydromorphone concentration remaining on the last study day was at least 97.8% of the initial concentration (range 97.8% to 107.2 [Table 2]), and the lower limit of the 95% confidence interval of the percent remaining on day 24 was at least 91.1% for all combinations of temperature and nominal concentration. The ketamine concentration remaining on the last study day in all samples was greater than 94.2% of the initial concentration (range 94.2% to 99.5 [Table 3]), and the lower limit of the 95% confidence interval of the percent remaining on day 24 was at least 90.9% for all combinations of temperature and nominal concentration. Inspection of chromatograms during the stability study showed no significant amounts of the degradation products that were observed during the accelerated portion of the study (Figure 2). The chromatograms did demonstrate some evidence of impurities; however, these contaminants did not change in concentration throughout the study period.

Multiple linear regression showed a significant association between hydromorphone concentration and study day ($p = 0.0006$). This association represented a difference of less than 2.4% over the course of the study and is not clinically important. All other factors (nominal ketamine concentration [$p = 0.3744$], nominal hydromorphone concentration [$p = 0.8724$], and temperature [$p = 0.6050$]) were not significantly associated with changes in the hydromorphone concentration.

Multiple linear regression also showed a significant association between ketamine concentration and nominal concentrations of ketamine ($p < 0.0001$) and hydromorphone ($p = 0.0424$). However, the associations represented differences of –2.2% and 1.0% in the nominal concentrations of ketamine and hydromorphone, respectively, and were not clinically important. Study day ($p = 0.2754$) and temperature ($p = 0.0949$) were not significantly associated with changes in the ketamine concentration.

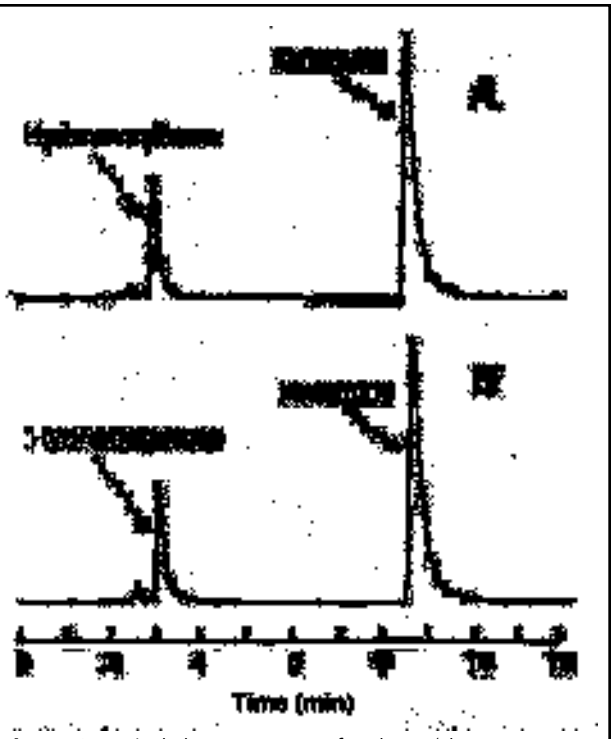

Figure 2. Typical chromatograms for day 0 (chromatogram A) and day 24 (chromatogram B) in the 24-day chemical stability study. Hydromorphone eluted at approximately 3.2 min and ketamine at approximately 8.7 min. The degradation products seen in the accelerated studies were not observed.

pH and Physical Inspection

All solutions remained clear and colourless. The pH of a 20 mg/mL hydromorphone hydrochloride (Dilaudid-XP for injection) solution in 0.9% sodium chloride was 4.0, and the pH of a 20 mg/mL ketamine hydrochloride (Ketalar for injection) solution in 0.9% sodium chloride was 4.7. The pH of the mixtures appeared to be primarily dependent on hydromorphone concentration. Solutions containing 1.0 mg/mL of hydromorphone had a mean initial pH of 4.29 ± 0.04, ranging from 4.25 to 4.33, whereas solutions containing 20.0 mg/mL of hydromorphone had a mean initial pH of 3.85 ± 0.02, ranging from 3.83 to 3.87. The pH of all hydromorphone and ketamine combinations remained unchanged over the study period. In no sample was the change in pH over the 24-day study period greater than 0.2 of a pH unit. All samples at all concentrations and both temperatures were initially clear and colourless and remained so for the entire study period.

DISCUSSION

Least-squares linear regression of the change in concentration with time showed that there was, on average, less than a 5% change in concentration for both ketamine and hydromorphone over the 24-day study period. In studies in which no change in the concentration of the drugs of interest can be detected, assurance that the analytical method is specific for the compound of interest is important. This assurance was obtained in the first component of the study, in which the products of accelerated degradation could be separated from both hydromorphone and ketamine. The ability to separate the degradation products of both drugs from both hydromorphone and ketamine and the ultraviolet spectral purity of hydromorphone and ketamine indicated that this method was specific for the compounds of interest and was therefore capable of indicating their stability.

Ketamine is a reasonably stable compound. Label expiry dates indicate that the solutions supplied by the manufacturer (10 and 50 mg/mL) are stable for more than 1 year when stored at room temperature. During the accelerated degradation portion of the study, less than 10% of the initial ketamine concentration was lost at pH 1.5 during incubation at 96°C over 45 h. The current study has also demonstrated chemical compatibility over 24 days for mixtures of ketamine with hydromorphone stored at room temperature and at 4°C. Significant degradation of ketamine occurred only in basic solution (pH 12.7) with heating at 96°C for 45 h.

A number of reports have been published concerning the compatibility of hydromorphone with various drugs.[7-16] Although some studies only assessed physical compatibility visually over no more than 4 h,[5,9-11] the chemical compatibility and stability of hydromorphone with other drugs over a period of at least 24 h has been reported for minocycline,[11] tetracycline,[11] dexamethasone,[12] phenytoin,[13] phenobarbital,[13] diazepam,[13] cloxacillin in 5% dextrose in distilled water,[13] dimenhydrinate,[15] heparin,[15] and high concentrations of cefazolin.[11,13] Hydromorphone has been observed to inactivate hyaluronidase, so although the combination was judged physically compatible, it is chemically unstable.[14] A similar observation has been made for the combination of hydromorphone and lorazepam: the stability of lorazepam in the presence of hydromorphone limits the expiry date of the mixture.[15]

In this study, hydromorphone and ketamine were physically compatible and chemically stable in all combinations of concentration and temperature that were tested. Therefore, a 24-day expiration date is recommended for the following mixtures, prepared in NS and stored in glass at 4°C or 23°C: hydromorphone 1.0 mg/mL and ketamine 0.5 mg/mL, hydromorphone

20.0 mg/mL and ketamine 0.5 mg/mL, hydromorphone 1.0 mg/mL and ketamine 20.0 mg/mL, and hydromorphone 20.0 mg/mL and ketamine 20.0 mg/mL. Mixtures with a wider range of concentrations of the 2 drugs were physically compatible over a 24-h period when stored in glass, but expiry dates for mixtures of these drugs at any specific institution should take into account the known contamination rate within the institution's IV additive program.

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Scott E. Walker, MScPhm, FCSHP, is Co-ordinator, Research and Quality Control, Department of Pharmacy and Division of Pharmacology, Sunnybrook and Women's College Health Sciences Centre, and Associate Professor, Faculty of Pharmacy, University of Toronto, Toronto, Ontario. He is also the Editor of *CJHP*.

Shirley Law, DipPharmTech, is a Research Assistant in Quality Control, Department of Pharmacy, Sunnybrook and Women's College Health Sciences Centre, Toronto, Ontario.

Carlo DeAngelis, PharmD, is Co-ordinator, Oncology, Department of Pharmacy and Division of Pharmacology, Sunnybrook and Women's College Health Sciences Centre, and Assistant Professor, Faculty of Pharmacy, University of Toronto, Toronto, Ontario.

Address correspondence to:
Scott Walker
Department of Pharmacy
Sunnybrook and Women's College Health Sciences Centre
2075 Bayview Avenue
Toronto ON
M4N 3M5

e-mail: scott.walker@schsc.on.ca

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