ARTICLE

Stability of Oxycodone Hydrochloride for Injection in Dextrose and Saline Solutions

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ABSTRACT

Objective: To evaluate the stability, over 35 days of storage at either 4°C or 24°C, of oxycodone hydrochloride 100 mg/mL in sterile water, stored in plastic syringes, and oxycodone hydrochloride 5 and 50 mg/mL in 0.9% sodium chloride (NS) or 5% dextrose in water (D5W), stored in polyvinylchloride (PVC) minibags.

Methods: Oxycodone concentrations were determined on each of the study days (days 0, 1, 3, 7, 10, 14, 17, 21, 28, and 35) by means of a validated, stability-indicating, liquid chromatographic method with ultraviolet detection at 230 nm. Physical inspections and pH determinations were also completed on each study day.

Results: Validation demonstrated that oxycodone could be quantified accurately and reproducibly. Maximum deviation from the nominal concentration of standards and quality control samples was less than 5%. Intra- and inter-day analytical reproducibility error, as measured by coefficient of variation, averaged less than 3%. During the study period, the concentrations observed in all study samples retained at least 95.6% of their initial concentrations. All solutions remained clear and colourless, with no visible precipitate, for the duration of the study. The pH of all solutions varied by less than 0.1 pH unit.

Conclusions: Oxycodone hydrochloride 100 mg/mL in sterile water retained more than 95% of the initial concentration during 35 days of storage in plastic syringes at 4°C and 24°C. Furthermore, 5 and 50 mg/mL solutions prepared by diluting the 100 mg/mL solution in NS or D5W retained more than 95% of their initial drug concentration during 35 days of storage in PVC minibags at 4°C and 24°C.

Key words: oxycodone hydrochloride, stability, drug storage

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RÉSUMÉ

Objectif : Évaluer la stabilité des solutions de chlorhydrate d'oxycodone entreposées pendant 35 jours à 4 °C ou 24 °C, mélangées d'une part dans de l'eau stérile, à des concentrations de 100 mg/mL, et conservées dans des seringues de plastique, et d'autre part, dans du chlorure de sodium à 0,9 % (NS) ou de dextrose à 5 % dans l'eau (D5W), à des concentrations de 5 et de 50 mg/mL, et conservées dans des minisacs de chlorure de polyvinyle (PVC).

Méthodes : Les concentrations d'oxycodone ont été mesurées à chaque jour de l'étude (jours 0, 1, 3, 7, 10, 14, 17, 21, 28 et 35) au moyen d'une épreuve validé de stabilité par chromatographie liquide à haute pression et par détecteur ultraviolet à 230 nm. L'inspection visuelle et la mesure du pH ont aussi été réalisées à chaque jour de l'étude.

Résultats : Les tests de validation ont démontré que les résultats pouvaient être mesurés quantitativement de façon précise et reproductible. L'écart maximal à partir des concentrations nominales des échantillons standards et de contrôle de la qualité était moins de 5 %. L'erreur de la reproductibilité analytique pour une même journée et d'une journée à l'autre, telle que mesurée par le coefficient de variation, était en moyenne de moins de 3 %. Tous les échantillons à l'étude pendant toute la période de l'étude ont conservé au moins 95,6 % leurs concentrations initiales. Toutes les solutions étaient claires et incolores, sans aucun précipité visible, pendant toute la durée de l'étude. Le pH de toutes les solutions a varié par moins de 0,1.

Conclusions : Les solutions de chlorhydrate d'oxycodone préparées à raison de 100 mg/mL d'eau stérile ont retenu plus de 95 % de leurs concentrations initiales durant les 35 jours qu'elles ont été conservées dans des seringues de plastique, à 4 °C et à 24 °C. De plus, les solutions à 5 et à 50 mg/mL, préparées en diluant la solution de 100 mg/mL dans du NS ou du D5W, ont retenu plus de 95 % de leurs concentrations initiales pendant les 35 jours qu'elles ont été conservées dans des minisacs de PVC, à 4 °C et à 24 °C.

Mots clés : chlorhydrate d'oxycodone, stabilité, entreposage

INTRODUCTION

Pain control continues to present major challenges in the care of cancer patients. Most patients eventually need a strong opioid to control their pain. Often, one opioid must be changed to another because of dose escalation or toxic effects. Although the oral route is preferred, many patients are unable to take medication orally in the final stages of the disease. The reliable portable infusion devices[1] now available can deliver continuous IV or SC infusions of narcotics to control chronic pain.[2] In addition to improving the control of chronic pain, the use of portable infusion pumps allows patients to be managed at home.[2] As a result, the availability of a parenteral formulation is useful and knowledge of its stability critical.

Oxycodone is a strong opioid that has been available for more than 70 years. However, a parenteral formulation (10 mg/mL) is available only in Finland (brand name Oxanest, manufactured by Leiras, Turku, Finland), although it will soon be available in the United Kingdom (through Napp Pharmaceutical Group, Cambridge, England) and Germany (through Mundipharma, Limburg, Germany). SC use of parenteral oxycodone solutions has been reported from Finland,[3] Australia,[4] and Canada,[5] and often these solutions are prepared extemporaneously by the hospital pharmacy department. At Grey Nuns Community Hospital and Health Centre in Edmonton, Alberta, approximately 30% of patients receiving parenteral opioids have been rotated intermittently to oxycodone (at concentrations between 5 and 50 mg/mL) because of opioid toxicity.[5,6] A parenteral formulation of 100 mg/mL oxycodone is prepared by diluting oxycodone hydrochloride in sterile water. This solution is then cold filtered with a 0.22-µm bacterial filter in a laminar flow hood. The concentrated stock solution is filtered again each time it is used to prepare the required dilutions, which are stored in polyvinylchloride (PVC) bags.[6] However, there are no published reports describing oxycodone stability.

The objective of this investigation was to study the stability of oxycodone in both normal saline (NS) and 5% dextrose in water (D5W) by means of a valid,[7] stability-indicating[8,9] method after storage over a period of 35 days at both 4°C and 24°C.

METHODS

Assay Validation

Following the development of a chromatographic system for oxycodone (see below), the suitability of this method as a stability-indicating assay was tested by analyzing samples of oxycodone that had been subjected to accelerated degradation. Oxycodone hydrochloride 20 mg (pharmaceutical grade; Medisca Pharmaceutique Inc., Montreal, Quebec, lot 26252, expiry June 2003) was dissolved in 20 mL of distilled water to make a 1 mg/mL stock solution (pH 6.7). A 6-mL aliquot of the stock solution was placed in a sterile 10-mL multidose vial (Bayer Corporation, Spokane, Washington, lot 5233). A second 6-mL aliquot of the stock solution was adjusted to pH 1.7 with 4 mol/L hydrochloric acid, and a third 6-mL aliquot was adjusted to pH 12.8 with 10 mol/L sodium hydroxide. Each of the pH-adjusted solutions was placed in a sterile 10-mL multidose vial and incubated in a water bath at 93°C for 1258 min, protected from light. Samples were drawn just before incubation and after 9, 35, 90, 140, 184, 253, and 1258 min of incubation. The samples were chromatographed, and the chromatograms were inspected for the appearance of additional peaks. The oxycodone peak was compared between samples for changes in concentration, retention time, and peak shape.

After this first phase of evaluation and validation, the accuracy and reproducibility of standard curves were tested over 5 days, and system suitability criteria (theoretical plates, tailing, and retention time) were developed to ensure consistent chromatographic performance on each study day.

Stability Study

On study day 0, oxycodone hydrochloride 22 g (pharmaceutical grade; Medisca Pharmaceutique Inc., Montreal, Quebec, lot 26252, expiry June 2003) was accurately weighed and diluted with sufficient sterile water to make 220 mL of a 100 mg/mL stock solution. To prepare solutions with concentration 5 mg/mL, 5 mL of the 100 mg/mL stock solution was diluted with 95 mL of either NS or D5W. To prepare solutions with concentration 50 mg/mL, 65 mL of the 100 mg/mL stock solution was diluted with 65 mL of either NS or D5W. Aliquots of each test solution were stored, at 4°C or 24°C, in 25-mL PVC minibags (Baxter Corporation, Toronto, Ontario, lots W9C04C1 and W9C11C1, expiry December 1999 and September 2000, respectively). Four minibags of each concentration–diluent–temperature combination (32 minibags in total) were prepared and stored under the specified storage conditions for the duration of the study. Three of these minibags were designated for liquid chromatographic analysis and one for pH determination and physical inspection.

The remaining 80 mL of the original 100 mg/mL stock solution was divided evenly among eight sterile 20-mL polypropylene syringes with a black rubber plunger (Becton, Dickinson and Company, Franklin Lakes, New Jersey, lot 9138476) and closed with a latex-free, luer-tip cap (Becton, Dickinson and Company). Four of these syringes were stored in a refrigerator at 4°C, protected from light, and the other 4 syringes were stored at 24°C, exposed to fluorescent light.

Samples were drawn from each study mixture immediately after mixing and after 1, 3, 7, 10, 14, 17, 21, 28, and 35 days of storage for the chemical and physical stability tests.

pH Determination

On each of the 10 study days, a sample was drawn from one bag or one syringe of each concentration–diluent–temperature combination and the pH measured to the nearest 0.001 of a pH unit (with an Accumet model 925 pH meter, Fisher Scientific, Ottawa, Ontario). The pH meter was standardized on each study day with commercially available buffer solutions (pH 7.00 and 4.00; Fisher Scientific).

Physical Inspection

On each of the 10 study days, the samples drawn for pH determination were inspected visually against both a black and a white background for particulate matter; colour and clarity were also assessed. Samples for physical inspection were placed in clear glass test tubes to avoid misinterpretations related to the opacity of the storage containers.

Oxycodone Analysis

On each study day, a standard curve was prepared as follows. A 325-mg sample of oxycodone hydrochloride (pharmaceutical grade; Medisca Pharmaceutique Inc., Montreal, Quebec, lot 26252, expiry June 2003) was accurately weighed and dissolved in distilled water to make 5 mL of stock solution. Samples of this stock solution were further diluted with distilled water to obtain standards with final nominal concentrations of 0.3, 1.3, 2.5, 5.0, 7.5, and 10 mg/mL. These standards, along with a blank, were used to construct the standard curve. Four-microlitre aliquots of each standard were chromatographed in duplicate. In addition, 3 quality control samples of oxycodone (concentrations 0.6, 3.1, and 6.3 mg/mL) were chromatographed in duplicate each day. The concentrations of the quality control samples were determined and compared with the known concentrations. Intra-day and inter-day errors were assessed by the coefficients of variation of the peak areas of both quality control samples and standards.

On each of the 10 study days, samples drawn from each storage container were assayed in duplicate for oxycodone content. Samples with a nominal concentration of 5 mg/mL were injected directly into the liquid chromatographic system, whereas samples with a nominal concentration of 50 or 100 mg/mL were diluted 1 in 10 or 1 in 20, respectively, with sterile water before injection. The injection volume for all solutions was 4 µL.

Chromatographic Analysis

The liquid chromatographic system consisted of a solvent delivery pump (model 600E, Waters Corporation, Toronto, Ontario), which pumped a mixture of 17% acetonitrile (EM Science, distributed by VWR Canlab, Toronto, Ontario, catalogue no. AX0142-1) and 83% potassium phosphate monobasic 0.05 mol/L (Fisher Scientific, catalogue no. P286). On each of the 10 study days, the strength of the mobile phase was adjusted to achieve a retention time for oxycodone between 390 and 420 s through a 25 cm x 4.6 mm reversed-phase Ultrasphere ODS (octadecylsilane) C18, 5-µm column (distributed in Canada by Beckman, Toronto, Ontario) at 1.0 mL/min. Samples were injected onto the chromatography column with an Ultra WISP 712 autoinjector (Waters Corporation).

The column effluent was monitored with a UV 3000 variable-wavelength ultraviolet absorbance detector (Thermo Separation Products, San Jose, California) set at 230 nm. The signal from the detector was integrated and recorded with a PC1000 chromatography data system (Thermo Separation Products). The area under the oxycodone peak at 230 nm was subjected to least-squares linear regression, and the actual oxycodone concentration in each sample was determined by interpolation from the standard curve. On the basis of the slope and variability (quantitative resolution) of the standards observed during assay validation, oxycodone concentrations could be resolved to the nearest 0.001 mg/mL but are reported to 0.1 mg/mL.

Data Reduction and Statistical Analysis

Data for the accelerated degradation study were analyzed by linear regression and log–linear regression, according to the methods of Box and Cox,[10,11] to determine if oxycodone degradation was better described by a first-order or a zero-order degradation rate.

Means were calculated for replicate analyses. The coefficient of variation of replicate measurements

averaged less than 2%. On the basis of this coefficient of variation and a power of 80%, it was estimated that the assay could detect at least a 10% difference in concentration with duplicate analysis of a single sample and that it could detect a difference of 5% with duplicate analysis of each of 3 replicate samples.[12,13]

The mean results from different days for each test were compared statistically to determine if an association existed between the observed result and storage time. Analysis of variance was used to test differences in degradation rate between various concentration, diluent and temperature combinations. The 5% level was used as the *a priori* cut-off for significance. Oxycodone concentrations were considered acceptable or within acceptable limits if the concentration on any day of analysis was greater than 95% of the initial (day 0) concentration and the lower limit of the 95% confidence interval of the percent remaining on day 35 was greater than 90%.

RESULTS

Accelerated Degradation Study and Assay Validation

At 93°C, 1 mg/mL oxycodone in water at pH 6.8 (the pH of the original solution) and pH 1.7 retained more than 94.1% and 88.0% of the initial concentration, respectively, over the 1258-min study period. No degradation products of oxycodone were observed in these 2 solutions. However, the solution that was adjusted to pH 12.8 degraded substantially. Less than 2% of the initial concentration remained after 1258 min of incubation at 93°C. This corresponds to a half-life of 48.1 min under these conditions. These data fit a first-order or pseudo-first-order degradation rate significantly better than a zero-order rate (for zero-order rate, $r = 0.7673$; for first-order rate, $r = 0.9664$).

At least 9 degradation products were observed in chromatograms from the pH 12.8 sample. Three of the largest peaks eluted at 2.7, 3.6, and 5.3 min (Figure 1). None of the degradation products interfered with oxycodone quantification. Furthermore, as a result of the predictable and virtually complete degradation of oxycodone in these accelerated studies, and the chromatographic separation of these degradation products from oxycodone, it was concluded that even though the degradation pathway or pathways of oxycodone are unknown, this analytical method was capable of indicating stability.[8,9]

Assay validation was completed with 5 consecutive standard curves. The deviation of the mean of 2 replicates for each of 6 standards over the validation period was less than 4.2% from the nominal concentration of every sample. For the quality control samples, the deviation from the expected concentration averaged 2.5%. Within-day analytical reproducibility error (as measured by coefficient of variation) averaged less than 2% for each of the 6 standards and 3 quality control samples.

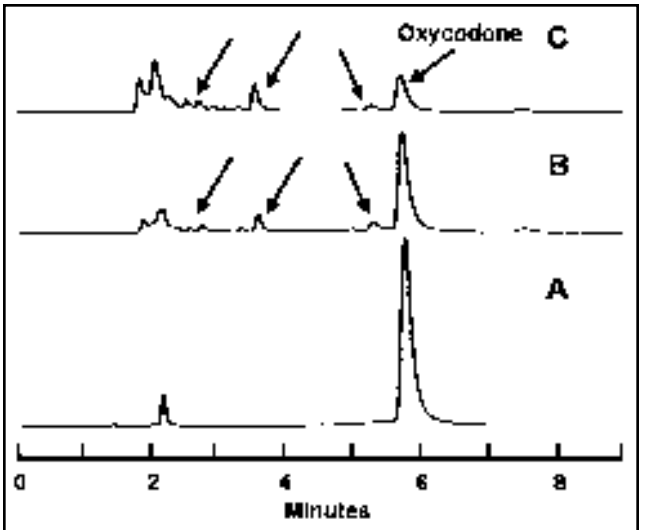

Figure 1. Chromatograms observed during the accelerated degradation study. All chromatograms represent the 1 mg/mL solution of oxycodone in water, with pH adjusted to 12.8 by addition of sodium hydroxide. A: Time zero. The peaks at approximately 5.9 and 2.1 min represent oxycodone and an impurity in the sodium hydroxide, respectively. B: After 140 min of incubation at 93°C. Approximately 52% of the oxycodone remains. C: After 253 min of incubation at 93°C. Approximately 18% of the oxycodone remains. The arrows in chromatograms B and C point to 3 of the larger peaks representing unidentified degradation products. No degradation product interfered with the measurement of oxycodone.

During the study period a total of 10 standard curves were prepared. Deviation from the expected concentrations for standards and quality control samples averaged 3%. Within-day analytical reproducibility error (as measured by coefficient of variation) averaged less than 1.5% for each of the 6 standards as well as the 3 quality control samples and inter-day reproducibility error averaged 1.4%, never exceeding 4.2%. The results of the prestudy validation and the observations made during analysis of the study samples indicate that differences of 10% or more could be confidently detected with acceptable error rates.[10,11]

Oxycodone Stability Study

During the study period, half of the study samples were stored in a refrigerator. The temperature of this

Table 1. Observed Concentration of Oxycodone Hydrochloride in NS, D5W, and Sterile Water (as Mean Percent of Initial Concentration ± SD*) after Storage at 4°C and 24°C

Study Day	Nominal 100 mg/mL in plastic syringes		Nominal 5 mg/mL in PVC minibags				Nominal 50 mg/mL in PVC minibags			
	4°C	24°C	4°C		24°C		4°C		24°C	
	Sterile Water	Sterile Water	NS	D5W	NS	D5W	NS	D5W	NS	D5W
Initial actual concentration (mg/mL)	98.2	100.7	4.9	4.9	4.9	4.9	49.6	47.7	49.7	47.8
1	99.2 ± 0.7	98.0 ± 0.9	100.1 ± 0.8	98.9 ± 1.3	98.8 ± 0.5	98.8 ± 1.6	98.2 ± 0.7	97.9 ± 0.4	97.0 ± 0.6	98.4 ± 2.3
3	100.1 ± 1.0	99.6 ± 2.2	97.9 ± 0.4	99.7 ± 1.1	100.5 ± 1.4	99.8 ± 0.2	99.9 ± 2.2	99.1 ± 2.6	99.2 ± 1.0	100.0 ± 2.2
7	101.0 ± 1.1	98.9 ± 2.2	99.8 ± 1.3	100.7 ± 1.6	102.6 ± 0.6	101.7 ± 0.4	99.0 ± 2.0	98.2 ± 0.7	100.5 ± 1.0	101.4 ± 1.2
10	98.2 ± 2.7	100.2 ± 2.5	102.0 ± 0.5	101.5 ± 1.5	99.3 ± 0.6	98.6 ± 1.7	99.4 ± 2.9	99.5 ± 2.5	102.2 ± 2.2	99.6 ± 3.1
14	97.3 ± 1.8	95.9 ± 0.4	98.2 ± 0.5	99.0 ± 0.8	100.2 ± 0.9	100.3 ± 1.3	97.6 ± 1.2	96.8 ± 1.1	101.2 ± 1.6	102.0 ± 1.4
17	96.9 ± 2.1	98.0 ± 1.5	98.3 ± 0.8	99.2 ± 0.5	100.7 ± 0.7	102.6 ± 0.7	97.5 ± 0.7	96.6 ± 0.1	102.5 ± 2.1	102.7 ± 2.1
21	98.4 ± 2.1	98.4 ± 2.6	102.2 ± 0.6	102.9 ± 0.8	102.2 ± 1.2	101.1 ± 0.4	102.2 ± 2.3	99.2 ± 1.5	98.1 ± 1.9	96.8 ± 1.9
28	97.2 ± 2.0	97.2 ± 0.5	97.2 ± 0.6	98.8 ± 1.5	102.3 ± 2.1	95.6 ± 1.1	98.8 ± 0.9	98.0 ± 1.3	102.9 ± 0.3	99.5 ± 2.2
35	101.5 ± 1.8	98.7 ± 1.4	97.8 ± 1.8	101.4 ± 1.9	100.6 ± 4.2	98.7 ± 2.4	98.5 ± 1.8	100.1 ± 2.4	103.5 ± 2.4	102.0 ± 0.6
% remaining on day 35†	99.3	98.5	98.3	101.1	101.7	98.2	99.7	100.2	104.2	100.9
Lower limit of 95% CI for % remaining on day 35‡	95.4	95.5	94.3	97.9	98.6	93.6	96.3	97.1	100.1	96.6

NS = normal saline (0.9% sodium chloride in water), D5W = 5% dextrose in water, SD = standard deviation, PVC = polyvinylchloride, CI = confidence interval.
*Each value is based on duplicate determination of concentration for 3 samples.
†Based on linear regression for each concentration–diluent–temperature combination.
‡Lower limit of the 95% CI of the slope calculated by linear regression for each concentration–diluent–temperature combination, according to the following formula: 100 x {[concentration on day 0 + (slope x 35 days)]/regression-determined initial concentration on day 0}

refrigerator was continuously recorded with a calibrated thermometer and remained between 3°C and 4°C. The initial concentration and the percent remaining on each study day for the 5, 50, and 100 mg/mL oxycodone solutions are presented in Table 1. All samples retained at least 95.6% of their initial concentration during the study period. The percent remaining on day 35, estimated by linear regression, was within 4.2% of the original concentration for all concentration–diluent–temperature combinations. On the basis of the lower limit of the 95% confidence interval for the slope, the amount remaining on day 35 averaged 96.5% and was not less than 93.6% for any concentration–diluent–temperature combination (Table 1). There was no significant trend in the changes in concentration for any concentration-diluent-temperature combination. The degradation products observed in the accelerated degradation portion of the study (Figure 1, chromatograms B and C) were not seen in any chromatograms during the stability study.

All solutions were initially clear and colourless and remained so for the duration of the study. No visible particles were observed in any test solution. The initial pH of the oxycodone solutions was dependent on both the concentration of the drug and the diluent. The initial pH of the 5 mg/mL solutions in D5W and NS was 4.3 to 4.5 and 5.1 to 5.2, respectively. The initial pH of the 50 mg/mL solutions ranged from 3.8 to 4.0, regardless of diluent, and the initial pH of the 100 mg/mL oxycodone solutions in sterile water ranged from 3.3 to 3.4. During storage at both 4°C and 24°C, the pH of all solutions varied by less than 0.1 pH unit.

DISCUSSION

This study has demonstrated that oxycodone is stable when diluted in sterile water, NS, or D5W and stored at either 4°C or 24°C.

Because only small changes in oxycodone concentration were detected under these storage conditions, assurance of the specificity of the analytical

method is important. During validation, the accelerated degradation studies (Figure 1) demonstrated the specificity of the method, and the replicate standard curves showed its accuracy and reproducibility. In these studies, oxycodone concentrations declined as the concentrations of apparent degradation products increased. Intact drug could be separated and detected in the presence of degradation compounds, so the method can be considered stability-indicating.[8,9]

Demonstration of a trend for decreasing concentration was considered more important than demonstration of a statistical difference in concentration between any 2 days. In fact, since the average absolute deviation in percent remaining on day 35 was only 1.4% and the amount remaining on day 35 was within 5% for all samples, with a lower limit for the 95% confidence interval within 6.4% of the initial concentration, daily fluctuations in concentration are not of practical importance and should be considered "noise" or experimental error. Degradation products were not observed in any chromatograms, providing further evidence that the daily concentration measurements represent estimates of an unchanging concentration. The average percent remaining on day 35 by linear regression was 100.2%. The inter-day reproducibility error averaged 1.4% and never exceeded 4.2% (coefficient of variation expressed as a percentage) on any study day. This is similar to the error observed during the assay validation of quality control samples and standards.

In conclusion, 100 mg/mL solutions of oxycodone hydrochloride dissolved in sterile water are stable and retain more than 95% of the initial concentration of the drug during 35 days of storage in plastic syringes at 4°C and 24°C. Furthermore, 5 and 50 mg/mL solutions prepared by dilution of the 100 mg/mL solution in NS or D5W also retained more than 95% of their initial concentration during 35 days of storage in PVC minibags at 4°C and 24°C.

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