Original Article

Microbiological and Physicochemical Stability of Oxycodone Hydrochloride Solutions for Patient-Controlled Delivery Systems

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Abstract

Context. The use of patient-controlled analgesia (PCA) allows patients to be managed at home and may increase the quality of life of patients with regard to drug administration. To ensure that intact drug is delivered to the patient in this setting, it is important to study its microbiological and physicochemical stability. Although these factors have been widely studied for many parenteral opioids, very few authors have investigated oxycodone stability associated with long-duration infusion in cancer patients.

Objectives. The aim of this study was to assess the microbiological and physicochemical stability of oxycodone hydrochloride solution in PCA devices and thereby to determine the feasibility of extending the expiration dates after mixing.

Methods. Sixteen CADD® reservoirs and 32 Rythmic® reservoirs were filled aseptically with pure (10 mg/mL) and diluted (1 mg/mL) oxycodone solution. Three different vehicles (0.9% sodium chloride, water for injection, and 5% dextrose) were used for dilution. Among the PCA systems stored over 28 days at room temperature, 16 Rythmic® reservoirs were protected from light. Microbiological stability was assessed by performing sterility tests. The physicochemical study was performed by determining aspect, pH, osmolality evolution, and weight. Drug concentrations were determined using the stability-indicating high performance liquid chromatography combined to ultraviolet detection technique.

Results. There was no significant change in pH, weight, and osmolality values of any solutions. No precipitation or change in color was observed in any of the sample solutions. There was no significant loss of oxycodone, and no trace of degradation products was detected.

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Conclusion. This study indicates that pure and diluted oxycodone solutions in the PCA systems are stable for 28 days at room temperature when prepared aseptically. J Pain Symptom Manage 2010;40:87–94. © 2010 U.S. Cancer Pain Relief Committee. Published by Elsevier Inc. All rights reserved.

Key Words
Oxycodone, microbiological stability, physicochemical stability, patient-controlled delivery system, quality assurance, analgesics, opioids, clinical pharmacy

Introduction

The regular administration of oral analgesics, given according to the World Health Organization (WHO) guidelines, is the mainstay of cancer pain treatment. However, many patients are unable to take medication orally in the final stages of disease. Patient-controlled analgesia (PCA), introduced in 1970, allows patients to self-administer bolus doses or maintain a continuous flow of analgesics. In addition to improving the control of chronic pain, especially pain caused by cancer diseases, the use of a PCA system allows patients to be managed at home and may increase the quality of life of patients with regard to drug administration in syringes. It reduces the time between the patient’s feeling of pain and the administration of preloaded analgesics in this multiple-dose device. As a result, the knowledge of opioid solution stability is critical.

Among other drugs, morphine and meperidine are commonly used in PCA devices to treat chronic pain patients. Morphine is the leader of the WHO classification of strong analgesics. These drugs, and others such as fentanyl and sufentanil, are agonists of μ-, δ-, and κ-opioid receptors and are widely used for anesthesia and analgesia in both adult and pediatric cancer pain treatment. Fentanyl citrate and sufentanil citrate injections are used in portable infusion pumps when patients experience intolerable side effects with morphine. The latter and related opioids produce their major effects on the central nervous system and gastrointestinal tract. They produce a selective attenuation of pain perception with dose-dependent effects.

Oxycodone is a semisynthetic opioid derivative with a phenanthrene structure (Fig. 1). Studies show that it is effective in the relief of moderate-to-severe malignant and nonmalignant pain. Oxycodone has been available for more than 70 years and is used worldwide to the same extent as morphine, but its approved indication varies across countries. It exerts full opioid agonist activity similar to that of morphine and other opioid analgesics.

Commercially available parenteral formulations OxyNorm® 10 mg/mL and, more recently, OxyNorm® 50 mg/mL are available in France and are currently indicated in chronic cancer pain that is severe or unresponsive to weaker analgesics in adults. The use of oxycodone in a PCA system is very interesting. In fact, oxycodone has several advantages compared with morphine. Oxycodone represents a valid therapeutic alternative to morphine, both first-line and second-line treatments, when the patient has trouble with adverse effects from other opioids. Clinicians have been requested to add this compound to the opioid drugs already used for the treatment of chronic pain in our Cancer Treatment Institute.

To ensure that the intact drug is delivered to the patient, it is important to study its microbiological and physicochemical stability. These questions have been widely studied for many parenteral opioids. However, very few
authors have investigated oxycodone stability associated with long-duration infusion in cancer patients.\textsuperscript{12,21}

The aim of this investigation was to guarantee the pharmaceutical quality of oxycodone solutions stored in PCA devices and determine their expiration periods. To reach this objective, we performed microbiological and physicochemical stability studies of pure and diluted oxycodone solutions in three different solvents and two different types of containers.

\textbf{Methods}

\textbf{Materials}

The pharmaceutical solution used, Oxynorm\textsuperscript{R} 10 mg/mL (Mundipharma Issy-les-Moulineaux, France), containing 20 mg of oxycodone hydrochloride in 2 mL of a pH 5 buffered isotonic solution in water for injection, was obtained from Mundipharma. Each volume of solution was taken by means of two 50 mL solution syringes and transferred without dilution for the 10 mg/mL solutions. For the 1 mg/mL oxycodone solutions, the taken volume was diluted in 20 mL of solvent after transfer. Three different solvents were used for dilution: water for injection, 0.9% sodium chloride (NaCl), and 5% dextrose solution. After homogenization, the residual air was evacuated by the use of the same syringes.

The solutions were transferred, under aseptic conditions, to 100 mL medication reservoirs for the following:

1. CADD\textsuperscript{R} pumps (Pharmacia-Deltec, St. Paul, MN). These reservoirs consist of medical-grade PVC infusion bags with an inner layer of phthalate ester placed in a light-protecting polycarbonate reservoir and a Luer-Lock\textsuperscript{R} PVC tube (Hospira, Meudon la forêt, France) with the plasticizer di-(2-ethylhexyl)phthalate, and

2. Rythmic\textsuperscript{R} pumps (Arcomed A.G. Medical Systems, Regensdorf, Switzerland). These reservoirs consist of medical-grade PVC infusion bags without a light-protecting polycarbonate reservoir.

Sixteen reservoirs for CADD\textsuperscript{R} pumps and 32 reservoirs for Rythmic\textsuperscript{R} pumps were used for this study. They were stored for more than 28 days at room temperature (15–25\textdegree C). Among them, 16 Rythmic\textsuperscript{R} reservoirs were stored under light protection.

\textbf{Microbiological Study}

\textit{Validation of the Absence of Antimicrobial Activity.}\n
According to the “General Methods” of the European Pharmacopeia, fifth edition,\textsuperscript{22} a preliminary microbial growing test is necessary to determine the presence, or the absence, of antimicrobial activity of studied active substances. This test was carried out for four microbial strains: Staphylococcus aureus (ATCC 6538, CIP 4.83), Pseudomonas aeruginosa (ATCC 9027), Clostridium sporogenes (ATCC 19404), and Candida albicans (ATCC 10231). This test compares the fertility of thioglycolate broth (TGB) and trypticase soy broth (TSB) with or without oxycodone. These broths allow the growth of anaerobic and aerobic bacteria as well as yeasts. \textit{S. aureus}, \textit{P. aeruginosa}, and \textit{C. albicans} were seeded in TSB, and \textit{Clostridium sporogenes} was seeded in TGB. Two series were prepared: 1) 2 mL of a 10 mg/mL oxycodone were added in each broth and 2) no substance was added in the series, which acts as the sterility control. Inoculated broth culture was incubated at +35\textdegree C for 48 hours. The reservoirs were stored at room temperature.

\textbf{Sterility Test.}\n
Forty-eight bags in PCA delivery systems were manufactured under aseptic conditions for this study. Investigators wearing surgical masks, caps, overshoes, gowns, and sterile gloves prepared medical devices on a clean class-100 vertical laminar-airflow bench. Twelve bags were made from the 10 mg/mL oxycodone pure solution, 12 from the 1 mg/mL oxycodone solution diluted in 0.9% NaCl, 12 from the solution diluted in 5% dextrose, and 12 from the solution diluted in water for injection. The reservoirs were stored for a period of 28 days at ambient temperature. A 5 mL volume of each infusion bag was aseptically sampled on days D0, D14, and D28 and directly seeded into TGB and TSB. Negative controls were performed with distilled water to guarantee the absence of interference caused by the handling conditions. An incubation time between +20 and +35\textdegree C is recommended by the European Pharmacopeia to allow the development of bacteria and fungi.
Physicochemical Study

pH, Weight, and Osmolality Evolution. A physicochemical study was conducted on the same 48 infusion bags. Each bag was weighed before and after each sampling day (D0, D14, and D28) to indicate the possible loss of solvent. A visual control of each sample against light was conducted to determine any change of aspect, color, limpidity, or appearance of turbidity.

Osmolality measurement was performed on an automatic osmometer (Roebeling, Messtechnik, Germany). The osmometer was calibrated on each study with a commercially available solution (300 mOsmol/mL), and pH measurements were recorded on a pH meter (Metrohm 713, Courtaboeuf, France). The pH meter was standardized on each study with commercially available buffer solutions (pH 4, 7, and 10).

Analytical Validation

According to the note for guidance on validation of analytical methods written by the International Conference of Harmonization (ICH topic Q2A and Q2B), the validation of an analytical technique requires demonstration of linearity, accuracy, precision, measurement range limits (limit of quantification [LQ] and limit of detection [LD]), robustness, and system suitability. According to the United States Pharmacopeia XXV, for quantitation of the active substance in hospital chemotherapeutic infusion bags, which is a finished pharmaceutical product, the data elements required for assay validation and analytical performance are selectivity (specificity), linearity and range, accuracy, and precision.

Calibration Function. The calibration function (relationship between peak area and the amount of substance applied) was determined by linear regression over a previously defined range. Each calibration curve was validated using two Quality Controls (QC): the low QC (QCL) corresponds to the midpoint of the first and the second standard and the high QC (QCH) corresponds to the midpoint of the fourth and the last standard.

Accuracy. The accuracy of the method, which gives information about the recovery of the analyte from the sample, was confirmed by analysis using in-system calibration of sample solutions of known substance content. The solutions were spiked with three different known concentrations of each substance, which were assigned low, medium, and high QC values (QCL, QCM, and QCH). The analysis of each QC sample was repeated six times in accordance.

Precision. In ICH guidelines, precision contains three components: repeatability, intermediate precision, and reproducibility. This parameter was not studied.

Repeatability. Repeatability expressed as the relative standard deviation (RSD), or coefficient of variation of repeatability (CVr), consists of multiple measurements of a homogenous sample according to the same analytical procedure with the same equipment and in the same laboratory. The analysis of each QC sample was repeated six times.

Intermediate Precision. Intermediate precision evaluates the reliability of the method in an environment different from that used during development of the method. Determination, expressed as the RSD or coefficient of variation of intermediate precision (CVi), consists of multiple measurements (n = 6) of each recommended level studied, that is, QC under the same analytical conditions, but on multiple days, by different analysts and different equipment with the exception of the high-performance liquid chromatography (HPLC) system.

Chromatographic Analysis

Forty-eight infusion bags in a PCA delivery system were aseptically prepared for this study. The reservoirs were stored for period of 28 days at room temperature conditions. A 2 mL volume of each infusion bag was aseptically sampled by the use of a polypropylene syringe and collected into 5 mL glass tubes on days D0, D3, D7, D10, D14, D21, and D28. Analyses were performed using D-7000 HSM software (Merck-Hitachi, Darmstadt, Germany) configured with an HPLC chromatographic system consisting of a quaternary pump L-7100 (Merck-Hitachi) and a MIDAS® autosampler equipped with column oven (Spark, AJ Emmen, The Netherlands). Analyses were separated on Macherey-Nagel Nucleodur® gravity...
C18 5 µm 100 Å column, 250 nm × 4 mm i.d. (Macherey-Nagel, Hoerdt, France) and an ultraviolet-visible detector (Jasco_UV-975; Tokyo, Japan) set at 230 nm.

Chromatographic conditions are those set by the European Pharmacopeia monography. Mobile phase was a mixture of sodium heptanesulfonate, phosphoric acid, and acetonitrile in elution gradient (1.2 mL/min). The flow rate was set to 1.2 mL/min resulting in retention times of 23 minutes (Fig. 2).

Results

Microbiologic Study

Validation of the Absence of Antimicrobial Activity. Culture broth supplemented with oxycodone solutions was found to allow growth of each of the four reference strains tested with the same delays and intensities as was observed with free control broth. No difference of cloud or tint appeared after incubation.

Sterility Test. Cultures of the 48 solutions from infusion bags were negative for the period of the study (35 days).

Physicochemical Study

pH, Weight, and Evolution of Osmolality. All solutions were initially clear and colorless and remained so for the duration of the study. No visible particles were observed in any test solution. As shown in Table 1, a limited loss of weight, up to 1% per month, was observed in the oxycodone solution in portable infusion pumps when stored at room temperature. The evaporation of solvent can be considered as negligible.

The oxycodone solutions’ osmolality values slightly decreased but were always below 4% (reduce to −3.8%) (Table 2) except for the water solutions. The values for the latter slightly increased but always below 4% (up to +3.9%). An increase in the pH values (up to +7.3%) was observed, particularly in oxycodone solution diluted with 5% dextrose or with water (Table 3).

Solutions diluted with water for injection presented relatively more important degradation values, that is, 3.9% loss in drug concentration, 3.9% increase in osmolality values, and increase of 6.8% in pH.

Analytical Validation

Calibration. The calibration function was determined by linear regression over the range 0–2000 µg/mL for both active substances with a target concentration of 1000 µg/mL. Mean equation of the linear regression study is \( y = 10,193 (x) - 176,802 \), with a mean \( \overline{r^2} \) calculated at 0.9997. These equations allow the determination of concentrations for each sample of oxycodone solutions.

Accuracy. The results show the accuracy of the method according to the mean values, close to the theoretical amount, and the RSD values, below 1%, calculated from the six analyses.
for each QC. In view of the calculated average concentrations, with regard to the theoretical value and of their dispersal, the analytical technique is considered exact.

**Precision.** The CVr and CVi for each active substance were below 5.0% for intermediate precision and repeatability.

**Limit of Detection-Limit of Quantification.** The LD and the LQ of the technique for each active substance were obtained by use of the slope ($b$) and the SD of the intercept (SDa) from six calibration curves determined by linear regression, as defined by the ICH topic Q2B. The LD ($\text{LD} = 3.3 \times \text{SDa}/b$) was 0.19 µg/mL, and the LQ ($\text{LQ} = 10 \times \text{SDa}/b$) was 12.89 µg/mL. The method is then completely adapted to the quantitation of the oxycodone solutions.

**Concentration Evolution Study**

Concentrations of oxycodone solutions were calculated through the integration of the surface areas of chromatographic peaks. Mean equation of the six linear regressions used for the concentration evolution study was $y = 10,193 \times x - 176,802$. The values show a slight decrease in concentration values, but these decreases remained lower than 4% (Table 4), and no degradation product was found during the stability study (Fig. 2).

**Discussion**

Although the microbiological results support the conclusion that oxycodone does not show significant antimicrobial activity, microbiological tests have established that PCA solutions of these therapeutic agents remain stable and sterile for at least 28 days at ambient temperature under normal operational conditions. Because only small changes in oxycodone concentration were detected under these storage conditions, assurance of the specificity of the analytical method is important. According to the physicochemical results, the loss of weight (evaporation of solvent) was not concomitant with an increase of the drug concentration. We can postulate that the observed decrease in drug concentration was probably because of an adsorption phenomenon of the active substance on the PVC bag. In fact, no degradation product was found during the stability study. Furthermore, the decrease in drug concentration was always below 4%, which is lower than the official compendial requirement defined at 10%.26 Storage conditions had no influence in the product stability. In fact, no impact of light protection has been observed.

This study has also demonstrated that oxycodone solution is stable when diluted in water for injection, 5% dextrose, or 0.9% NaCl either in a CADD® medical device or in the Rythmic® one. The data reported by Turnbull et al.21

<p>| Table 1 | Weight Values of Infusion Reservoirs | Weight Loss Over 28 days (%) |</p>
<table>
<thead>
<tr>
<th>PCA delivery systems</th>
<th>Pure Solution, 10 mg/mL</th>
<th>Diluted Solution, 1 mg/mL (0.9% NaCl)</th>
<th>Diluted Solution, 1 mg/mL (Water for Injection)</th>
<th>Diluted Solution, 1 mg/mL (5% Dextrose)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CADD® reservoirs</td>
<td>-0.7</td>
<td>-0.5</td>
<td>-0.6</td>
<td>-0.4</td>
</tr>
<tr>
<td>Rythmic® reservoirs</td>
<td>-0.9</td>
<td>-0.6</td>
<td>-1.5</td>
<td>-0.6</td>
</tr>
<tr>
<td>Rythmic® reservoirs</td>
<td>-1.0</td>
<td>-0.6</td>
<td>-0.3</td>
<td>-0.5</td>
</tr>
<tr>
<td>(protected from light)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<p>| Table 2 | Osmolality Values of Oxycodone Solutions | Osmolality Variations Over 28 days (%) |</p>
<table>
<thead>
<tr>
<th>PCA delivery systems</th>
<th>Pure Solution, 10 mg/mL</th>
<th>Diluted Solution, 1 mg/mL (0.9% NaCl)</th>
<th>Diluted Solution, 1 mg/mL (Water for Injection)</th>
<th>Diluted Solution, 1 mg/mL (5% Dextrose)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CADD® reservoirs</td>
<td>-2.6</td>
<td>-3.8</td>
<td>+3.9</td>
<td>-0.6</td>
</tr>
<tr>
<td>Rythmic® reservoirs</td>
<td>-2.5</td>
<td>-3.7</td>
<td>+3.5</td>
<td>-0.6</td>
</tr>
<tr>
<td>Rythmic® reservoirs</td>
<td>-0.4</td>
<td>-2.8</td>
<td>+2.0</td>
<td>-0.4</td>
</tr>
<tr>
<td>(protected from light)</td>
<td></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>
demonstrated a 35-day period of stability of oxycodone hydrochloride at 100 mg/mL in sterile water in plastic syringes stored at 4°C or at 24°C. They have also studied oxycodone hydrochloride solutions diluted in PVC mini bags at 5 and 50 mg/mL in 0.9% NaCl or in 5% dextrose and stored in the same conditions. Our results confirm the similar period of physicochemical stability, as we report a 28-day period of stability for pure solution at 10 mg/mL and for the 1 mg/mL solutions diluted in the three selected vehicles stored in PCA devices at room temperature (15–25°C). The study was done in these vehicles to obtain complete data for this compound, knowing that the 0.9% NaCl is the major vehicle used in clinical practices. Gardiner et al.12 already reported physicochemical stability data of 10 and 1 mg/mL of oxycodone solutions diluted in the same vehicles and prepared in syringes and tubing and infusion bags made from various materials. They also investigated the compatibility of oxycodone hydrochloride with some drugs used in this clinical context. The choice of a diluent has to consider interaction with drug selected for potential drug combinations, as crystal formation was seen in the high dose combination of oxycodone and cyclizine lactate injection when 0.9% NaCl was used as diluent. This large work was done over a period of seven days only, when solutions were diluted in plastic devices, and over a period of 14 days in glass vials. They demonstrated that these solutions in devices prepared for patient administration were stable for up to seven days at room temperature.

However, to ensure that a good-quality product is delivered to the patient, it is important to study not only the ingredient stability and the compatibility with the reservoir and tubing in the delivery devices but also the microbiological issues. Only a few authors have investigated bacteriologic issues associated with long-duration infusions of opioids in cancer patients treated at home.27,28 As we have reported for fentanyl and sufentanil solutions in PCA devices,5 we report here microbiological data on oxycodone hydrochloride solutions and we are able to guarantee the microbiological stability of the devices when prepared according to the conditions defined by the use of Good Manufacturing Practices.

In practice, the Department of Clinical Pharmacy is now able to produce qualified batches of oxycodone in PCA devices with expiration dates of 28 days. Many clinical and economic benefits of this work have resulted, with a better guarantee of the pharmaceutical quality of available therapeutic agents and devices, small risk of losing product, better organization in PCA production and, essentially, net improvements in care chain reactivity relative to the needs of suffering patients.

### Table 3
**pH Values of Oxycodone Solutions**

<table>
<thead>
<tr>
<th>PCA delivery systems</th>
<th>Pure Solution, 10 mg/mL</th>
<th>Diluted Solution, 1 mg/mL (0.9% NaCl)</th>
<th>Diluted Solution, 1 mg/mL (Water for Injection)</th>
<th>Diluted Solution, 1 mg/mL (5% Dextrose)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CADD® reservoirs</td>
<td>+0.7</td>
<td>-0.4</td>
<td>+6.8</td>
<td>+5.6</td>
</tr>
<tr>
<td>Rythmic® reservoirs</td>
<td>+0.9</td>
<td>+0.1</td>
<td>+6.3</td>
<td>+3.6</td>
</tr>
<tr>
<td>Rythmic® reservoirs (protected from light)</td>
<td>+1.0</td>
<td>-0.8</td>
<td>+0.6</td>
<td>+7.3</td>
</tr>
</tbody>
</table>

### Table 4
**Concentration Values of Oxycodone Solutions**

<table>
<thead>
<tr>
<th>PCA delivery systems</th>
<th>Pure Solution, 10 mg/mL</th>
<th>Diluted Solution, 1 mg/mL (0.9% NaCl)</th>
<th>Diluted Solution, 1 mg/mL (Water for Injection)</th>
<th>Diluted Solution, 1 mg/mL (5% Dextrose)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CADD® reservoirs</td>
<td>+ 0.3</td>
<td>-1.4</td>
<td>-3.8</td>
<td>-2.8</td>
</tr>
<tr>
<td>Rythmic® reservoirs</td>
<td>+1.6</td>
<td>+1.5</td>
<td>-3.4</td>
<td>-3.5</td>
</tr>
<tr>
<td>Rythmic® reservoirs (protected from light)</td>
<td>+2.0</td>
<td>-3.9</td>
<td>-3.5</td>
<td>-0.4</td>
</tr>
</tbody>
</table>
Acknowledgments

The authors are grateful to Pr. J.-C. Darbord for supplying microbial strains and Mundipharma Laboratories for financial support.

References