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Availability of Morphine Oral Solution for Childhood Cancer Patients in Low-Income Countries: Compounding and Stability Study in a Cote d'Ivoire University Teaching Hospital

To the Editor

Cancer is an important cause of morbidity and mortality worldwide. In Africa, studies focusing on childhood cancer showed a constant increase in the annual number of new cases and a very low overall survival rate.¹ Cancer treatment is often associated with pain management. The World Health Organization's guidelines recommend oral morphine (hydrochloride or sulfate) for severe chronic pain treatment in children. A previous work evidenced the good feasibility of oral morphine solution in Uganda.² However, the authors highlighted several limitations to successfully replicate this pain management in other African countries. In low-income and middle-income countries, such as Côte d'Ivoire, limitations include both expense and restricted access to active pharmaceutical ingredients. This lack of access can prevent pain relief and a peaceful end of life for children suffering from cancer.³

Low concentrations of morphine solutions for oral administration are not commercially available in several countries. Various compounding formulations were developed, but only a few have been reported in the literature.^{4–7} The purpose of our study was to develop an affordable and easily available oral morphine formulation for pediatric patients with cancer pain. We devised an easy-to-make and low-cost morphine syrup formulation using local African (Côte d'Ivoire) raw materials and commercial injectable morphine. In this report, we describe the results of a study to assess the required quality controls and stability of this formulation.

Methods

Reagents and Instrumentation

Ampoules of morphine reference standard (Cerilant Corporation, Round Rock, TX) at 1.00 mg/mL

in methanol were used for method validation, and morphine hydrochloride trihydrate (Aguettant, Lyon, France) of pharmaceutical grade was used for the forced degradation study. The high-performance liquid chromatography (HPLC) mobile phases were prepared using ultrapure water (HiPerSolv Chromanorm[®]; VWR International, Radnor, PA), methanol (HiPerSolv Chromanorm[®]; VWR International), and acetonitrile (HiPerSolv Chromanorm[®]; VWR International) of HPLC grade. Sodium lauryl sulfate buffer was prepared from sodium lauryl sulfate (0.65 g/L; Rectapur[®]; Prolabo, Sion, Switzerland) and sodium sulfate (1.625 g/L; Merck, Darmstadt, Germany) in ultrapure water adjusted to pH 2.5 with 0.1 M of sulfuric acid. The mobile phases were filtered using 0.45 µm of Millipore cellulose filters. Volumes were aliquoted with a precision pipette (Thermo Scientific Finnpipette[®]; F2 500 µL, Thermo Scientific, Waltham, MA). pH was determined with a Thermo Scientific Orion 4 Star[®] pH meter, calibrated with Radiometer Analytical standard etalons[®] (pH 4.005, 7.000, and 10.012).

The chromatographic method was carried out on an automatic HPLC Dionex Ultimate 3000[®] with a ultraviolet diode array detector. The apparatus was connected to an HP 1702 computer equipped with chromatographic data processing software (Chromeleon[®] Chromatography Management System, Version 6.80 SRH Biold 3161; 1994–2011 Dionex Corporation, Sunnyvale, CA). Morphine separation was achieved using a Stability[®] C18 column with a particle size of 5 µm (150 × 4.6 mm).

Viscosity was determined with a viscometer (Brookfield[®] LVDV-1M), equipped with a thermostatically controlled low-volume adaptor and its mobile (SC4-31). Measures were done at 100 rpm, 25°C.

Evaluation of the suitability of microbiological analyses was realized with reference strains (Biomérieux Bioball[®]; Biomérieux, Marcy L'Etoile, France): *Staphylococcus aureus* NCTC10788, *Bacillus subtilis* NCTC10400, *Pseudomonas aeruginosa* NCTC12924, *Candida albicans* NCPF3179, and *Aspergillus brasiliensis* NCPF2275. Microbiological analyses were done on Tryptic Soy Agar (Biomérieux) and Sabouraud chloramphenicol gentamicin agar (Biomérieux) under a microbiological safety cabinet (Herasafe[®] KS; Thermo

Scientific). Nine milliliter tubes of pharmacopeia diluent with Tween 80 (Dominique Dutcher, Brumath, France) and incubators (Heratherm[®] and Heraeus[®] Thermo Scientific) were also used.

Stability and Microbiological Methods

Morphine quantification by HPLC was based on a methodology previously described,⁸ and forced degradation studies were conducted to prove the stability-indicating capability of our chromatographic method. Degradation products did not interfere with morphine determination. About 1.0 mg/mL of morphine syrup samples were treated as follows: 200 μ L of syrup were mixed and vortexed with 1800 μ L of ultrapure water to obtain a solution of theoretically 100 μ g/mL of morphine hydrochloride trihydrate (approximately 75.92 μ g/mL of morphine base form).

The stability of the morphine syrups was evaluated for six months, under several storage conditions: classical ambient temperature (25°C), hot ambient temperature (40°C), and refrigeration (2°C/8°C). We studied four parameters on three independent batches: morphine concentration (triplicate), pH (one batch analyzed), viscosity (triplicate), and microbiological contamination (triplicate for initial and final points and one batch analyzed for other points).

Microbiological analyses of morphine syrups were done by surface-spread method. Suitability of the method was done according to European Pharmacopeia standards with five reference strains (*Staphylococcus aureus*, *Bacillus subtilis*, *Pseudomonas aeruginosa*, *Candida albicans*, and *Aspergillus brasiliensis*).

Results

Formulation

Morphine syrup was compounded from commercial parenteral morphine. This choice was supported by the fact that morphine sulfate and morphine hydrochloride active pharmaceutical ingredients are not only less readily available in developing countries (anecdotally, also in France) than parenteral marketed morphine but also because the stability and storage parameters of commercial glass vials can be easily managed. To ensure an easy-to-made formulation, only one excipient was chosen to have a single dilution step of parenteral morphine. Because microbiological stability could be problematic, a simple syrup was selected for the formulation. The cost and availability of the pharmaceutical commercial form of a simple syrup were important limitations in Côte d'Ivoire. A simple syrup was therefore extemporaneously compounded from local mineral water (Céleste[®]; Ciprem-Ci, Bonoua, Côte d'Ivoire, calcium 59.2 mg/

L, magnesium 6.90 mg/L, bicarbonates 202.50 mg/L, and chloride 14.2 mg/L) and local commercial sugars (Batch 1: Princesse Tatïe[®]; SUCAF, Fer-kessédougou, Côte d'Ivoire, and Batch 2: Sucrivoire[®]; SIFCA, Abidjan, Côte d'Ivoire). Briefly, 320 g of sugar were dissolved in 200 mL of water and heated at 105°C. Two batches were prepared from two different commercial sugars. From these two batches of simple syrup, three batches of 1 mg/mL of morphine syrups were compounded (from simple syrup Batch 1, from simple syrup Batch 2, and from a mixture in equal parts of the two simple syrup batches).

Glycerol and citric acid were added to the formulation to avoid morphine syrup hydration and ensure a low pH, respectively. Specifically, 54 g of glycerol (Fagron, Thiais, France) and 3.6 g of citric acid (Cooper, Melun, France) were mixed in 36 mL of morphine hydrochloride 10 mg/mL (Aguettant). Thereafter, simple syrup was added at 360 mL, and the morphine syrup was finally aliquoted in 30-mL glass bottles (Coopération Pharmaceutique Française, Melun, France) (20 mL per bottle).

Stability and Microbiological Study

The initial values of the morphine hydrochloride formulation were of concentration 1.01 ± 0.03 mg/mL, pH 2.38, and viscosity 162 ± 18 Cp. The International Conference on Harmonization defined significant changes as a 5% change in assay from its initial value for stability studies conducted in the pharmaceutical industry. This 5% limit is often increasing to a 10% change in assay from its initial value for hospital compounded preparations done in a smaller scale.⁹ In the present study, 10% limit were used to define significant changes. These batches were individually analyzed by quality control laboratory with regard to European Pharmacopeia specifications.

Under all the studied conditions, pH and viscosity remained stable, and morphine concentration was also found to be stable for four months under refrigerated temperature (2°C/8°C) and for one month at ambient (25°C) and hot ambient temperature (40°C). There were no decreases of morphine content in syrup and no significative increase of detectable degradation product for these time points investigated. Results are summarized in [Table 1](#).

Total aerobic microbial count was found to be lower than 200 CFU/mL, and total combined yeasts and mold count was found to be lower than 20 CFU/mL. At all periods of the stability study and for each storage condition, microbiological contamination was found to be lower than the method detection limit (total aerobic microbial count and total combined yeasts and mold count lower than 10 CFU/mL).

Table 1
pH, Viscosity, and Morphine^a Content of Morphine Syrups

| Parameter | T0 | 1 Day | 7 Days | 15 Days | 30 Days | 45 Days | 60 Days | 90 Days | 120 Days |
|----------------------------------|-------------|-------------|-------------|-------------|-------------|-----------|-----------|-----------|-------------|
| +2/+8°C | | | | | | | | | |
| pH | 2.38 | 2.38 | 2.38 | 2.46 | 2.18 | 2.28 | 2.36 | 2.29 | 2.32 |
| Viscosity (Cp) | 162 ± 18 | 163 ± 20 | 157 ± 19 | 174 ± 19 | 159 ± 17 | 164 ± 17 | 160 ± 13 | 161 ± 12 | 157 ± 9 |
| Morphine ^a (mg/mL) | 1.1 ± 0.3 | 1.3 ± 0.2 | 1.6 ± 0.1 | 1.7 ± 0.1 | 1.3 ± 0.6 | 1.3 ± 0.4 | 1.8 ± 0.1 | 1.0 ± 0.5 | 1.01 ± 0.05 |
| 25°C | | | | | | | | | |
| pH | 2.38 | 2.42 | 2.39 | 2.46 | 2.25 | — | — | — | — |
| Viscosity (Cp) | 162 ± 18 | 163 ± 17 | 158 ± 22 | 166 ± 16 | 157 ± 16 | — | — | — | — |
| Morphine ^a (mg/mL) | 1.01 ± 0.03 | 1.03 ± 0.02 | 1.03 ± 0.09 | 1.01 ± 0.08 | 1.08 ± 0.01 | — | — | — | — |
| 40°C | | | | | | | | | |
| pH | 2.38 | 2.39 | 2.37 | 2.42 | 2.24 | — | — | — | — |
| Viscosity (Cp) | 162 ± 18 | 162 ± 15 | 158 ± 19 | 163 ± 16 | 157 ± 16 | — | — | — | — |
| Morphine ^a (mg/mL) | 1.01 ± 0.03 | 0.98 ± 0.05 | 1.02 ± 0.07 | 1.02 ± 0.04 | 1.04 ± 0.01 | — | — | — | — |

^aExpressed in morphine hydrochloride trihydrate.

Comment

This study demonstrates that a new formulation of oral morphine 1.00 mg/mL compounded with simple syrup made from Côte d'Ivoire local ingredients had no contamination and was stable for 120 days at +4°C and 30 days at +25°C and +40°C. These results are in accordance with the literature. Several studies proved the long-term stability of morphine hydrochloride compounded as oral solutions.^{4–7}

In low-income countries, opioids are mainly available in solid dosage forms (capsule and tablet), but their cost is an important limitation to their use.¹⁰ Drinkable oral morphine formulations are more suitable for pediatric uses. Several oral morphine formulations have been described, but they contain excipients that could be problematic in countries like Côte d'Ivoire. Problems include the unavailability of excipients and aqueous solutions at risk of microbiological contamination. Our formulation is a solution to these problems because a syrup form inhibits microbiological growth, and its formulation made from local ingredients decreases costs.

Pain management is a key element for patient suffering from cancer, including children. Drinkable morphine solutions have been developed for palliative care in Africa,² but there is a critical lack of oral formulations that can be used by children. Preliminary studies showed the necessity not only to train health care workers but also to develop morphine supply chain. Our formulation can reduce undertreatment of pain and delay or prevent the transition to parenteral administration. It can also improve acceptance by children because of its sugar taste and reduce nurse miscalculations by the use of a fixed concentration. It also eliminates the need for nurses to prepare oral morphine, which is time consuming and at risk of error.

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