Evaluation of 30-days stability of morphine hydrochloride and clonidine at high and low concentrations in polypropylene syringes

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ABSTRACT

Objectives Clonidine is an alpha-2 adrenoreceptor agonist and is frequently combined with opioids (ie, morphine hydrochloride (HCl)) for the management of chronic pain. In palliative care, the administration of clonidine and morphine HCl is recommended in case of tolerance effect. This study aimed to evaluate the physical and chemical stability of this admixture at high and low concentrations in 14 and 48 mL polypropylene syringes.

Methods The stability of a low concentration admixture of clonidine (Catapressan 0.15 mg/mL, Boehringer Ingelheim, Germany) and morphine (morphine HCl 40 mg/mL, Sterop, Belgium) at 0.003 and 0.417 mg/mL, respectively, was evaluated by using five polypropylene syringes of 48 mL. The high concentration admixture consisted of 0.032 mg/mL clonidine and 4.286 mg/mL morphine HCl and was evaluated by using five polypropylene syringes of 14 mL. All syringes were stored for 30 days at 5°C±3°C. Periodic samples were visually and microscopically examined to observe any particle appearance or colour change. pH and absorbance at three wavelengths (350, 410 and 550 nm) were monitored. The concentrations were measured by ultra-high performance liquid chromatography—photodiode array detection.

Results During the 30 days, there was no change in colour or appearance of opacity, turbidity or precipitation, and pH remained stable. The low and high concentration admixtures were considered chemically stable since the lower limit of the 90% CI remained superior to 90% of the initial concentration. Concentration measurements showed that the degradation rate was less than 1% over 10 days for each component in both admixtures.

Conclusions The admixture of clonidine and morphine HCl at low and high concentrations in polypropylene syringes appeared to be physically and chemically stable throughout the study period of 30 days at 5°C±3°C. In conclusion, the admixture can be prepared in advance under aseptic conditions by a centralised intravenous additive service in the pharmacy department.

INTRODUCTION

Opioid receptor agonists (ie, morphine hydrochloride for parenteral injection) are the key WHO level III analgesics for nociceptive pain management.[1] Morphine has an affinity for delta, kappa, and mu opioid receptors, but its pharmacological action occurs through direct interaction with the mu opioid receptor within the central and peripheral nervous system. However, the utility of morphine is restricted by the incidence of morphinic-derived side effects, including respiratory and cardiovascular depression, sedation, constipation, nausea, cognitive impairment, pruritus and the appearance of tolerance.[2 3]

Clonidine is a selective alpha-2 adrenoreceptor agonist with both central and peripheral action. Through central activation of presynaptic alpha-2 adrenoreceptors, clonidine decreases blood pressure and causes central analgesic activity as well as sedation.[4] Administration of alpha-2 adrenoceptor agonists with opioids often results in a greater-than-additive (ie, synergistic) interaction and is particularly important when managing patients with conditions that are under-responsive to conventional opioid therapy, such as in the palliative care unit.[3] The indication of this synergistic adrenergic-opioid combination is preconised because of the expectation of improved efficacy and/or the ability to reduce dose escalation to minimise side effects and improve the therapeutic index.[5] Until now, the mechanistic pathway of this combination remains unclear.[3]

The administration of clonidine and morphine through previously prepared syringes presents numerous advantages for a patient's comfort and safety, including reducing the perfusion volume and preventing fluid overload.[6] The admixture can be prepared in advance under aseptic conditions by a centralised intravenous additive service (CIVAS) in hospital pharmacy department, resulting in decreased workload and fewer preparation errors.[7]

A literature review of physicochemical stability[8–10] shows that the admixture of clonidine and morphine is physically stable under certain conditions[11 12] and has good long-term stability at 37°C, notably in implantable infusion systems for at least 90 days.[13–15] However, the combination of clonidine and morphine HCl in specific concentrations that are used in the palliative care unit have not been analysed.[16]

The aim of this study was to evaluate the physical and chemical stability of adrenergic-opioid combination therapy at low and high concentrations in 14 mL and 48 mL polypropylene syringes stored at 5°C±3°C with the objective of preparing them in advance by using a CIVAS.

Table 1 Calibrators and controls concentrations (µg/mL)

	Morphine HCl (µg/mL)	Clonidine (µg/mL)
Calibrator 1	100	1
Calibrator 2	500	10
Calibrator 3	1000	20
Calibrator 4	2500	40
Calibrator 5	5000	60
Control 1	250	5
Control 2	1250	15
Control 3	4500	45

MATERIAL AND METHODS

Preparation of admixtures

Five 48 mL polypropylene syringes (Becton Dickinson, lot 1903268, New Jersey, USA) containing the mixture at the lowest concentration were prepared under aseptic conditions by adding 0.5 mL morphine HCl (40 mg/mL, lot 190103, Sterop, Belgium) and 1.0 mL clonidine HCl (Catapressan 0.15 mg/mL, lot 925137, Boehringer Ingelheim, Germany) to NaCl 0.9% (Viaflo 1000 mL, lot 19J12T1D, Baxter, Belgium). Low concentration solutions contained 417 µg/mL morphine HCl and 3 µg/mL clonidine. Additionally, five 14 mL polypropylene syringes containing the highest concentration mixture were prepared by adding 1.5 mL of morphine HCl and 3.0 mL of clonidine HCl to NaCl 0.9%. High concentration solutions contained 4286 µg/mL morphine HCl and 32 µg/mL clonidine.

Stability study design

Syringes were stored at 5°C±3°C for 30 days and periodically analysed (day (D) 0, D1, D2, D3, D4, D9, D15, D22, D30 for 14 mL syringes and D0, D1, D2, D3, D4, D7, D9, D11, D13, D15, D17, D20, D22, D24, D27, D30 for 48 mL syringes). Each sampling day, physical stability was assessed immediately on an aliquot of 0.5 mL of all samples while aliquots of 100 µL in triplicate were stored at −80°C for further chemical analyses.

Physical stability

Each solution of 0.5 mL was visually examined on black and white backgrounds for the detection of any colour change or particle appearance. The crystal formation was microscopically verified (at magnification ×80) after centrifugation at 2150 g for 5 min of each solution. Additionally, the turbidity was evaluated by spectrophotometric measurements (Genesys 10 series, USA) at three wavelengths (350, 410 and 550 nm)[17] and pH was monitored with a glass electrode pH meter (Inolab level 1, WTW Weilhem, Germany, with biotrode electrode, Hamilton, Switzerland) throughout the testing period.

Chemical stability

Chromatographic assay

Molecule concentrations were measured by ultra-high performance liquid chromatography (UHPLC; Acquity UPLC H-Class, Waters, Milford, USA) coupled with a photodiode array (PDA) detector (Acquity, Waters). Data were acquired and processed by the Empower three software (Waters). The separation was performed on a reverse phase column (Luna Omega polar C18 1.6 µm 100 Å, LC column 100×2.1 mm, lot H16-356030, Phenomenex, Belgium) and heated at 30°C. An elution gradient was carried out with potassium dihydrogen phosphate (KH_2PO_4) 10 mM (lot A0360673 202, Merck, USA) adjusted to pH 2.5 with phosphoric acid (H_3PO_4) 85% (lot Z0542328 847, Merck) and acetonitrile (lot 1332661, Biosolve, France). The run started with 8% of organic phase before being gradually increased to 25% in 1 min. The column was washed with 25% of organic phase for 2 min and then reequilibrated with 8% of organic phase for 1.5 min before the next run. The flow rate was fixed at 0.4 mL/min. Chromatograms were obtained at 285 nm for morphine HCl and 220 nm for clonidine.

Standard and control solutions

A calibration curve was created each working day of the UHPLC analysis based on five calibrator solutions and a weighted regression procedure, and three controls were used (table 1). All solutions were prepared from a fresh admixture of morphine HCl and clonidine.

Validation of the UHPLC method

Validation of the developed method was carried out as per the International Conference on Harmonisation (ICH) guidelines Q2 (R1)[18] and included an evaluation of the following characteristics: linearity, precision, limits of detection (LOD) and quantification (LOQ) and stability-indicating capability.

Linearity

The range of linearity of the analytical response was determined by a two-fold serial dilution (a total of 14 dilutions) from 10 000 µg/mL for morphine hydrochloride and from 120 µg/mL for clonidine, equal to twice the highest point of the calibration.

Precision

Intra-assay variation was evaluated by the relative standard deviation (RSD) of 10 successive injections of the same sample while inter-assay variation was determined by the injection of 10 samples prepared on different days. Both intra-assay and inter-assay variations were evaluated on the three levels of controls.

Limits of detection and quantification

Injectable water (lot 192628091, B. Braun) was injected 10 times as a blank to calculate the LOD and LOQ as follows: LOD=mean of blank +3*SD and LOQ=mean of blank +10*SD

Stability-indicating capability

Samples were forcibly degraded to evaluate the stability-indicating capability of the method. The main peaks were observed to verify their decrease in case of degradation and any possible interference with the degraded products.[19] The test was performed on fresh admixtures at low and high concentrations and on solutions containing pure active *princeps* at high

Table 2 Validation criteria, namely linearity, limit of detection (LOD) and quantification (LOQ)

	Linearity				
	Range (µg/mL)	Equation	R^2	Limit of detection (µg/mL)	Limit of quantification (µg/mL)
Morphine HCl	19.5–10 000	y=0.9674×−6.9625	0.99	0.121	0.311
Clonidine	0.06–120	y=0.9705×+0.295	0.99	0.068	0.121

Table 3 Intra-assay and inter-assay variations of morphine and clonidine (n=10); results are expressed as mean±SD (relative SD %)

		Intra-assay (n=10)			Inter-assay (n=10)		
Morphine HCl (µg/mL)	Expected	250	1250	4500	250	1250	4500
	Calculated	238.0±1.9 (0.8)	1255.5±4.1 (0.33)	4478.7±17.6 (0.4)	244.4±7.8 (3.2)	1243.1±8.8 (0.7)	4472.2±54.4 (1.2)
Clonidine (µg/mL)	Expected	5	15	45	5	15	45
	Calculated	5.0±0.0 (0.1)	15.3±0.0 (0.1)	44.9±0.0 (0.1)	5.1±0.1 (2.2)	15.2±0.1 (0.6)	45.2±0.2 (0.4)

concentration (morphine HCl 4285.714 µg/mL and clonidine 32.143 µg/mL). Vials containing the aforementioned solutions were subject to different conditions: natural, acidic (HCl 0.1 M), alkaline (NaOH 0.1 M) and oxidation (H_2O_2 3% (w/w), lot STBH5484, Sigma-Aldrich). Samples were immediately analysed and after 4 days at room temperature and 60°C, and they were neutralised before the UHPLC injection.

Chemical stability study

All aliquots from one syringe were withdrawn at predefined time points at room temperature and analysed during the same run by chromatography. Samples of 5 µL were injected by the UHPLC system without any previous dilution for the clonidine measurement and 0.3 µL for morphine HCl. Analyses were performed in triplicate.

Statistical analysis

According to the ICH Q1E guidelines,[20] pharmaceutical solutions were considered chemically stable while the lower limit of the 90% CI on the mean remains superior to 90% of the initial concentration. For each syringe, the initial concentration was defined as the intercept of the slope representing the linear evolution of product concentration over time and was computed through linear models. The relative concentrations of all syringes under the same conditions were then combined to measure the mean slope of the relative concentration through linear models. These models were used to calculate the concentration above which the mean should be (with the lower limit of the 90% CI) or 95% of the observations should be (with the lower limit of the 90% prediction interval). Statistical analyses were performed using R 3.3 (R Foundation for Statistical Computing, Austria, Vienna, 2017).

RESULTS

Physical stability

The admixtures at high and low concentrations appeared physically stable throughout the study period. No pH shift was observed for the low concentration (mean±SD: 6.63±0.03) or for the high concentration (mean±SD: 5.85±0.07). Visual examination against a black and white background did not reveal any colour change or the presence of aggregates. The absence of turbidity was confirmed by spectrophotometric measurements at 350 nm (low: 0.006±0.000; high: 0.022±0.000), at 410 nm (low: 0.000±0.000; high: 0.006±0.000) and at 550 nm (low: 0.000±0.000; high: 0.001±0.000). During the 30 days of storage, aggregate formation was not observed in high and low concentration solutions by light microscopy.

UHPLC method development

A C18 column was chosen based on the hydrophobic profile of the two components (partition coefficient (logP): 0.90 for morphine and 2.49 for clonidine). The pH-dependent species distribution shows that a unique ionised species is in solution at pH below 6 for each molecule. The pH was set at 2.5 in order to neutralise residual silanols and to limit secondary interactions while morphine and clonidine are positively charged at acidic pH. Thus potassium dihydrogen phosphate was adjusted

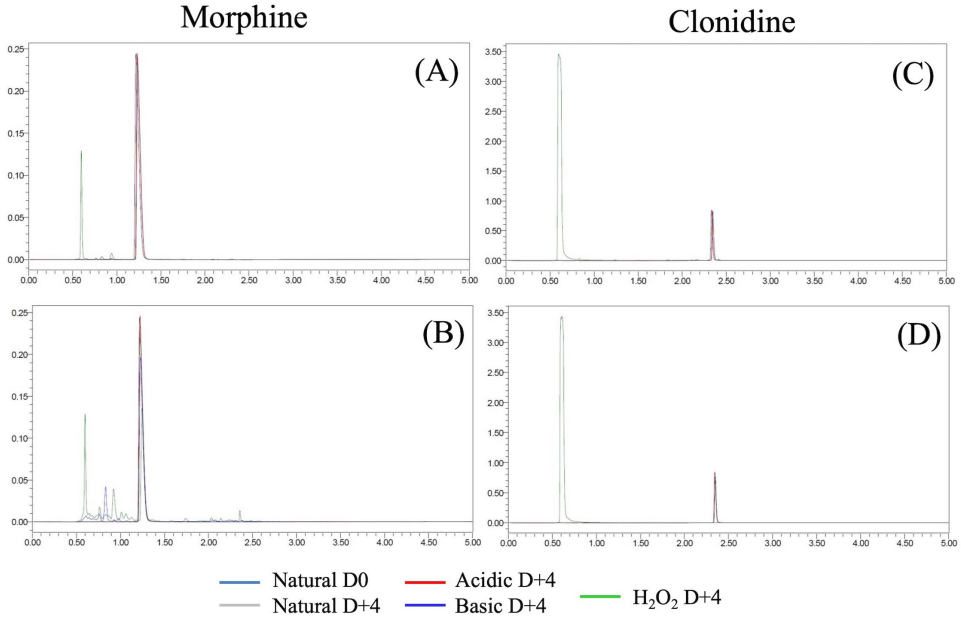

Figure 1 Evaluation of stability-indicating capability of the method by forced degradation at day 4 under different conditions: morphine at room temperature (A) and at 60°C (B); clonidine at room temperature (C) and at 60°C (D). Chromatogram in black was under natural conditions at day 0, in grey was natural at day 4, in red was acidic at day 4, in blue was basic at day 4, and in green was oxidative at day 4.

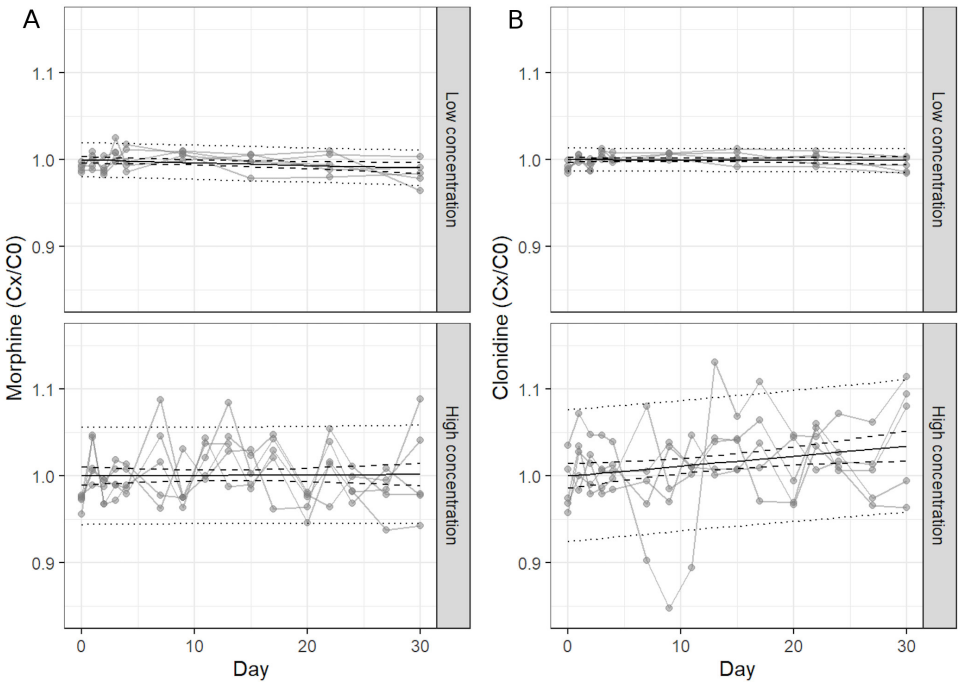

Figure 2 Relative concentration evolution over time for morphine HCl (A) and clonidine (B). Grey lines represent observations for each studied syringe. Black line represents the mean estimated by the linear regression. Dashed line represents the limits of the 90% CI and dotted line represents the limits of the 90% prediction interval.

to pH 2.5 with phosphoric acid 85%. The flow rate was fixed at 0.4 mL/min, corresponding to a good agreement between a fast analysis and a decrease in peaks tailing. Several injection volumes of samples were tested before choosing an injection of 0.3 µl for morphine and 5 µL for clonidine, both without any dilution. According to the molecule spectra, chromatograms were extracted and quantified at the maximum absorption wavelengths, namely at 285 nm (morphine) and 220 nm (clonidine).

UHPLC validation method

The analytical response was linear between 19.5 and 10 000 µg/mL for morphine quantification and between 0.06 and 120 for clonidine quantification (table 2). In addition, the precision of the developed method was assessed. The intra-assay and inter-assay variations (n=10 for each) were evaluated at the three levels of controls (table 3).

Forced degradation study proved that the method indicated stability given that a decrease in each main peak was observed under different conditions tested: natural, acidic, basic and oxidative. Moreover, some degradation products could be detected on chromatograms and were not interfering with the main peaks of morphine and clonidine. Figure 1 presents the forced degradation chromatograms after 4 days at room temperature (A and C) and 60°C (B and D) for solutions containing one active *princeps* at high concentration.

Chemical stability

Figure 2 shows the chemical stability throughout the study period. The morphine content was not found to decrease with mean slope (90% CI) of −0.031% per day (−0.066% to +0.0037 %) and +0.0059% per day (−0.072% to +0.084 %) for low and high concentrations, respectively. Degradation rates of morphine content at high and low concentrations should not exceed −7% every 100 days. The clonidine content decrease was undetectable for the lowest concentration with −0.0029% per day (−0.026% to +0.020 %) and a slight increase of +0.12% per day (+0.0096% to +0.2 %) was observed for the highest concentration. After 30 days, the relative concentration of morphine at low and high concentration was unchanged (98.4% and 100.6% of the initial content, respectively) with lower limits of the 90% CI on the means of 98.4% and 98.9 %, respectively, which are higher than the threshold of 90% required to deem the product chemically stable following the ICH rules. The upper limits of the 90% CI for morphine were 99.7% and 101.5% for low and high concentration solutions, respectively. The relative concentration of clonidine remained stable with 99.4% and 104.9% of the initial content after 30 days at low and high concentration and lower limits of the 90% CI of 99.5% and 101.7 %, respectively. The upper limits of the 90% CI were 100.4% and 105.2% for low and high concentration of clonidine, respectively.

Both molecules, morphine and clonidine, can thus be considered chemically stable for at least 30 days.

DISCUSSION AND CONCLUSION

Opioids are used to manage all types of pain, but related adverse effects have led to an underutilisation of these compounds for adequate pain relief. One strategy to improve their therapeutic utility is to administer them with other analgesic agents such as agonists acting at αlpha-2-adrenergic receptors such as clonidine.[3 4] Indeed, the admixture of clonidine with opioids can result in a synergistic interaction which is indicated to improve efficacy and/or to reduce the dose escalation, to minimise side effects and to improve the therapeutic index.[5] The administration of morphine and clonidine together presents advantages for patients' comfort and safety, and avoids fluid overload.[6] Moreover, the admixture should be prepared in advance under aseptic conditions by a CIVAS in the hospital pharmacy department, resulting in decreased workload and fewer preparation errors.[7] The physicochemical stability of mixtures of morphine HCl and clonidine has been studied under certain conditions and the

literature review found the majority of studies used morphine sulfate.[8–16] The sixth edition of the palliative care formulary does not mention any compatibility of the binary mixture of morphine and clonidine.[21] The consultation of the *Stabilité des medicaments en perfusion* database released in January 2021 did not provide additional information.[9 10] A UHPLC method has been specifically developed and validated for this circumstance and chemical stability results are presented in figure 2.

In this study, we show that the admixture of morphine HCl and clonidine at low concentration (417 µg/mL and 3 µg/mL) and at high concentration (4286 µg/mL and 32 µg/mL), previously prepared in polypropylene syringes, appeared to be physically and chemically stable throughout the study period of 30 days at 5°C±3°C. At the highest concentration, clonidine presented a daily increase of 0.12%, probably due to the presence of experimental bias, by random fact or by evaporation. This observation did not affect the degradation rate since concentration measurements demonstrated that degradation rate was less than 1% over 10 days for each component in both admixtures, and this slight increase was not due to the presence of a new interference such as degradation product since no new peak was observed on the chromatograms.

These results allow us to add these solutions at the specific concentrations used in our hospital to the list of ready-to-use long-term intravenous drug solutions.[22] Despite the absence of studies on microbiological aspects, our pharmaceutical preparations can be assimilated to low-risk compounding based on criteria such as process complexity, the time of administration and the environment.[23] Our study presents some limitations. We focused on stability at 4°C and this was limited to 30 days, and it was based on the working flow in the production department of the hospital pharmacy.

In conclusion, the admixture of morphine HCl and clonidine at clinical concentrations corresponding to doses used in our university hospital is stable and can be prepared in advance under aseptic conditions by a CIVAS in hospital pharmacy departments.

What this paper adds

What is already known on this subject

- A combination of alpha-2 adrenoreceptor agonist with opioids results in a synergistic interaction.
- An admixture of clonidine and morphine presents good long-term stability at 37°C in implantable infusion systems.
- Pharmaceutical preparation in advance by a centralised intravenous additive service (CIVAS) results in decreased workload and fewer errors.

What this study adds

- The admixture of morphine HCl and clonidine at low and high concentrations previously prepared in polypropylene syringes is physically and chemically stable over 30 days at 5°C±3°C.
- This pharmaceutical preparation can be added to the list of ready-to-use long-term intravenous drug solutions in hospital pharmacy.

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Contributors All the authors conceived and planned the experiments. EC and MLC carried out the experiments. CN, JH and LS contributed to sample preparation. EC, MLC, MC, BB, JJ, JDH and LG contributed to the interpretation of the results. EC wrote the draft of the manuscript. MLC, MC, BB, JJ, JDH and LG provided critical feedback and helped shape the research, analysis and manuscript. JDH and LG are the guarantors for the work.

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