BELGIAN JOURNAL OF HOSPITAL PHARMACY

Short Report | Physical stability of an IV mixture of morphine and clonidine in syringe

Catry Emilie[1], Colsoul Marie-Lise[1,2], Closset Mélanie[1,2], Nyssen Caroline[2], Hubert Justine[2,3], Soumoy Laura[2,3], Galanti Laurence[1,3] and Hecq Jean-Daniel[2,3]*

[1]*Medical laboratory, CHU UCL Namur, Avenue Dr Gaston Therasse 1, 5530 Yvoir, Belgium*
[2]*Hospital Pharmacy, CHU UCL Namur, Avenue Dr Gaston Therasse 1, 5530 Yvoir, Belgium*
[3]*Drug Stability Research Group (DSRG), CHU UCL Namur, Avenue Gaston Therasse 1, 5530 Yvoir, Belgium*

*Corresponding author: jean-daniel.hecq@uclouvain.be

KEY WORDS
Clondine, morphine, physical stability, palliative care, injectable drugs

ABSTRACT

BACKGROUND AND AIM
Clonidine is frequently combined to opioids for the management of chronic pain. The aim of this study was to evaluate the physical stability of this combination at high and low concentrations in polypropylene syringes at 5±3°C and at 22±3°C.

METHODS
Five syringes with low concentration of clonidine (0.003 mg/mL) and morphine hydrochloride (0.417 mg/mL) and five syringes with high concentration of clonidine (0.032 mg/mL) and morphine hydrochloride (4.286 mg/mL) were evaluated. The turbidity, the pH and the crystal formation were controlled after the production and until 72h post-production..

RESULTS
No changes in color or appearance of opacity or turbidity were observed. Spectrophotometric measurements (at 350, 410 and 550 nm) and pH were not affected. The microscopic analysis did not detect any aggregate or crystal formation.

DISCUSSION AND CONCLUSION
The mixture of clonidine and morphine hydrochloride at low and high concentrations is physically stable for at least 72 hours post-production at 5±3°C and at 22±3°C. These results paved the way for a subsequent chemical stability study.

INTRODUCTION

Clonidine, an alpha2-adrenoreceptor agonist, is frequently combined with opioids (i.e., morphine hydrochloride) for the management of chronic pain. In the palliative care, the combination of clonidine and morphine is recommended when a tolerance effect is suspected, to minimize side-effects or to improve the therapeutic index[1]. The co-administration of clonidine and morphine through previously prepared syringes presents numerous advantages for patient's comfort and safety. The palliative care unit from CHU UCL Namur will use this mixture in order to limit the volume and the time of the injection and the mixture could be prepared in advance by the centralized intravenous additive service (CIVAS) in our hospital pharmacy[2].

A literature review on its physicochemical stability indicates that the mixture of clonidine and morphine sulfate has a good long-term stability[3-6]. However, the combination with morphine hydrochloride and the specific concentrations used in our palliative care unit have never been studied before.

The aim of this study is to evaluate the physical stability of clonidine-morphine hydrochloride combination therapy at low and high concentrations in 14 mL and 48 mL polypropylene syringes at 5±3°C and at 22±3°C with the objective of preparing them in advance by a CIVAS.

METHODS

Following a previously described method[7-10], ten polypropylene syringes with a final volume of 48 mL (Becton Dickinson, lot 1903268, New Jersey, USA) containing the mixture at the lowest concentration were prepared under aseptic conditions with 0.417 mg/mL of morphine hydrochloride (40 mg/mL, lot 190103, Sterop, Anderlecht, Belgium) and 0.003 mg/mL of clonidine (Catapressan® 0.15 mg/mL, lot 925137, Boehringer Ingelheim, Brussels, Belgium) in NaCl 0.9 % (NaCl 0.9 % Viaflo, lot 19J12T1D, Baxter, Lessines, Belgium). Ten other polypropylene syringes with a final volume of 14 mL contained 4.286 mg/mL of morphine hydrochloride and 0.032 mg/mL of clonidine, corresponding with the highest concentration mixture. The physical stability was evaluated at 5±3°C and at 22±3°C with all syringes protected from light.

All samples were examined immediately after the production and after 1 h, 4 h, 8 h, 24 h, 48 h and 72 h post-production. Firstly, the particles formation was visually inspected on black and on white background. Secondly, the apparition of turbidity or opacity was controlled by spectrophotometry at three wavelengths (350, 410 and 550 nm)[11]. Thirdly, pH was monitored with glass electrode pH-meter (Inolab level 1, WTW Weilhem, Germany with biotrode electrode, Hamilton, Switzerland) after the production and after 1h, 4h, 8h, 24h, 48h and 72h post-production. Finally, the crystal or aggregate formation has been microscopically (at magnification x80) after centrifugation at 2,150 g for 5 minutes of each sample.

RESULTS

During the 72 hours study period, both mixtures at low and high concentrations appeared physically stable. No pH shift was observed for the low concentration at 22±3°C (mean ± SD: 6.45 ± 0.03) and at 5±3°C (mean ± SD: 6.42 ± 0.05) and for the high concentration at 22±3°C (mean ± SD: 5.57 ± 0.03) and at 5±3°C (mean ± SD: 5.58 ± 0.05). Visual examination against black and white background did not reveal any color change. The absence of turbidity was confirmed by spectrophotometric measurements at 350 nm, at 410 nm and at 550 nm (Table 4). During the 72 hours, aggregate formation was not observed in high and low concentrated solutions at 5±3°C and at 22±3°C by light microscopy.

		350 nm	410 nm	550 nm
Low Concentration	22±3°C	0,002 ±0,004	0,000 ±0,001	-0,001 ±0,001
	5±3°C	0,003 ±0,002	0,000 ±0,001	0,000 ±0,001
High Concentration	22±3°C	0,020 ±0,006	0,008 ±0,002	0,001 ±0,001
	5±3°C	0,020 ±0,002	0,008 ±0,001	0,001 ±0,001

Table 4: Spectrophotometric measurements at 350 nm, at 410 nm and at 550 nm, results are expressed as mean ± standard deviation.

DISCUSSION

Consequently, the mixture of clonidine and morphine hydrochloride at low and high concentrations in polypropylene syringes is physically stable for at least 72 hours at 5±3°C and at 22±3°C. However, our results cannot exclude a possible chemical degradation during the period test or the impact of bacterial contamination at 22±3°C. It would be therefore interesting to conduct a study to evaluate the chemical stability of the active substances and whether they retain their efficiency in clinical use.

CONCLUSION

The mixture of clonidine and morphine hydrochloride in polypropylene syringes at low and high concentrations, usually used in our palliative care unit, is physically stable for at least 72 hours at 5±3°C and at 22±3°C. These results paved the way for a subsequent study of chemical stability.

ACKNOWLEDGEMENTS

No conflict of interest

REFERENCES

1. Twycross R, Wicock A, Howard P. Palliative care formulary 6th edition. Pharmaceutical Press 2018, London UK
2. Hecq JD. Centralized Intravenous Additive Services (CIVAS): The state of the art in 2010. Annales Pharmaceutiques Françaises 2011 ;69 :30 - 37
3. Hecq JD. Stabilité des médicaments injectables en perfusion. Edition 2019. Association Belge des Pharmaciens d'Hôpitaux – Belgische Vereniging van Ziekenhuis Apothekers, Bruxelles, Belgique.
4. Xu QA, Trissel LA, Pham L. Physical and chemical stability of low and high concentrations of morphine sulfate with clonidine HCl repackaged in plastic syringes. Int J Pharm Compound 2002 6 66-69
5. Hildebrand KR, Elsberry DD, Hassenbusch SJ. Stability and compatibility of morphine-clonidine admixtures in an implantable infusion system. J Pain Symptom Manage 2003 25 464 - 471
6. Perez Juan E, Maqueda Palau M, Amoros cerda S, Arevalo Rubert M, Ribas Nicolau B. Compatibilité physique de médicaments administrés dans l'unité de soins intensifs. Pharmactuel 2015;48:146-152
7. Anrys P, Magnette A, Jamart J, Galanti L, Hecq JD. Compatibilité physique d'un mélange d'alizapride et de clorazépate dans des poches souples de 100 ml glucose 5 % pour perfusion. Journal de Pharmacie de Belgique 2014 ;96 :38-39
8. Huvelle S, Godet M, Gillet P, Jamart J, Galanti l, Hecq JD. Compatibilité physique d'un mélange d'alizapride et de dexamethasone dans des poches souples de 100 ml glucose 5 % pour perfusion. Journal de Pharmacie de Belgique 2015 97:38-39
9. Simar J, Delcave C, Godet M, Decoster C, Gillet P, Bihin B, Jamart J, Galanti LM, Hecq JD. Stabilité physique du chlorhydrate d'amiodarone dans des seringues de glucose 5 % pour perfusion. Journal de Pharmacie de Belgique 2016 ;98 (1) : 24-25
10. Closset M, Hecq JD, Soumoy L, Simar J, Gonzalez E, Charlet L, Declave C, Gillet P, Galanti L. Physical stability of highly concentrated injectable drugs solutions used in intensive care units. Ann Pharm Fr. 2017 Feb 13. pii: S0003-4509(16)30055-4. doi: 10.1016/j.pharma.2016.12.004.
11. Lahlou A, Blanchet B, Carvalho M, Paul M, Astier A. Mechanically-induced aggregation of the monoclonal antibody cetuximab. Ann Pharm Fr. 2009 Sep;67(5):340–52.

The BJHP is not responsible for the scientific content/contribution. Authors have full responsibility.