

Long-term stability of an infusion containing ketamine, morphine and lorazepam in syringe at 5±3°C

M.-L. Colsohl, J.-D. Hecq, L. Defrene, N. Goderniaux, M. Closset,
L. Soumoy, B. Bihin, J. Jamart, L. Galanti
CHU UCL Namur, 1 avenue Therasse, 5530 Yvoir, Belgium



BACKGROUND AND OBJECTIVE

Patients in palliative care are injected with a sedation infusion containing ketamine, morphine and lorazepam in order to relieve pain. The awareness of the infusion stability could allow a preparation in batch and in advance by a Centralized IntraVenous Additive Services (CIVAS). The aim of this study was to evaluate the physicochemical stability in syringes at 5±3°C of the injectable with two different levels of concentration commonly used.

METHOD

- Five syringes prepared under aseptic conditions for each level of concentration
 - o Low concentration: ketamine 1.5 mg/ml, morphine 1.5 mg/ml and lorazepam 0.1 mg/ml
 - o High concentration: ketamine 5 mg/ml, morphine 6 mg/ml and lorazepam 0.3 mg/ml
 - Storage of solutions: 5±3°C for 25 days
 - Stability evaluation: each day the first week, then 3 times a week
- Physical stability:
- o Visual inspection → detection of particle appearance or colour change
 - o Microscopic inspection → research of crystals
 - o pH → assessment of its stability
 - o Optical densities (350, 410 and 550 nm) → evaluation of the solution turbidity
- Chemical stability:
- o Ultra-High Performance Liquid Chromatography (UHPLC)
 - diode array detection → measurement of the molecules concentrations
 - o Solutions considered chemically stable while the lower one-sided confidence limit at 95% remains superior to 90% of the initial concentration (ICH guidelines).

RESULTS

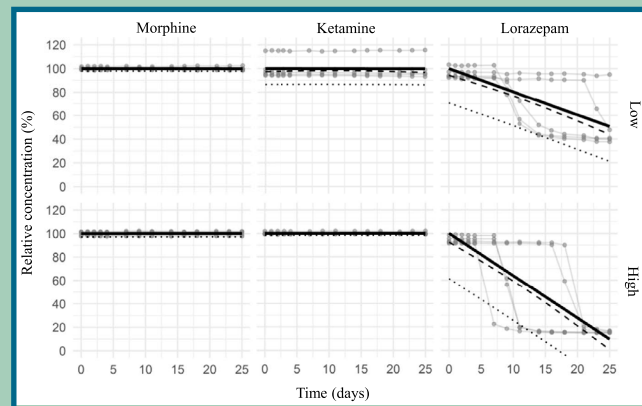
Physical stability:

- Crystals were visible to the naked eye after 23 days (low concentration solutions) and 11 days (high concentration solutions).
 - Some crystals were observed under the microscope after 7 days in high concentration solutions (Fig. 1)
 - pH was stable
 - Optical densities at 410 and 550 nm were stable
 - Decrease of the optical density at 350 nm after 11 days (low concentration solutions) and 7 days (high concentration solutions), suggesting the degradation of a compound absorbing at this wavelength
- Chemical stability (Fig. 2)
- Ketamine and morphine were stable for 25 days
 - Lorazepam was unstable after 3 days (low concentration solutions) and 1 day (high concentration solutions)

Fig. 2: Relative concentration versus time for morphine, ketamine and lorazepam in low and high concentration solutions. Grey = observations in each syringe, black line = fitted mean, dashed line = 95% unilateral confidence interval.



Fig. 1: Crystals observed under the microscope after 7 days in high concentration solutions



CONCLUSION

Infusions containing ketamine, morphine and lorazepam used in palliative care are unstable at 5±3°C after 3 or 1 day(s), depending of the concentration. Consequently, it is not possible to consider their preparation in advance by a CIVAS.