

Stability of bendamustine reconstituted with water for injection at 2.5 mg/mL and diluted with 0.9% or 1.5% sodium chloride at 0.25 and 0.60 mg/mL

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INTRODUCTION

Bendamustine (Levact®) is a nitrogen mustard used for the treatment of chronic lymphocytic leukemia (CLL), non Hodgkin lymphoma and myeloma. Bendamustine must be reconstituted with water for injection (WFI) to obtain a 2.5 mg/mL solution. There is no data on the stability of this solution. The drug must be further diluted with 0.9% sodium chloride to be administered intravenously by infusion. There is only one publication on the stability of this drug (Krämer et al, Pharmazie 1994 ; 49, 10: 775-777.) which gives a stability of 9 hours at room temperature and 4 days in the refrigerator.

OBJECTIVES

The objectives of this work were to study the **stability of the reconstituted solution** and then, the **influence of the concentration of sodium chloride** (0.9% versus 1.5%) on the stability of diluted solutions at 0.25 and 0.6 mg/mL in glass vials.

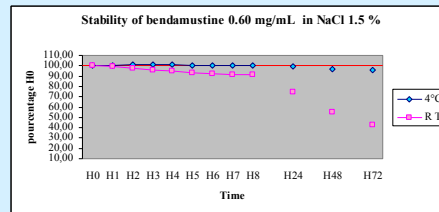
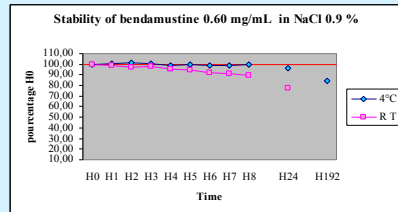
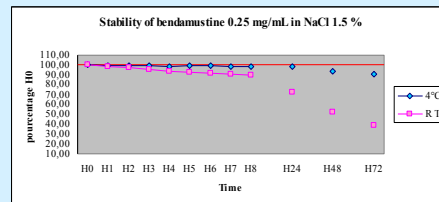
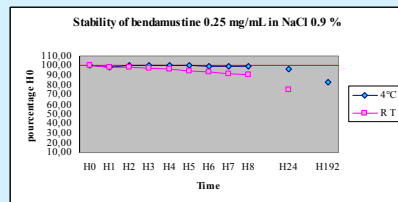
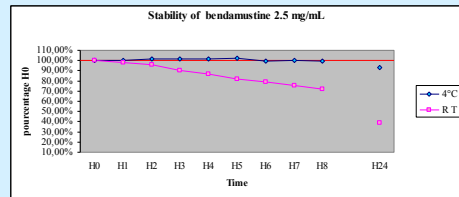
METHOD

Analytical conditions : HPLC method of Krämer et al
Column: C18, 5µ, 200 mm x 4.6 mm
Mobil phase: Sodium sulfate buffer pH3/Methanol (40/60)
UV detection: 331 nm
Linear from 0.15 to 0.35 mg/mL
Intraday and interday reproducibility: 1.5 and 1.8%

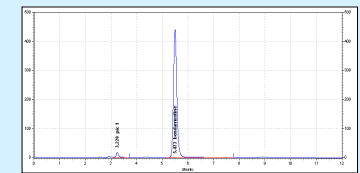
Preparation of the samples:
- Reconstitution of Bendamustine 25 mg with 10 mL of water for injection
- Dilution in 0.9% NaCl or 1.5% in glass vials (10 mL)
- 3 samples for each condition (results expressed as the mean of 3 values)
Storage temperatures: 4°C and 22°C not protected from light

Definition of the stability according to ICH Guideline Q1A: concentration above 95% of the initial concentration

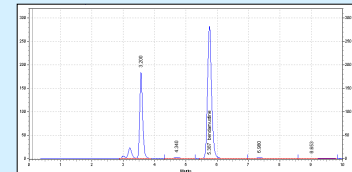
Evolution of concentrations



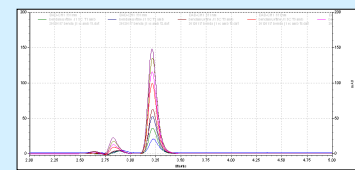
Some chromatograms



Freshly prepared 2.5 mg/mL bendamustine solution



Degradation of bendamustine with NaOH 0.1 N



Focus on the degradation products between 2 and 5 minutes: Superimposition of the degradation products from H0 to H 8 in the reconstituted solution at 2.5 mg/mL

DISCUSSION - CONCLUSION

Bendamustine is a very unstable drug. It can be hydrolysed and its stability depends on the presence of chloride ions.

The stability of the reconstituted solution at 2.5 mg/mL is 8 hours in the refrigerator. The solution is unstable at room temperature with a T95% around 2 hours. The stability of the infusion prepared in 0.9% sodium chloride is in accordance with the manufacturer's recommendations (3.5 hours at RT and 2 days at 2-8°C) but could not be extended if the T95% is retained for the definition of stability.

The stability of the infusion prepared in 1.5% sodium chloride is only slightly better at the higher concentration studied 0.6 mg/mL (99.3% in NaCl 1.5% versus 96.4% in NaCl 0.9% at H 24 and 90.5% versus 84.6% at H 192), but not at 0.25 mg/mL. These results can be hardly used in the daily practice. Like for other drugs (melphalan or cisplatin), stability studies should be performed in more concentrated sodium chloride solutions to enhance the stability.

What is new and applicable in daily practice ?

Bendamustine 2.5 mg/mL reconstituted solution with WFI is stable for 8 hours at 2-8°C.
Advantage: re-use of vial is possible and cost savings

What is new and needs further investigations ?

Bendamustine 0.6 mg/mL diluted in 1.5% sodium chloride is more stable than solution diluted in normal saline (but not the 0.25 mg/mL).
The stability in 3% sodium chloride should be investigated

