Stability of 2 mg/mL melphalan in 0.9% sodium chloride under sequential storage conditions

J. Vigneron*, H Zenier*, I. May*, A Nicolas*
*University Hospital Brabois, Vandoeuvre, France - j.vigneron@chu-nancy.fr

INTRODUCTION

The stability of melphalan solutions depends on temperature and ion chloride concentration. The manufacturer indicates 1h 30 stability at room temperature. This period is very short for the preparation, transport and administration.

OBJECTIVE

To study the stability of 2 mg/mL melphalan solutions diluted with 0.9% sodium chloride prepared with an infusion bag of sodium chloride at 4°C, storage of this melphalan infusion bag at 4°C and then at room temperature to simulate the steps "preparation, transport and administration".

METHOD

Analytical methods :
- Visual inspection
- CLHP current monograph of European Pharmacopoeia

Three steps:
First step : To define the stability criteria for the acceptable melphalan concentration and the concentration of degradation products and impurities >> Analysis of a 2 mg/mL melphalan solution at Time 0 and 90 minutes after storage at room temperature (stability data from the manufacturer) (n=3).
Second step : Preliminary stability study in glass tubes for a 2 mg/mL melphalan solution stored in the refrigerator to determine the storage duration of the infusion bags in the third step (n=3)
Third step : Stability study in daily practice conditions.

RESULTS

First step : To define the stability criteria

Storage of the infusion bags: 1h30 at room temperature (22-25°C) according to the manufacturer's recommandations

- Melphalan concentration at 1h30 : 92%
- Impurities (European Pharmacopoeia)
    - Impurity D : 4,5%
    - Impurity G : 0,6%
- Secondary impurities
    - Secondary impurity 1 : 2,4%
    - Secondary impurity 2 : 0,30%
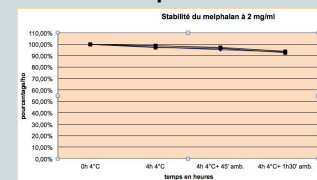- Total of secondary impurities : 2,7%
- Total impurities : 7,8%

Chromatogram after 1 h 30 at room temperature

Second step : Preliminary stability study in glass tubes at 2-8°C (n=3

Melphalan 2 mg/mL - NaCl 0,9% +4°C (n=3)		
Time	**Area**	**Area % / T0**
0h	18 060 719	100,00%
1h	17 870 250	98,95%
2h	17 549 683	97,17%
3h	17 496 980	96,88%
4h	17 177 954	95,11%
5h	16 807 521	93,06%
6h	16 782 863	92,92%
7h	16 369 615	90,64%

Decisions to conduct the third step : Maximum storage time in the refrigerator : 4 hours (95% of melphalan concentration remaining) then storage at room temperature until it reaches of the stability criteria defined during the first step.
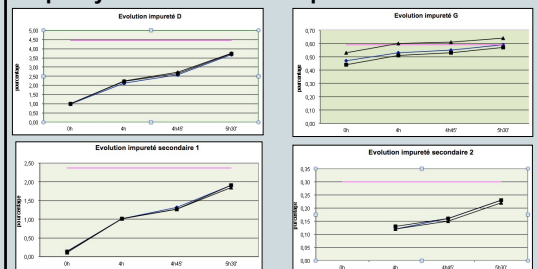
Third step : Stability study of infusion bags in the daily practice conditions (n=3)
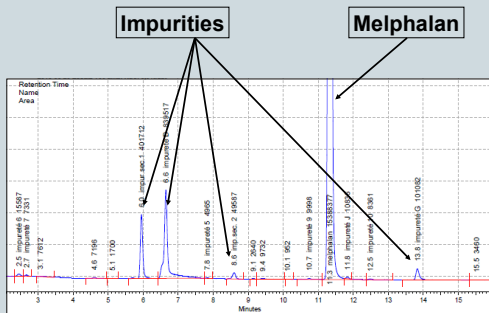
Evolution of melphalan concentration

Monitoring of impurities
- Impurity D below the acceptance criteria
- Impurity G reaches the acceptance criteria

- After 4 hours at 2-8°C and then 1h30 at room temperature, the melphalan concentration reaches 93% of the initial concentration.
- Impurities concentrations are below or reached the acceptance criteria defined in the first step.

DISCUSSION

- The melphalan concentration is around 93% of the initial concentration after 4 hours at 4°C and 1h30 at room temperature
- The impurities concentrations are below the acceptance criteria except for impurity G which reaches the acceptance criteria defined in the first step. The stability could not be extended after 5h30 due to impurity G that would be outside acceptance criteria.
- This stability study shows the importance of evaluating the degradation products according to the ICH Q1A and the European consensus on stability studies of anticancer drugs (Bardin et al, Ann Pharm Fr 2011; 69, 4: 221-231).

CONCLUSION : New data for the daily practice

1- Preparation of melphalan infusions by using refrigerated 0.9% sodium chloride solutions.
2- Stability of 2 mg/mL melphalan infusion bags at 4°C (send to the ward in a cold box) then 1 h 30 at room temperature for the administration to the patient (maximum stability data due to the concentration of impurity G).
3- Better organization for pharmacy staff and nursing staff with a 5h30 stability instead of 1h30 according to the manufacturer.

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