

Ifosfamide induced encephalopathy: quality control of intravenous solution of methylene blue formulated and prepared in pharmacy using a disposable closed system transfer device-a case report

M. BENABBES^{1,2}, M. ALAMI CHENTOUFI^{1,2}, A. LAKHDISSI³, H. ABAHSSAIN³, H. ERRIHAN³, B. MEDDAH⁴

1-National Institute of Oncology, Service of Pharmacy, Oncology-University Hospital Center Ibn Sina, Rabat, Morocco.

2-Faculty of Medicine and pharmacy- Mohammed V University, Laboratory of Analytical Chemistry, Rabat, Morocco.

3-National Institute of Oncology- Service of Medical Oncology-University Hospital Center Ibn Sina, Rabat, Morocco.

4-Faculty of Medicine and Pharmacy- Mohammed V University, Laboratory of Pharmacology, Rabat, Morocco.

3PC-038

Objective

Ifosfamide is an alkylating agent used in the treatment of a variety of solid tumours. Its use may be limited by specific side effects. One of the most serious of these is the encephalopathy. Methylene blue (MB) may be used in the treatment of this encephalopathy. The purpose of this study was the formulation and control quality analysis of injectable MB preparation and safety case of encephalopathy associated with Ifosfamide in the absence of MB injectable in the pharmaceutical market in the country.

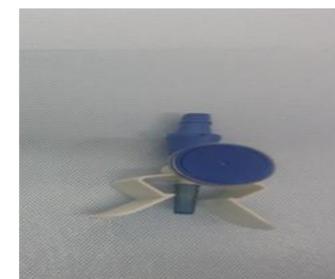
Study design

- ❖ Case female, 65 years, with uterine leiomyosarcoma and received doxorubicin (20mg/m²), Ifosfamide (2,5g/m²) and mesna (2,5g/m²). On the third day of treatment, the patient presented obnubilation and awareness troubles. Ifosfamide-induced encephalopathy was suspected. Once diagnosed, a treatment based on MB was proposed. Unfortunately, the product is not marketed in the country. the MB solution 10mg/ml for intravenous administration was prepared at the pharmacy.
- ❖ A disposable closed system transfer device with filter 0.15 µm was used, so as to perform a sterile filtration. Next, an analytical control of drug substance and drug product was carried out in accordance with united state pharmacopeia. Finally, the preparation was administrated to the patient.

Results

- ❖ The MB solution 10mg/ml for intravenous administration was prepared with serum glucose 5%. Due to the unavailability of an adequate method of sterilization, it was decided to use a disposable closed system transfer device with filter 0.15 µm to perform a sterile filtration (Figure 1).
- ❖ A quality control of active substance and finished product was done in accordance with United state Pharmacopeia (USP). The Methylthionium chloride chemical substance reference (SCR) was obtained from USP (USP Lot N°: R03520; CAS N°:122965-43-9).

Figure 1: disposable closed system transfer device



Active substance

- ❖ **Identification:** infrared Absorption (IA). The figure 2 show a comparative Spectrum of MB-active substance and MBS-SCR. The percentage of correlation was 84,66%.

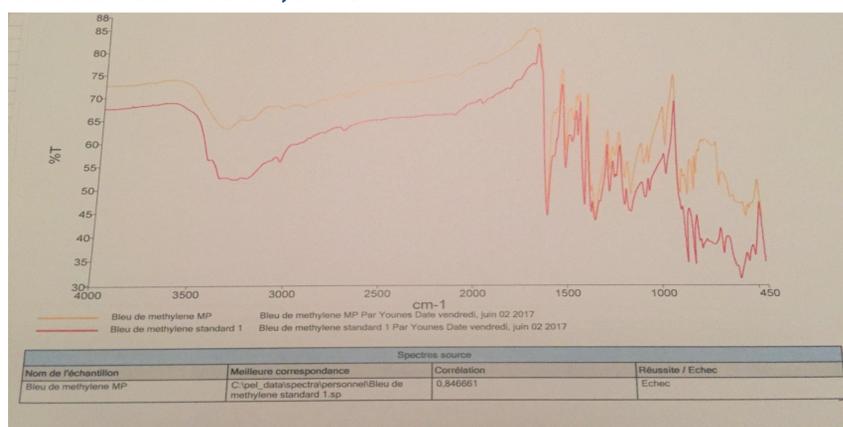


Figure 2: IA Spectrum of MB-active substance and MBS-SCR

- ❖ **Loss on drying:** MB loses 16% of its weight at 75° in 4 hours.
- ❖ **Chromatography purity:** The figure 3 show the chromatogram of both MB-active substance and MB-SCR. It has the same Rf in chromatogram.
- ❖ **Assay:** performed using UV-visible spectrometer at 663nm . The MB contain 102,67% of C₁₆H₁₈ClN₃S anhydre (not less than 98% and not more than 103%)

Discussion and Conclusion

The patient received MB solution with a posology of 6×50 mg per day, which it was sufficient for the management of encephalopathy. The preparation of MB using a disposable closed system transfer device was a original idea and performed for the first time in our institution. This practice has made it possible to treat toxicities of Ifosfamide and has become a routine practice in pharmacy.

Acknowledgements

We would like to show our gratitude to the pharmacy team of National Institute of Oncology for their assistance.

Quality control

Finished Product

- ❖ **Identification:** The figure 4 show the chromatogram of both MB-Injection and MB-SCR.
- ❖ **Bacterial endotoxin:** Carried out using Limulus ameobocyte lysate Test (LAL Test). The preparation contain less than 2.5 USP endotoxin Units per ml.
- ❖ **pH :** 4,76.
- ❖ **Osmolality:** 308 mosmole/Kg.
- ❖ **Microbiology:** The preparation was sterile.
- ❖ **Assay:** performed using UV-visible spectrometer at 663nm. The concentration on MB (C₁₆H₁₈ClN₃S, 3H₂O) 9,6mg/ml.

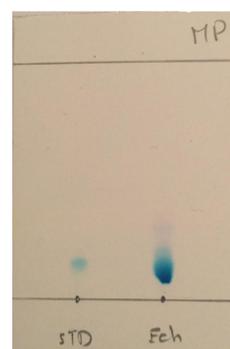


Figure 3: Chromatogram of MB-active substance and MB-SCR

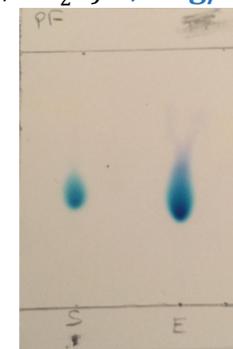


Figure 4: Chromatogram of MB-Injection and MB-SCR