4CPS-033

Development and evaluation of an amitriptyline topical form for the treatment of cancer-related neuropathy

J. Bonamour[1], M-A. Seveque[1], A. Choquer[1], T. Fleury[1], E. Daguet[1], H. Aboudagga[1], S. Laurent[1], R. Kotabaoui[1], A. Rieutord[1], M. Annereau[1]

[1]Gustave Roussy Cancer Campus, Villejuif, France

juliebonamour96@gmail.com

BACKGROUND AND IMPORTANCE

In France, 6.9% of the general population suffer from neuropathic pain[i]. Among the causes are surgery (20%), including cancer surgery, and chemically induced paresthesia (4.1%)[ii]. There is few treatment developed in this indication, and patients quickly find themselves in a therapeutic impasse. In addition, oral treatments could possibly cause undesired systemic effects.

Aim and Objectives :

- Develop a topical form of amitriptyline at 10%
- Treat the second line patients

MATERIAL AND METHODES

Develop of the cream:

- Formulation development : test of different excipients
- Stability evaluation according to the International Consensus Organisation (ICH)
  - Method validation and forced degradation
  - pH, osmolality, chemical, organoleptic and biological analyses
- Measures of the galenic properties of the cream : release, diffusion and rheology

Evaluation of the pain :

- According to the VAS (Visual Analogical Scale) : the pain was measured before and after the treatment
  - A 30% reduction in pain was considered effective
  - Reduction between 10% and 30% was considered partially effective
  - A reduction less than 10% was considered ineffective

RESULTS

Table 1. Final formulation of amitriptyline cream

Agent	Function	Proportion for 100g of cream
Amitriptyline chlorydrate	Active ingredient	11,34g
VERSATILE® cream	Excipient	86,6g
Urea	Emollient	2g

Table 2. Regression data from amitriptyline calibration

Parameters	Results
Time of retention	2,45 minutes
λ	254 nm
Linearity	200-1000 µg/ml
Regression curve	y = 764x - 6.57
R^2	0,9991
Linearity	200-1000 µg/ml
Regression	p<0.05
Limit of detection	28.34 µg/ml
Limit of quantification	85.91 µg/ml
RSD	1.69%

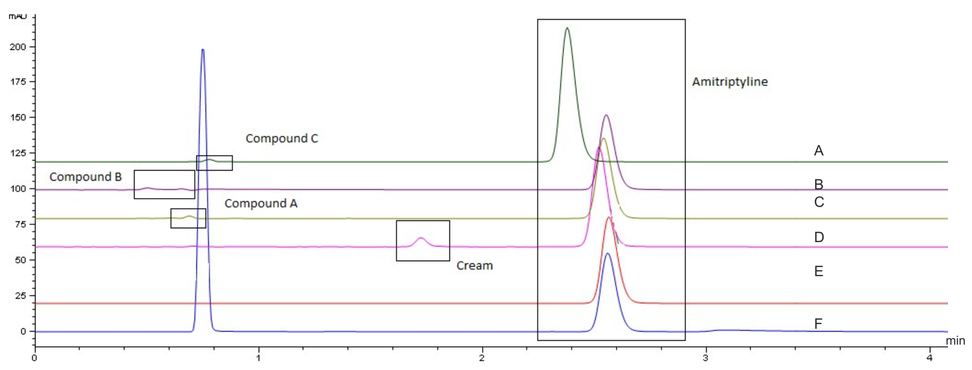

Figure 1

(A)Chromatogram of AMT under heat conditions showed ; (B) Chromatogram of AMT under basic conditions ; (C) Chromatogram of AMT under acidic conditions ; (D) Chromatogram of the AMT cream ; (E) Standard chromatogram of AMT ; (F) Chromatogram of AMT under oxidative conditions

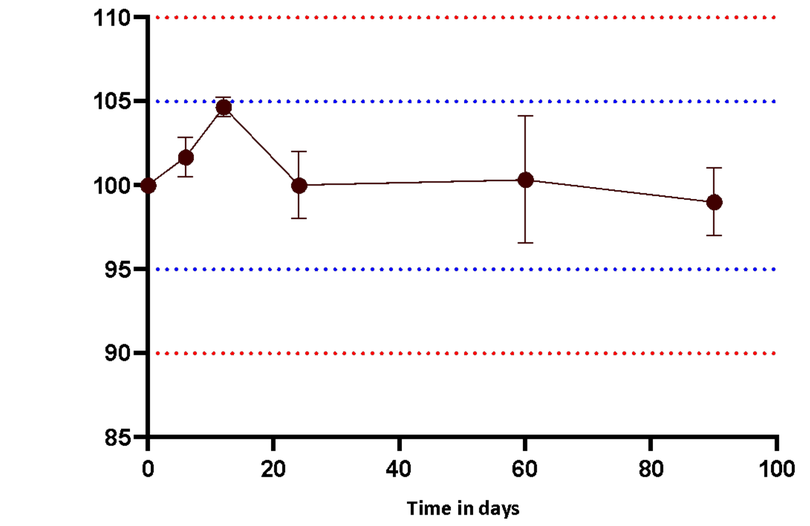

Figure 2

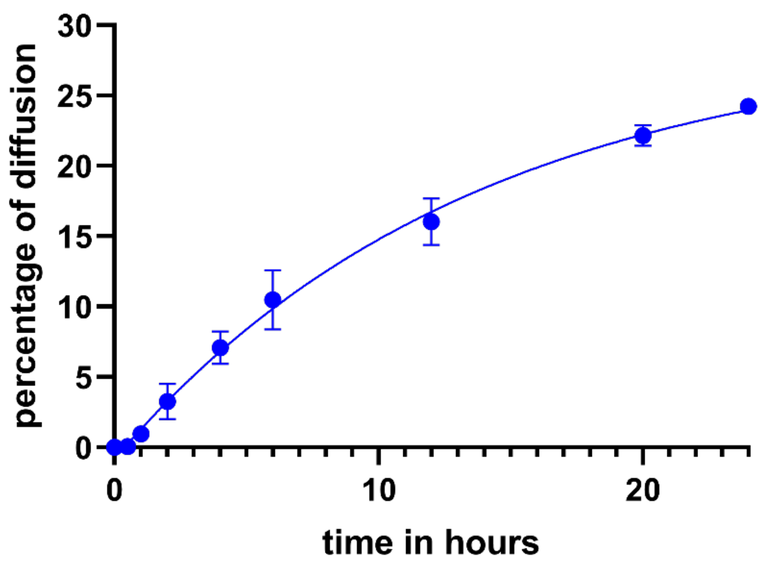

Figure 3

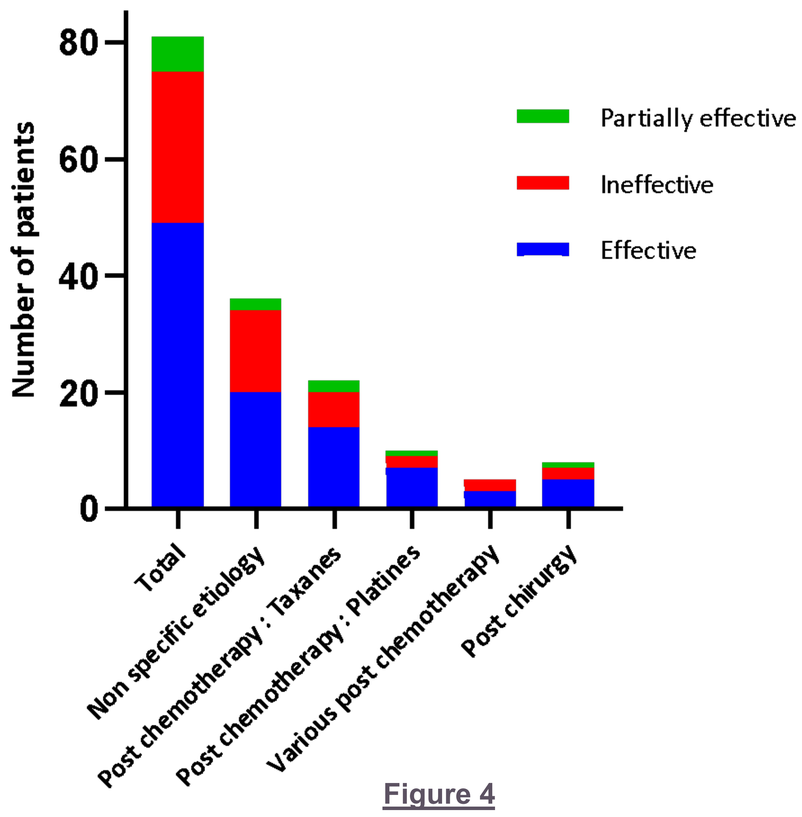

Figure 4

Figure 1: Chromatogram of amitriptyline (AMT) and degradation products under different stress conditions at 254nm ; Figure 2 : Evolution of amitriptyline content in three months ; Figure 3 : Cumulative amitriptyline diffusion from Versatile® cream (n=6) ; Figure 4 : Effectiveness of amitriptyline cream according to etiology

CONCLUSION AND RELEVANCE

This cream keeps its diffusion properties, its organoleptic characteristics but also its physicochemical and microbiological stability in a PVC/ALU packaging.
For the 81 patients included, the cream was effective on 60,5% of them.
The development of this topical, has allowed to relieve neuropathic patients, these data are very encouraging and will be confirmed through the implementation of a clinical trial.

REFERENCES

[i] Bouhassira D, Lantéri-Minet M, Attal N, Laurent B, Touboul C. Prevalence of chronic pain with neuropathic characteristics in the general population. Pain. juin 2008;136(3):380-7.

[ii] Torrance N, Smith BH, Bennett MI, Lee AJ. The epidemiology of chronic pain of predominantly neuropathic origin. Results from a general population survey. J Pain Off J Am Pain Soc. avr 2006;7(4):281-9.