

INTRODUCTION

High doses of amoxicillin (100-300 mg/kg/j) are recommended for treatment of severe infections (endocarditis, bone...). PK-PD of β -lactams suggests the use of continuous infusion. Therefore, physico-chemical stability of amoxicillin is crucial to ensure safety and efficacy. Few data are available in the literature about amoxicillin stability with a poor level of proof especially concerning analytical methods performed. In a previous work (Binson *et al.*, *PLoS ONE* 2019), we have demonstrated that amoxicillin stability depends on concentration and temperature and we have determined optimized conditions for continuous infusion of high doses of amoxicillin. However, to our knowledge, those conditions require infusion device (20 ml/h, 240 ml) not yet available, at least in France. Recently, Asept InMed has commercialized an innovative portable pump (ANAPA®) suitable for our conditions. ANAPA® is a safe CO₂ pressured infusion device containing a special relief valve for maintaining gas pressure and a glass capillary, allowing accurate flow rate.

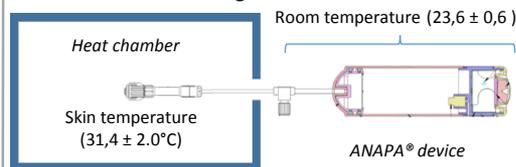
The aim of this work was to assess amoxicillin chemical stability in ANAPA® and to investigate its infusion flow rate accuracy.

MATERIAL AND METHODS

Filling up of ANAPA® devices

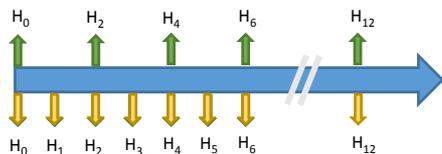
- ANAPA® devices were filled up with 6 g of Amoxicillin reconstituted with 120 ml of sterile water
- 120 mL of NaCl 0.9% were added to reach the target concentration (25 mg/mL)

Storage conditions



Study design & sample analysis (n = 3)

Amoxicillin content assay



Infusion flow rate assessment

HPLC-UV analysis

- Column : Purospher STAR® RP-18 (150x4.6 mm, 5 μ m) Merck®
- Mobile phase : methanol/water (20:80, v:v), flow rate = 1 ml/min
- Detection : λ = 225 nm
- Method validated according to international guidelines

Infusion flow rate assessment

- Density measurement of diluted Amoxicillin
- Evaporation evaluation
- Weighing a beaker at H₀ then every hour
- Flow rate measurement (mL/h) :

$$F_R = \frac{M_{H+\Delta t} - M_H}{\Delta t \times d}$$

RESULTS

Amoxicillin content assay

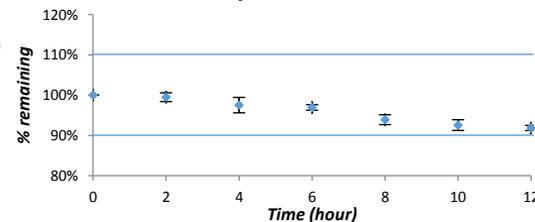
Initial concentration 25,4 ± 0,3 mg/l (n=3)



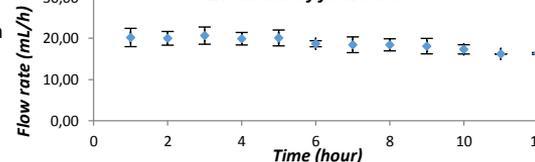
Infusion flow rate assessment

Amoxicillin density after reconstitution and dilution: 1.055
Evaporation rate: 0.243 mL/h
Average flow rate over 12h : 18,7 mL/h (±1.5 mL/h)

Evolution of amoxicillin concentration



Evolution of flow rate



CONCLUSION

Amoxicillin (25 mg/ml) is stable up to 12h in ANAPA® device using easy and realistic storage conditions (device stored at room temperature and administration site near to body temperature). Moreover, our results show that the infusion flow rate remains accurate all along the use of the ANAPA®. In case of continuous infusion of high doses of amoxicillin (12g/24h), ANAPA® 250 ml device allows an easy, accurate and safe administration suitable for outpatient treatment. The use of this device could be extended to other drugs administered by continuous infusion (anti-infectious, chemotherapies, analgesics ...) provided that stability studies are available.