# STABILITY OF INJECTABLE CEFTOBIPROLE MEDOCARIL (ZEVTERA™) IN THE INTERMATE® AMBULATORY INFUSION SYSTEM

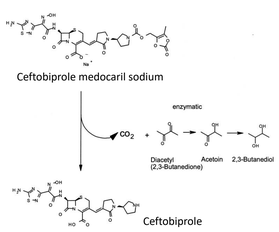
Audrey Vachon[1-3], Alexandra Porlier[3], Isabelle Cloutier[1-3], Benoît Drolet[2,3], Chantale Simard[2,3].
[1]Département de pharmacie, Institut universitaire de cardiologie et de pneumologie de Québec-Université Laval, Québec (Québec), Canada.
[2]Faculté de pharmacie, Université Laval, Québec (Québec), Canada.
[3]Centre de recherche, Institut universitaire de cardiologie et de pneumologie de Québec-Université Laval, Québec (Québec), Canada.

## Background

- Ceftobiprole medocaril (Zevtera™) is an injectable broad spectrum antibiotic belonging to the fifth-generation cephalosporin family.[1]
- It falls under the group of pyrrolidinone-3-ylidene-methyl cephalosporins and, like β-lactams, exerts its antimicrobial activity by binding to the transpeptidase fraction of penicillin binding proteins essential for the bacterial cell wall synthesis. This binding inhibits cell growth and ultimately leads to bacterial cell death. [2,3]
- Ceftobiprole has a rapid bactericidal mode of action against a broad spectrum of Gram-positive and Gram-negative bacteria, including *Pseudomonas aeruginosa* and methicillin-resistant *Staphylococcus aureus* (MRSA). It is therefore recommended for the treatment of community-acquired pneumonia and non-ventilator-associated-hospital-acquired pneumonia.[4]
- At IUCPQ-ULaval, some patients, including those with cystic fibrosis, may simultaneously carry both bacteria, have resistance to one or the other, or present contraindications to the use of other antibiotics. Although Zevtera™ is usually initiated in hospitalized patients, some may need to complete their treatment at home through the outpatient and home intravenous antibiotic therapy program (*ATIVAD*: *Antibiothérapie intraveineuse à domicile*).

## Rationale

- Ceftobiprole is derived from a water-soluble prodrug : ceftobiprole medocaril sodium, which is available as a powder for reconstitution. The conversion to ceftobiprole, carried out by plasma esterases is rapid and complete.[4]




Adapted figure from Dechambre et al. 2016

- The United States Pharmacopeia (USP) specifies that a variation of ± 10% from the expected concentration is acceptable for most preparations.[6] Therefore, the actual concentration of ceftobiprole should not be less than 90% of the expected concentration, regardless of the preparation methods or storage conditions used. An insufficient concentration could result in plasma levels below the minimum inhibitory concentration (MIC), and consequently, negatively affect the effectiveness of antimicrobial treatment.[5]

## Aim

The aim of this study was to assess the stability of ceftobiprole medocaril reconstituted in 0.9% NaCl within the Intermate® LV 100 infusion system, in view of optimizing drug administration for ambulatory patients at home.

## Methods

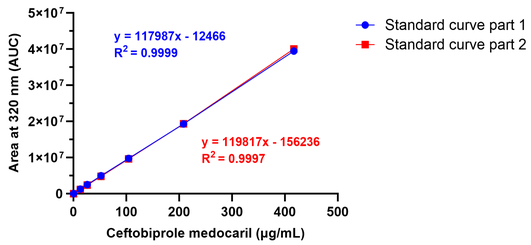
Fifteen vials of ceftobiprole medocaril (Zevtera™, AVIR Pharma Inc., Blainville, QC, Canada) were prepared under a laminar flow hood according to the usual practices at IUCPQ-ULaval, as follows:

- 500 mg ceftobiprole (10 mL) in 190 mL of 0.9% NaCl in Intermate® LV 100, at a final concentration of 2.5 mg/mL (3.34 mg/mL ceftobiprole medocaril).

- In triplicate, the preparations were stored at 4°C until the time of analysis at 0 hour (T0) and then left at room temperature (RT) for 8 hours (T8). A sample of each preparation was collected at T0 and T8 and diluted by a factor of 10 immediately before analysis, at each of the following days: part 1: Day 0 to Day 4, part 2: Day 6 and Day 9.

- The concentration of ceftobiprole medocaril sodium was determined by HPLC using a method validated by Cloutier *et al.*,[7] which had previously been used in our laboratory to verify the stability of ceftobiprole in PVC bags. In summary, the chromatographic separation of ceftobiprole medocaril was performed at 30°C using the Prominence system from Shimadzu (Columbia MD, USA) , consisting of :
  - SIL-20AC autosampler at 6°C
  - Ultrasphere ODS column, 5 µ, 250 X 4.6 mm (Canadian Life Technologies, Burlington ON, Canada)
  - µ-Bondapack C18 pre-column (Waters, Mississauga ON, Canada)
  - Mobile phase: phosphate buffer 10 mM, pH 8.0/acetonitrile (80/20)
  - UV detector SPD-20A at 320 nm
  - Flow rate: 1 mL/min

- The linearity of the method was confirmed using standard curves prepared by successively diluting a vial of ceftobiprole medocaril sodium that had been previously reconstituted in a known volume (666.6 mg/200 mL).




## Results

### HPLC: *Typical chromatogram*

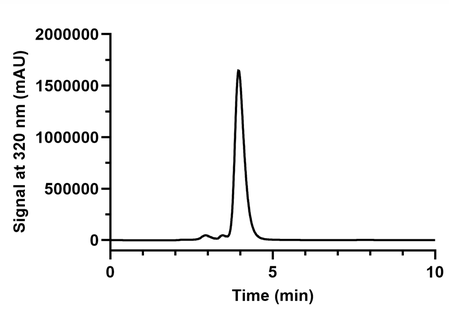



**Figure 1.** Under these analytical conditions, the peak corresponding to ceftobiprole medocaril elutes at 4 minutes.

### *Impact of storage in Intermate® LV 100 (0.9% NaCl)*

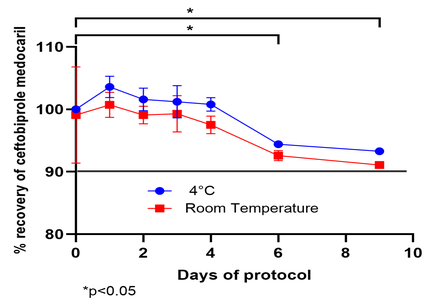



**Figure 2.** Percentage recovery calculated from the initial concentration of ceftobiprole medocaril, evaluated from the initial time (T0) at 4 °C (blue), followed by 8 hours (T8) of storage in the Intermate® LV 100 infusion system at room temperature (red).

**Table 1. Recovery of ceftobiprole medocaril from Day 0 Time 0h at 4°C (%)**

| Day/Time (hours) | 0h - 4°C | 8h - RT |
|---|---|---|
| Day 0 | **100** | 99.1 ± 7.7 |
| Day 1 | 103.6 ± 1.7 | 100.7 ± 2.0 |
| Day 2 | 101.6 ± 1.8 | 99.1 ± 1.4 |
| Day 3 | 101.2 ± 2.6 | 99.3 ± 2.9 |
| Day 4 | 100.8 ± 1.1 | 97.5 ± 1.4 |
| Day 6 | 94.4* ± 0.4 | 92.6* ± 0.8 |
| Day 9 | 93.3* ± 0.5 | 91.1* ± 0.6 |

Mean ± SD
*p< 0.05 vs Day 0 Time 0h at 4°C

When stored at 4°C, more than 93% of the initial amount of ceftobiprole medocaril remains available 9 days after preparation in Intermate® at 3.34 mg/mL (2.5 mg/mL ceftobiprole). When the same Intermate® are kept at room temperature for 8 hours, more than 91% of the initial amount of ceftobiprole medocaril remains available up to 9 days post-preparation.

Statistically significant less recovery is observed at Day 6 and Day 9 when compared to Day 0, although both remaining above 90%.

## Conclusion

The development of bacterial resistance has become a major threat to public health. This necessitates, among other things, optimizing the quality of antibiotic prescriptions in terms of preparation and storage methods to prevent their inactivation before administration, as well as in terms of administration to maximize their effectiveness. [5]

The United States Pharmacopeia (USP) defines stability as the ability of a product to retain at least 90% of the initial concentration of the active ingredient throughout its storage and usage period.

Therefore, the data from this study confirms that solutions of ceftobiprole medocaril, prepared at IUCPQ-ULaval, are suitable for maintaining optimal stability and physicochemical parameters, even if administered at home. Indeed, ceftobiprole medocaril in a solution of 0.9% NaCl remains stable for up to 9 days following the preparation of Intermate® LV 100 stored at 4°C, and for up to 8 hours when the Intermate® is kept at room temperature, allowing patients to benefit from the *ATIVAD: Antibiothérapie intraveineuse à domicile* program.

## References

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