

Requirement of Very High Doses of Colistin in a Critically-ill Patient with Augmented Renal Clearance

D. Fage¹, A. Herpain¹, G. Deprez¹, F. Wolff¹, M. Hites¹, F. Van Bambeke², F. Cotton¹, F. Jacobs¹
¹ CUB Erasme Hospital ULB, Brussels, Belgium ² Louvain Drug Research Institute UCL, Brussels, Belgium

INTRODUCTION

Colistin (Fig. 1) is an old antibiotic, discarded because of reported side effects. However, the increase in the incidence of multidrug-resistant Gram-negative bacteria, associated with an absence of new promising antibiotics in the drug development pipeline, has led to a re-use of colistin.

As a last resort antibiotic, colistin is mainly used in cystic fibrosis and critically-ill patients, who show altered PK characteristics leading to unpredictable drug plasma levels. Therefore, the optimal dosage is still currently under debate. Moreover, total colistin has a narrow therapeutic range (2 - 3 mg/L), higher levels being associated with nephro- and neurotoxicity. These reasons justify the added value of therapeutic monitoring for colistin.

In this context, we report the case of a patient treated during a long period with very high doses of colistin adapted to pharmacokinetic data, without acute kidney injury.

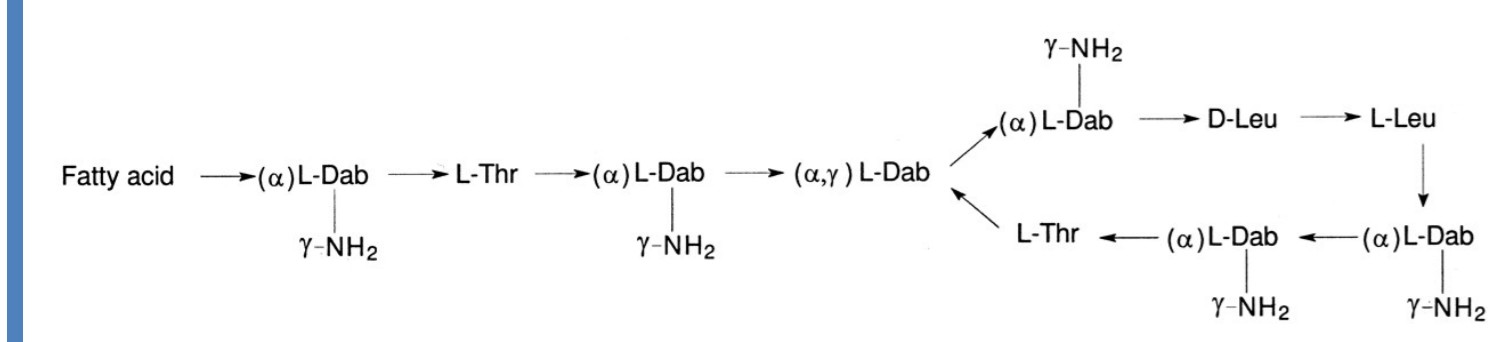


Fig. 1: Structure of colistin A and B. Fatty acid: methyl octanoic acid for colistin A and methylheptanoic acid for colistin B.

PATIENT AND METHODS

Patient

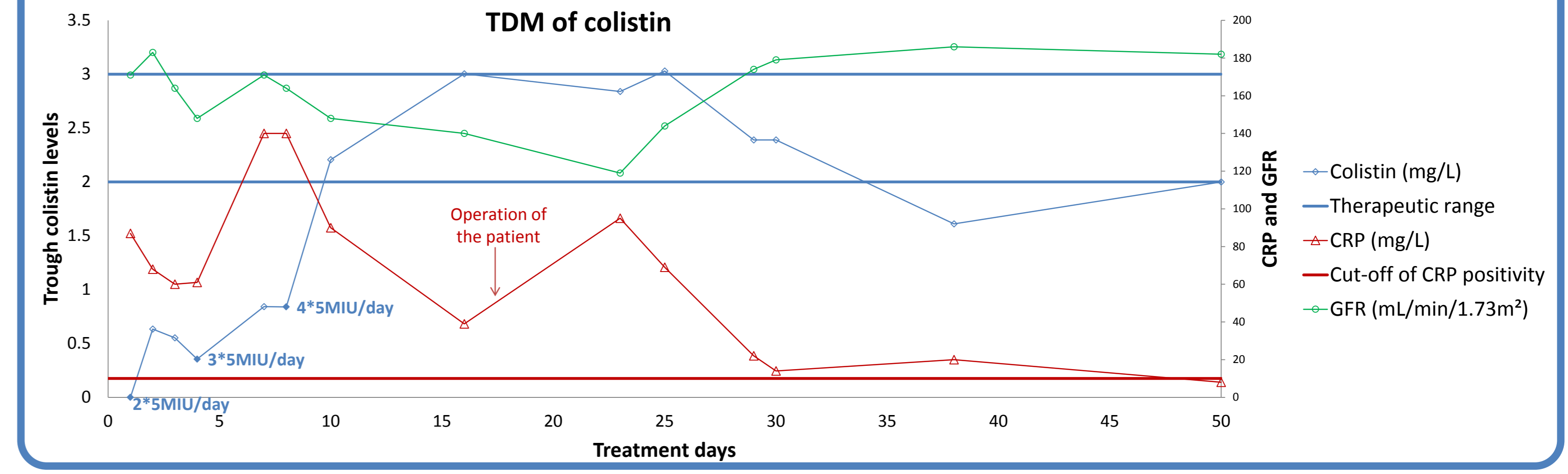
A 28-year-old woman was hospitalised in Intensive Care Unit for a severe trauma. She developed a left femoral osteitis due to multidrug-resistant *P. aeruginosa* and *K. pneumoniae*. Both strains were susceptible to colistin only with a MIC <0.5 mg/L (EUCAST breakpoints MIC <2 mg/L). Therapy with I.V. colistin was started using a loading dose of 9 MIU and a maintenance dose of 2*5 MIU per day, combined with meropenem and fosfomycin. At this moment, the patient showed an augmented renal clearance (ARC) (in mean: sCr 35.4 μmol/L and GFR with CKD-EPI formula: 138 mL/min/1.73m², diuresis >3 liters/day). Therapeutic Drug Monitoring (TDM) of colistin was done once a week, according to the protocol described below, to adapt the dosage regimen in function of colistin concentrations at trough levels (therapeutic target: 2 - 3 mg/L).

Methods

After a protein precipitation step by acetonitrile, colistin concentration was determined using liquid chromatography-tandem mass spectrometry (LC-MS/MS) with an Agilent 1260 LC instrument connected to a 6490 triple quadrupole detector (Agilent). The internal standard was polymyxin B which is not used for a therapeutic purpose in Europe. The analytical ranges, validated by the accuracy profiles approach, were 0.5-20.0 mg/L for colistin A+B.

RESULTS

The first colistin concentration measured on day 4 was largely below the therapeutic target (0.36 mg/L). The recommended maintenance dose was therefore increased to 3*5 MIU per day. On day 7, a new colistin determination showed again a subtherapeutic concentration (0.84 mg/L). As no clinical or biological improvement was noted, the dosage regimen was therefore increased to 4*5 MIU per day on day 8. With this dose, between day 10 and the end of therapy (day 51), colistin concentrations remained within therapeutic ranges. The inflammatory biomarkers decreased gradually and the clinical situation improved. Colistin therapy was stopped after two months, because there were no more biological or clinical signs of acute infection. Renal function, followed every day (sCr, GFR and diuresis) remained unchanged during the entire duration of colistin therapy.



CONCLUSIONS

This case report illustrates that TDM can be helpful to guide colistin therapy, in order to reach the therapeutic target. This could be particularly useful in patients with ARC as very high doses of colistin may be needed in this situation. No toxicity was observed even after a very long treatment (2 months). In conclusion, very high doses of colistin, guided by TDM, can be used without nephrotoxicity in patients with ARC.