FACULTEIT FARMACEUTISCHE WETENSCHAPPEN

SWITCH FROM INTRAVENOUS TO ENTERAL MOXIFLOXACIN IN CRITICALLY ILL PATIENTS: A PILOT STUDY

J. De Smet[1], K. Colpaert[2], P. De Paepe[3], J. Van Bocxlaer[1], J. Decruyenaere[2] and K. Boussery[1]

[1] Laboratory of Medical Biochemistry and Clinical Analysis, Faculty of Pharmaceutical Sciences, Ghent University, Harelbekestraat 72, B-9000 Ghent, Belgium
[2] Department Intensive Care Unit , Ghent University Hospital, De Pintelaan 185, B-9000 Ghent, Belgium
[3] Heymans Institute of Pharmacology, Ghent University, De Pintelaan 185, B-9000 Ghent, Belgium

1. Introduction

Moxifloxacin is a fluoroquinolone antibiotic, characterized by rapid bactericidal activity with a broad spectrum against both Gram-negative and Gram-positive micro-organisms. It is mainly used for the treatment of serious respiratory tract infections, such as severe community-acquired pneumonia (CAP) and acute exacerbations of chronic obstructive pulmonary disease (COPD). In the intensive care unit (ICU), moxifloxacin is generally administered intravenously (IV) to achieve rapid bacterial killing. However, a switch from IV to enteral or oral administration is considered as early as possible, not only because of pharmacoeconomic reasons (reducing medication costs) but also because of the benefits for the patient (i.e. reducing catheter-related infections). In ICU patients that are not able to swallow, a switch to enteral administration through a feeding tube is often performed. However, no pharmacokinetic/pharmacodynamic (PK/PD) data in ICU patients are available to guarantee adequate antibiotic plasma levels after such a switch.

2. Aim

Although moxifloxacin demonstrated a good oral bioavailability in healthy volunteers, critically ill patients frequently exhibit physiological alterations that can affect the pharmacokinetic processes and, consequently, the efficacy of drugs. Not only organ dysfunction, but also the simultaneous use of a variety of drugs can result in a disturbed absorption of a drug .
This study therefore aims to investigate whether enteral administration of moxifloxacin is bioequivalent to IV administration in critically ill patients.

3. Methods

Study population

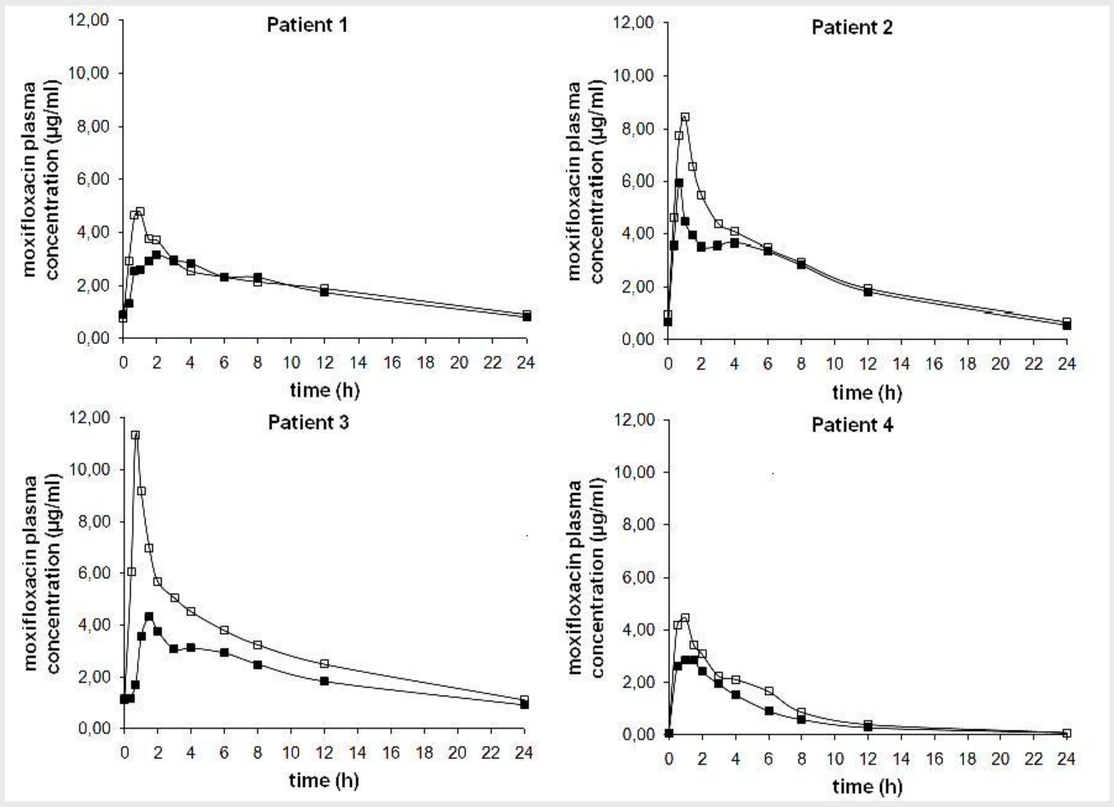
• 4 adult, critically ill patients receiving IV moxifloxacin once daily and being eligible for a switch to enteral moxifloxacin

Patient	Sex	Age (yrs)	BMI (kg/m²)	Dose	Diagnosis
1	F	64	40	400mg	Left pneumonia with empyema
2	F	60	34	400mg	Pneumonia and aspergillosis
3	M	60	62	600mg	Pleuropneumonia
4	M	41	31	400mg	Pneumonia (Enterobacter)

Study design

• Single-centre, prospective, open-label bioequivalence study
• Blood sampling during switch (protocol I: patient 1-3) or at steady state conditions (protocol II: patient 4), after both IV and enteral administration
• Moxifloxacin plasma levels were determined by a validated HPLC method with fluorescence detection
• Non-compartmental methods were applied for all pharmacokinetic evaluations and the EUCAST clinical breakpoints for susceptible micro-organisms against moxifloxacin were used as MIC value

4. Results



Plasma concentration-time curves of moxifloxacin following a daily dosage of moxifloxacin given enterally (■) or by 1-hours IV infusion (□).

Patient (protocol)	1 (I)		2 (I)		3 (I)		4 (II)	
Therapy	IV	Enteral	IV	Enteral	IV	Enteral	IV	Enteral
Cl_{cr} (ml/min)	143	135	109	68	112	172	292	332
t_{max} (h)	1.00	2.00	1.00	0.67	0.67	1.50	1.00	1.00
C_{max} (µg/ml)	4.78	3.16	8.48	5.95	11.34	4.32	4.47	2.86
AUC_{24h} (h*µg/ml)	47.57	43.66	60.89	51.51	72.90	48.53	23.46	16.80
$t_{1/2}$ (h)	13.35	10.43	7.66	6.79	10.34	10.90	5.03	6.15
% reduced C_{max}	-	33.9	-	29.8	-	61.9	-	36.0
% reduced AUC_{24h}	-	8.2	-	15.4	-	33.4	-	28.4
C_{max}/MIC	9.56	6.32	16.96	11.90	22.68	8.64	8.94	5.72
AUC_{24h}/MIC	95.14	87.32	121.78	103.02	145.80	97.06	46.92	33.60

The cutoff levels for the PK/PD parameters:

- Optimal C_{max}/MIC ≥10 *(Preston et al, 1998, JAMA 279: 125-129)*
- AUC_{24h}/MIC > 100 -125 but < 250: slow bacterical killing
- AUC_{24h}/MIC > 250: rapid bacterical killing *(Schentag et al, 2003, Ann Pharmacother 37: 1478-1488)*

5. Conclusions

Notwithstanding its preliminary character, this study reveals 3 major issues.

1) It demonstrates that, in critically ill patients, enteral administration of moxifloxacin is not bioequivalent to IV administration, and therefore, a switch from IV to enteral moxifloxacin administration is contraindicated in this patient population.

2) The low AUC_{24h}/MIC values (<125) imply that, with both enteral and IV administration of moxifloxacin, rapid bacterial killing was not obtained using the standard dosage regimen, irrespective of which pathogen caused the infection.

3) In 1 out of 4 patients in this study, augmented renal clearance occurred, resulting in a lower drug exposure (AUC_{24h}) and , consequently, in ineffective moxifloxacin plasma levels.

Taking these 3 issues into account, further studies are required to optimise moxifloxacin dosing in ICU patients.