Scandinavian Journal of Infectious Diseases, 2012; Early Online: 1–5

informa
healthcare

SHORT COMMUNICATION

Switch from intravenous to enteral moxifloxacin in critically ill patients: A pilot study

JULIE DE SMET[1], KIRSTEN COLPAERT[2], PETER DE PAEPE[3], JAN VAN BOCXLAER[1], JOHAN DECRUYENAERE[2] & KOEN BOUSSERY[1]

From the [1]*Laboratory of Medical Biochemistry and Clinical Analysis, Faculty of Pharmaceutical Sciences, Ghent University,* [2]*Department Intensive Care Unit, Ghent University Hospital, and* [3]*Heymans Institute of Pharmacology, Ghent University, Ghent, Belgium*

Abstract
Critically ill patients generally receive moxifloxacin intravenously to achieve rapid bacterial killing. An early switch from intravenous to enteral moxifloxacin may be considered because of its good oral bioavailability in healthy volunteers. Since bioavailability may be altered in critically ill patients due to pathophysiological changes, this study aimed to investigate whether enteral moxifloxacin is bioequivalent to intravenous moxifloxacin in such patients. Blood samples were obtained from 4 critically ill patients before and at serial time-points after intravenous and enteral administration. In all patients, lower maximum plasma concentration (C_{max}) and area under the plasma concentration–time curve during the 24-h observation period (AUC_{24h}) values were observed after enteral administration compared to those after intravenous administration. This resulted in lower C_{max}/minimum inhibitory concentration (MIC) and AUC_{24h}/MIC values, which are 2 indices predicting the antibacterial efficacy of moxifloxacin. Despite the limited number of subjects, we conclude that a switch from intravenous to enteral moxifloxacin is not recommended in these patients, because the 2 administration forms are not bioequivalent.

Keywords: *Moxifloxacin, intensive care, pharmacokinetics, enteral, intravenous*

Introduction

Moxifloxacin is a fluoroquinolone antibiotic, characterized by a rapid bactericidal action, with a broad spectrum of activity against both Gram-negative and Gram-positive microorganisms. 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) [1]. In the intensive care unit (ICU), moxifloxacin is usually administered intravenously (IV). However, a switch from IV to enteral or oral administration is considered as early as possible, not only for pharmacoeconomic reasons (reducing drug and drug-administration costs), but also because of the benefits for the patient (i.e., reducing the incidence of infusion-related complications such as phlebitis, local and systemic infections, and excess fluid administration) [2,3]. In ICU patients who are not able to swallow, a switch to enteral administration through a feeding tube is often performed. In clinical practice, the same standard dose of 400 mg moxifloxacin is used in the switch from IV to enteral administration. Consequently, such a switch without dose adjustments is only justified if the 2 administration forms show equivalent systemic exposure. However, no pharmacokinetic/pharmacodynamic (PK/PD) data in ICU patients are available to guarantee adequate antibiotic plasma levels after such a switch.

Although moxifloxacin has demonstrated a good oral bioavailability in healthy volunteers [4,5], critically ill patients frequently exhibit pathophysiological alterations that can affect the pharmacokinetic processes and, consequently, the efficacy of drugs. As well as these pathophysiological changes (e.g., organ dysfunction, modified intestinal permeability, decreased

Correspondence: J. de Smet, Laboratory of Medical Biochemistry and Clinical Analysis, Faculty of Pharmaceutical Sciences, Ghent University, Harelbekestraat 72, B-9000 Ghent, Belgium. Tel: +32 9 264 81 14. Fax: +32 9 264 81 97. E-mail: Julie.desmet@ugent.be

(Received 20 December 2011; accepted 8 May 2012)

ISSN 0036-5548 print/ISSN 1651-1980 online
DOI: 10.3109/00365548.2012.693194

gastrointestinal blood flow), the simultaneous use of a variety of drugs can result in disturbed absorption of a drug [6–8]. This study therefore aimed to investigate whether enteral administration of 400 mg moxifloxacin is bioequivalent to IV administration in critically ill patients and to evaluate whether dose adjustments are needed to achieve equivalent systemic exposure.

Materials and methods

This single-centre, prospective, open-label bioequivalence study involved 4 critically ill patients in the ICU of Ghent University Hospital. Between June 2007 and December 2009, all patients who had received monotherapy with 400 mg of IV moxifloxacin once daily for at least 3 days and who were eligible for a switch to enteral administration of moxifloxacin were included in the study. Patients were routinely regarded as eligible for a switch when they were haemodynamically stable and capable of receiving normal enteral feeding without using prokinetics, and when the treating physician agreed to the switch. Exclusion criteria were the use of vasopressors, use of prokinetic agents such as metoclopramide or erythromycin, severe renal impairment (creatinine clearance <30 ml/min or haemodialysis), and severe hepatic impairment (transaminase levels more than 5 times the upper limit of normal). Written informed consent was obtained from the patient or a legal representative. The study protocol was approved by the local ethics committee of Ghent University Hospital (Belgium), and the study was performed in accordance with the Declaration of Helsinki and the Good Clinical Practice Guidelines of the European Commission.

In protocol I, the plasma concentration–time profiles were determined after the last IV administration (as a 1-h infusion of 400 mg Avelox® IV; Bayer Healthcare, Diegem, Belgium) and after the first enteral administration (Avelox® Oral 400 mg tablet, suspended in 20 ml water and flushed through the feeding catheter over 2 min; Bayer Healthcare, Diegem, Belgium). For both profiles, all blood samples were drawn from the arterial catheter at 13 time-points (pre-dose, and at 20 and 40 min, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, and 24 h post-dose). In order to evaluate the influence of the switch on steady-state conditions, protocol II involved blood sampling (pre-dose and 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12 and 24 h post-dose) after the last IV administration and after the fourth enteral administration, with trough samples being collected on the intervening days.

The blood samples were centrifuged (5 min, 1500 rpm, 15°C) to prepare plasma samples, which were stored at −80°C prior to analysis. The moxifloxacin plasma levels were determined by a validated high performance liquid chromatography (HPLC) method with fluorescence detection, as described elsewhere [9]. For each patient, creatinine clearance (Cl_{cr}) was measured on each blood sampling day, using serum creatinine and the 2-h urine output.

Non-compartmental analysis was performed for pharmacokinetic evaluations using PKSolver [10]. The maximum plasma concentration (C_{max}) and time to reach C_{max} (T_{max}) values were taken directly from the plasma concentration–time curves. The area under the plasma concentration–time curve during the 24-h observation period (AUC_{24h}) was determined using the log-linear trapezoidal method, and the terminal half-life ($T_{1/2}$) was calculated by linear regression analysis of the last data points after log-transformation of the data. We estimated the efficacy of moxifloxacin by its 2 most relevant PK/PD indices: C_{max}/MIC and AUC_{24h}/MIC, using the EUCAST (European Committee on Antimicrobial Susceptibility Testing) clinical breakpoints for susceptibility of Enterobacteriaceae, Staphylococcus sp., Streptococcus sp., and Haemophilus influenzae against a specific antibiotic as MIC (minimum inhibitory concentration). All these microorganisms have the same MIC breakpoint, namely ≤ 0.5 μg/ml (http://www.eucast.org).

Results

Four critically ill patients (age range 41–64 years, 2 females) treated with moxifloxacin because of pneumonia (patient 1, left pneumonia with empyema; patient 2, pneumonia and aspergillosis; patient 3, pleuropneumonia; patient 4, pneumonia (Enterobacter)) were included in this study. For patients 2 and 3, inflammatory parameters decreased during moxifloxacin therapy. Data on the outcomes of patients 1 and 4 could not be registered because of loss to follow-up. The PK/PD indices are summarized in Table I and the individual plasma concentration–time curves are shown in Figure 1. Importantly, patient 3 received 600 mg moxifloxacin instead of 400 mg due to morbid obesity with a body mass index (BMI) of 62 kg/m^2.

Protocol I was used to determine the plasma concentration–time profiles during the switch from IV to enteral administration for patients 1–3. For patient 4, protocol II was used to evaluate the PK profiles at steady-state conditions for both IV and enteral administration.

For all patients, C_{max} and AUC_{24h}, and consequently C_{max}/MIC and AUC_{24h}/MIC, were lower after enteral administration than after IV administration:

Table I. Creatinine clearance and PK/PD indices per patient.

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

PK/PD, pharmacokinetic/pharmacodynamic; Cl_{cr}, creatinine clearance; T_{max}, time to reach C_{max}; $T_{1/2}$, terminal half-life; C_{max}, maximum concentration; AUC_{24}, area under the plasma concentration–time curve during the 24-h observation period; MIC, minimum inhibitory concentration; IV, intravenous.

a mean reduction of approximately 40% was observed in C_{max} and a mean reduction of approximately 21% in AUC_{24h}. It should also be noted that, compared to the other 3 patients, patient 4 had a markedly lower AUC_{24h} and AUC_{24h}/MIC after enteral as well as after IV administration. This was also evident in the lower trough plasma concentrations (C_{trough}) after the switch. In patients 1, 2, and 3, C_{trough} levels of 0.79, 0.54, and 0.90 μg/ml, respectively, were obtained directly after the first enteral administration. However, patient 4 had a mean C_{trough} of 0.09 μg/ml (standard deviation 0.01 μg/ml, $n = 4$) determined on the intervening days.

Discussion

In healthy volunteers, it has been demonstrated that the pharmacokinetics of a single 400 mg moxifloxacin oral dose are similar to those of an IV dose (AUC_{24h} for oral administration 39.00 ± 2.16 h*μg/ml vs 39.13 ± 5.80 h*μg/ml for IV administration, and C_{max} for oral administration 4.98 ± 1.01 μg/ml vs 5.09 ± 1.11 μg/ml for IV administration) [11]. This high bioavailability of the oral formulation suggests that a switch from IV to oral administration could be justified and, moreover, could be recommended because of benefits to patients and for pharmacoeconomic reasons (the drug cost for oral

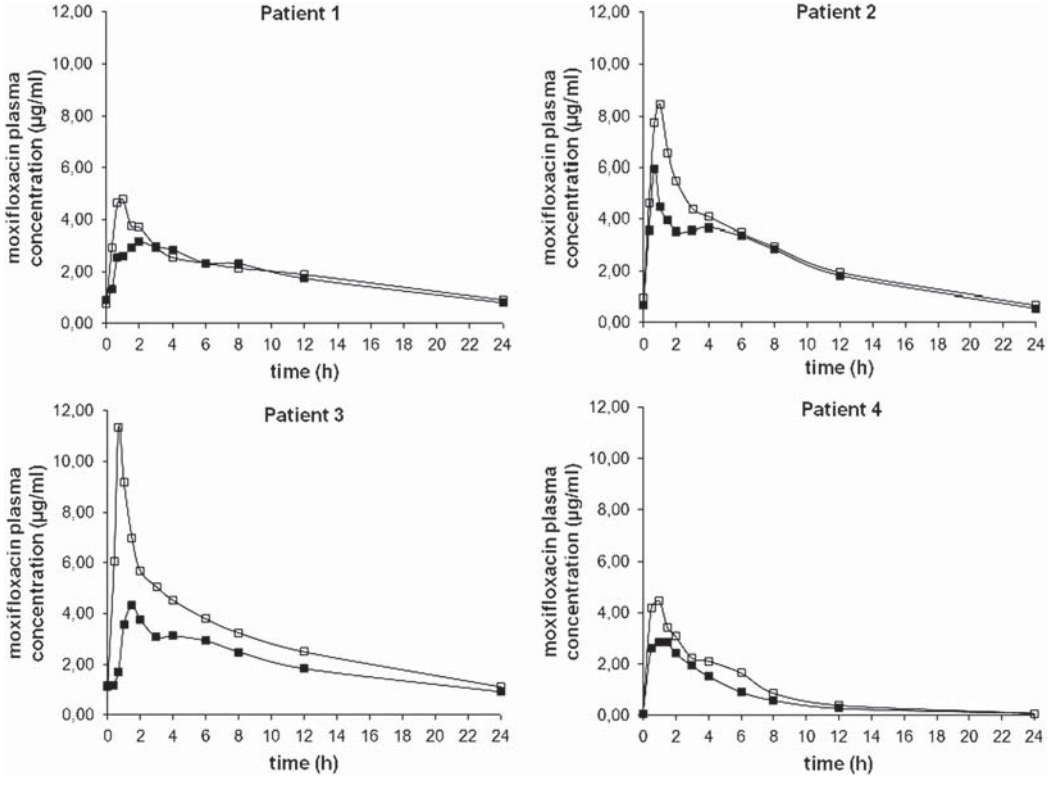

Figure 1. Individual plasma concentration-time curves of moxifloxacin after intravenous (□) and enteral (●) administration.

moxifloxacin therapy is approximately 10 times lower than that for IV therapy). In contrast, our data showed a lower C_{max} and AUC_{24h} after enteral administration compared to IV administration in 4 ICU patients. There was, however, great inter-individual variability in this small study population. Our limited data suggest that enteral administration of moxifloxacin may not be bioequivalent to IV administration in critically ill patients.

Although this study was not designed to provide data on clinical outcome, the efficacy of enteral moxifloxacin therapy may, as a consequence, also be reduced, which increases the risk of clinical failure. In order to estimate the efficacy, we used the cut-off levels for the PK/PD indices AUC_{24h}/MIC and C_{max}/MIC suggested by Schentag et al. [12] and by Preston et al. [13], respectively.

Depending on the Gram staining of the pathogens, 2 different cut-off levels for the AUC_{24h}/MIC ratio have been proposed: AUC_{24h}/MIC $>$25–35 for Gram-positive pathogens and AUC_{24h}/MIC $>$100–125 for Gram-negative pathogens [14]. According to Schentag et al., AUC_{24h}/MIC values >125 but <250 produce slow bacterial killing of Gram-negative pathogens, usually by day 7 of treatment. However, in critically ill patients, AUC_{24h}/MIC values >250 should be preferred, since these values represent rapid bacterial killing, regardless of whether the organism is Gram-negative or Gram-positive, and bacterial eradication occurs within 24 h [12]. However, none of the patients in our study exhibited an AUC_{24h}/MIC >250; nor were the AUC_{24h}/MIC values >125 after enteral administration. In fact, this also applied to the AUC_{24h}/MIC values after IV administration, except in patient 3. Even optimal C_{max}/MIC ratios of 10:1, recommended by Preston et al. [13], were not obtained in most patients in our study. Not only do these findings indicate that a switch from IV to enteral moxifloxacin is not optimal in critically ill patients, they also raise the question of whether the standard dosage regimen (400 mg moxifloxacin once daily) is suitable for critically ill patients.

Our data should be interpreted with caution because the MIC values in the treated patients were not determined in this study; the most recently published EUCAST MIC breakpoints were used instead. Therefore, the efficacy could be underestimated in our study. Nevertheless, due to an increasing resistance of pathogens against moxifloxacin during the last 10 years, the MIC values have been increased in comparison with previous studies [15,16]. In addition, infections with resistant pathogens, which require higher plasma concentrations, occur more often in a critical care unit. Also total plasma concentrations have been used to estimate efficacy, even though only unbound drug is responsible for the clinical effect (moxifloxacin exhibits 40% protein binding [5]) and critically ill patients frequently suffer from hypoalbuminaemia [17], which may increase the unbound fraction of the drug. However, the free plasma concentration is always a fraction of the total plasma concentration and could therefore never be higher. Since our results suggest that the estimated PK/PD indices, based on total plasma concentrations, may not be sufficient to meet the pre-specified ones, using the free plasma concentrations to estimate efficacy would not have changed our findings.

Furthermore, restrictive inclusion and exclusion criteria were used for the safety of the ICU patients. Extremely critically ill patients were excluded because the use of vasopressors and gastroprokinetics could lead to a reduced absorption of enterally administered drugs and, consequently, to ineffective antibiotic therapy. The limited number of patients in our study is explained by these restrictive criteria. Nevertheless, all patients included shared the trend towards a reduced AUC_{24h}/MIC after enteral administration. Increasing the number of patients would probably not have changed the conclusions of this study. Moreover, if the same study was performed in extremely critically ill patients, the systemic exposure to moxifloxacin after enteral administration and the efficacy, expressed as AUC_{24h}/MIC, would probably have been lower.

In patient 4, remarkably low AUC_{24h} values were obtained for both formulations. One would expect higher plasma concentrations in patient 4 compared to patients 1–3, since all measures were taken under steady-state conditions for patient 4. However, steady-state assumptions may not hold in patient 4 as the terminal half-life of approximately 5–6 h obtained in this patient suggests almost complete washout of the drug for a once-daily dosage regimen, which is in agreement with the low observed trough value of 0.09 μg/ml. In addition, this patient had an increased creatinine clearance, which may have resulted in a higher plasma clearance of the drug and consequently in a lower drug exposure. Although this renal hyperfiltration occurred in only 1 out of 4 cases in this study, it has been described with increasing regularity in ICU patients [18,19].

Clearly, our results necessitate further investigation of the efficacy of both IV and enteral moxifloxacin therapy in a larger number of critically ill patients. Particular attention should be given to the impact of hyperfiltration on the pharmacokinetics of moxifloxacin and to the dosage regimen. The low AUC_{24h}/MIC values obtained in our study suggest that higher doses may be required in ICU patients. Stass et al. demonstrated that a dose of 600 mg oral moxifloxacin once daily had a good tolerability

profile in healthy men [20]; however, there are no safety data on higher doses in ICU patients. Therapeutic drug monitoring (TDM) may be of value for dose personalization of moxifloxacin in ICU patients [21].

Notwithstanding its preliminary character, this study reveals 3 major issues. Firstly, 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. Secondly, the low AUC_{24h}/MIC values (< 125) imply that one cannot be certain that therapeutic efficacy will be reliable. Finally, augmented renal clearance occurred in 1 out of 4 patients in this study, resulting in very low and probably ineffective moxifloxacin plasma levels.

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

Acknowledgements

The authors would like to thank the Clinical Trial Unit of Ghent University Hospital (Charlotte Clauwaert and Luc Decrop) for their assistance in this study.

Declaration of interest: No conflict of interest to declare.

References

[1] Balfour JA, Lamb HM. Moxifloxacin—a review of its clinical potential in the management of community-acquired respiratory tract infections. Drugs 2000;59:115–39.
[2] Davis SL, Delgado G, McKinnon PS. Pharmacoeconomic considerations associated with the use of intravenous-to-oral moxifloxacin for community-acquired pneumonia. Clin Infect Dis 2005;41:S136–43.
[3] Mertz D, Koller M, Haller P, Lampert ML, Plagge H, Hug B, et al. Outcomes of early switching from intravenous to oral antibiotics on medical wards. J Antimicrob Chemother 2009;64:188–99.
[4] Ballow C, Lettieri J, Agarwal V, Liu P, Stass H, Sullivan JT. Absolute bioavailability of moxifloxacin. Clin Ther 1999;21:513–22.
[5] Stass H, Kubitza D. Pharmacokinetics and elimination of moxifloxacin after oral and intravenous administration in man. J Antimicrob Chemother 1999;43:83–90.
[6] Boucher BA, Wood GC, Swanson JM. Pharmacokinetic changes in critical illness. Crit Care Clin 2006;22:255–71.
[7] Power BM, Forbes AM, van Heerden PV, Ilett KF. Pharmacokinetics of drugs used in critically ill adults. Clin Pharmacokinet 1998;34:25–56.
[8] Haglund U. Systemic mediators released from the gut in critical illness. Crit Care Med 1993;21:S15–8.
[9] De Smet J, Boussery K, Colpaert K, De Sutter P, De Paepe P, Decruyenaere J, Van Bocxlaer J. Pharmacokinetics of fluoroquinolones in critical care patients: a bio-analytical HPLC method for the simultaneous quantification of ofloxacin, ciprofloxacin and moxifloxacin in human plasma. J Chromatogr B 2009;877:961–7.
[10] Zhang Y, Huo M, Zhou J, Xie S. PKSolver: an add-in program for pharmacokinetic and pharmacodynamic data analysis in Microsoft Excel. Comput Methods Programs Biomed 2010;99:306–14.
[11] Wise R, Andrews JM, Marshall G, Hartman G. Pharmacokinetics and inflammatory-fluid penetration of moxifloxacin following oral or intravenous administration. Antimicrob Agents Chemother 1999;43:1508–10.
[12] Schentag JJ, Meagher AK, Forrest A. Fluoroquinolone AUIC break points and the link to bacterial killing rates—part 2: human trials. Ann Pharmacother 2003;37:1478–88.
[13] Preston SL, Drusano GL, Berman AL, Fowler CL, Chow AT, Dornseif B, et al. Pharmacodynamics of levofloxacin—a new paradigm for early clinical trials. JAMA 1998;279:125–9.
[14] Craig WA. Does the dose matter? Clin Infect Dis 2001;33:S233–7.
[15] Turnidge J. Pharmacokinetics and pharmacodynamics of fluoroquinolones. Drugs 1999;58:29–36.
[16] Zhanel GG, Ennis K, Vercaigne L, Walkty A, Gin AS, Embil J, et al. A critical review of the fluoroquinolones—focus on respiratory tract infections. Drugs 2002;62:13–59.
[17] Ulldemolins M, Roberts JA, Rello J, Paterson DL, Lipman J. The effects of hypoalbuminaemia on optimizing antibacterial dosing in critically ill patients. Clin Pharmacokinet 2011;50:99–110.
[18] Dumoulin A, Janssen A, De Waele JJ, Decruyenaere J, Hoste EA. Epidemiology of hyperfiltration in ICU patients. Intensive Care Med 2010;36:S140.
[19] Udy AA, Roberts JA, Boots RJ, Paterson DL, Lipman J. Augmented renal clearance: implications for antibacterial dosing in the critically ill. Clin Pharmacokinet 2010;49:1–16.
[20] Stass H, Kubitza D, Schuhly U. Pharmacokinetics, safety and tolerability of moxifloxacin, a novel 8-methoxyfluoroquinolone, after repeated oral administration. Clin Pharmacokinet 2001;40:1–9.
[21] Roberts JA, Ulldemolins M, Roberts MS, McWhinney B, Ungerer J, Paterson DL, Lipman J. Therapeutic drug monitoring of beta-lactams in critically ill patients: proof of concept. Int J Antimicrob Agents 2010;36:332–9.