J Antimicrob Chemother 2012; **67**: 226–229
doi:10.1093/jac/dkr436 Advance Access publication 10 October 2011

Journal of Antimicrobial Chemotherapy

Oral bioavailability of moxifloxacin after Roux-en-Y gastric bypass surgery

Julie De Smet[1]*, Pieter Colin[1], Peter De Paepe[2], Johannes Ruige[3], Hélène Batens[3], Yves Van Nieuwenhove[4], Dirk Vogelaers[5], Stijn Blot[5], Jan Van Bocxlaer[1], Luc M. Van Bortel[2] and Koen Boussery[1]

[1]Laboratory of Medical Biochemistry and Clinical Analysis, Faculty of Pharmaceutical Sciences, Ghent University, Harelbekestraat 72, B-9000 Gent, Belgium; [2]Heymans Institute of Pharmacology, Ghent University, De Pintelaan 185, B-9000 Gent, Belgium; [3]Department of Endocrinology and Metabolic Diseases, Ghent University Hospital, De Pintelaan 185, B-9000 Gent, Belgium; [4]Department of Gastro-intestinal Surgery, Ghent University Hospital, De Pintelaan 185, B-9000 Gent, Belgium; [5]Department of General Internal Medicine, Infectious Diseases and Psychosomatics, Ghent University Hospital, De Pintelaan 185, B-9000 Gent, Belgium

*Corresponding author. Tel: +32-9-264-81-14; Fax: +32-9-264-81-97; E-mail: julie.desmet@ugent.be

Received 8 August 2011; returned 30 August 2011; revised 6 September 2011; accepted 18 September 2011

Objectives: Roux-en-Y gastric bypass surgery is the most commonly performed procedure for the treatment of morbid obesity. This anatomical alteration may affect the absorption and consequently the bioavailability of oral drugs. This study aims to investigate the oral bioavailability of moxifloxacin in 12 healthy volunteers who underwent gastric bypass surgery.

Patients and methods: In this randomized crossover study, each subject received two single standard doses of 400 mg of moxifloxacin orally or intravenously administered on two occasions separated by a washout period of 1 week. Serial venous blood samples were drawn up to 72 h after dosing and moxifloxacin plasma levels were measured by a validated HPLC method with fluorescence detection. [clinicaltrials.gov database (identifier: NCT01130922).]

Results: After oral dosing, moxifloxacin plasma concentrations reached a maximum (C_{max}) of 3.38 ± 1.41 mg/L after 1.75 h (0.75–4.00). After intravenous dosing, C_{max} and T_{max} were 4.53 ± 1.43 mg/L and 1.03 h (0.75–2.50), respectively. The mean areas under the plasma concentration time curve extrapolated to infinity (AUC_{∞}) were 46.2 ± 1.4 mg·h/L after oral dosing and 52.3 ± 1.3 mg·h/L after intravenous dosing, resulting in a mean oral bioavailability of 88.32% [90% confidence interval (CI) 85.64%–91.08%].

Conclusions: This study confirms that exposure to moxifloxacin is equivalent for oral and intravenous administration of 400 mg dosages in healthy volunteers who underwent gastric bypass surgery. But these exposures were more than 50% higher than those described for subjects without gastric bypass. This may suggest a higher enterohepatic recirculation of moxifloxacin after gastric bypass.

Keywords: fluoroquinolones, pharmacokinetics, bariatric surgery

Introduction

Obesity is a worldwide problem, reaching epidemic proportions. According to the WHO in 2008, 1.5 billion adults were overweight and 500 million were obese.[1] Due to this increased prevalence of obesity, the demand for an effective treatment has risen exponentially. Although lifestyle therapies should be the first line of management, bariatric surgery has been demonstrated to be the most effective treatment for morbid obesity in terms of long-term weight loss and co-morbid medical conditions.[2] Roux-en-Y gastric bypass is the most commonly performed technique nowadays.[2,3] This is considered a combined restrictive/malabsorptive procedure; a small gastric pouch is created, and a jejunal limb is anastomosed to that pouch to bypass the majority of the stomach, the duodenum and the proximal 50 cm of jejunum. These anatomical alterations of the gastrointestinal system may affect the solubility of oral drugs, the available surface area for absorption and blood flow to the gastrointestinal tract, possibly resulting in a changed bioavailability and consequently a changed efficacy. Based on mainly theoretical considerations, it was suggested that the potential effect of gastric bypass on drug absorption is drug specific.[3]

Only limited clinical data are available on the effect of gastric bypass on the bioavailability of drugs.[3] For most drugs, testing

plasma concentrations to ensure therapeutic levels is not really necessary since clinical endpoints (e.g. blood pressure, glycaemia etc.) can be measured much more easily. In contrast, no such clinical endpoint is available for antibiotics. Moreover, antibiotics used for the treatment of severe or complicated infections require achieving rapid bacterial killing.

To our knowledge, no previous study has evaluated the oral bioavailability of moxifloxacin, a fluoroquinolone antibiotic mainly used for the treatment of severe respiratory infections, after gastric bypass surgery. Therefore, this study investigates the oral bioavailability of moxifloxacin in healthy volunteers that have undergone gastric bypass surgery.

Patients and methods

Subjects

Twelve healthy volunteers (eight women and four men; aged 25–57 years) who underwent gastric bypass surgery at least 6 months prior to inclusion, and who had reached a stable bodyweight during the last 3 months [body mass index (BMI) 23–38 kg/m^2], were enrolled in this study after giving written informed consent. Subjects qualified for the study if they had normal findings on a pre-study medical history (except for the gastric bypass surgery), physical examination, electrocardiogram (ECG), pregnancy test and routine laboratory blood tests.

Subjects were excluded if they: (i) had contraindications to moxifloxacin treatment; (ii) had undergone other forms of bariatric surgery before gastric bypass surgery; (iii) had a history of impaired renal function (creatinine clearance <80 mL/min); (iv) had a fasting glycaemia >7 mmol/L; (v) had a history of epilepsy; (vi) had abnormal thyroid function; or (vii) suffered from any other clinically relevant disorders that were considered to potentially interfere with the study.

Study design

The study protocol was approved by the local Ethics Committee of Ghent University Hospital (Belgium) (EudractNr: 2010-018628-14), was performed in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines of the European Commission, and was registered in the clinicaltrials.gov database (identifier: NCT01130922). The absolute oral bioavailability of moxifloxacin was investigated in a single-centre, open-label, randomized crossover study following oral and intravenous administrations. Each subject received two single standard doses of 400 mg of moxifloxacin administered on two occasions separated by a washout period of 1 week. Intravenous moxifloxacin was given as a 1 h infusion of AVELOX® IV (Bayer Healthcare, Diegem, Belgium) and oral moxifloxacin was administered as an AVELOX® oral 400 mg tablet (Bayer Healthcare, Diegem, Belgium). Subjects fasted from midnight prior to administration to 4 h post-dose, except for water ad libitum, and they were not permitted to take any medication starting from midnight to 4 h post-dose. An ECG was continuously recorded during intravenous infusion.

Sampling and determination of drug concentration

On the study days, venous blood samples were taken before and at serial timepoints up to 72 h post-dose. These blood samples were collected in heparinized tubes. Plasma was separated by centrifugation and stored frozen at −80°C until analysis.

The moxifloxacin plasma levels were measured by a validated HPLC method with fluorescence detection, as described previously.[4] Accuracy and inter-day imprecision ranged from 97.8% to 99.6% and from 3.1% to 4.3%, respectively.

Pharmacokinetics

Non-compartmental methods were applied for all pharmacokinetic evaluations using PKSolver (a freely available add-in program for Microsoft Excel). The maximum plasma concentration (C_{max}) and the time to reach C_{max} (T_{max}) values were directly taken from the plasma concentration–time curves. The area under the plasma concentration–time curve extrapolated to infinity (AUC_∞) 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. The clearance of the drug (CL) was calculated as dose/AUC. All parameters are presented as a geometric mean with geometric standard deviation (SD), except for T_{max}, where median and minimum–maximum ranges are given.

Results

All volunteers included in the study completed both study periods. No serious adverse events were observed. A total of 17 adverse events were reported by six volunteers; 8 after intravenous administration and 9 after oral administration. Most of these adverse events were mild (13 of 17) and self-limiting and resolved spontaneously without intervention. No changes in ECG (Q-T interval) during intravenous infusion were observed.

The non-compartmental pharmacokinetic parameters are summarized in Table 1. The calculated mean absolute bioavailability of oral moxifloxacin was 88.32% [range 80.12%–96.31%; 90% confidence interval (CI) 85.64%–91.08%]. C_{max}, however, was approximately 25% lower after oral administration, with a geometric mean ratio $C_{max,oral}/C_{max,iv}$ of 74.57% (range 50.56%–107.48%; 90% CI 65.78%–84.53%). In 5 of 12 patients, a plateau in the plasma concentration over time profile was observed at the end of the intravenous infusion (Figure 1). This is also noticeable in the wide range for T_{max} after a 1 h intravenous infusion of moxifloxacin (Table 1).

Discussion

The growing number of gastric bypass procedures performed has generated wide interest in the effect of this surgery on the absorption of drugs. Our study demonstrates an almost complete (88%) oral bioavailability of moxifloxacin in healthy volunteers with a gastric bypass. The ratio $AUC_{\infty,oral}/AUC_{\infty,iv}$ even meets the bioequivalence criteria according to the FDA guidelines.[5] This confirms that exposure to moxifloxacin is equivalent

Table 1. Non-compartmental pharmacokinetic parameters of moxifloxacin after single 400 mg oral and intravenous doses

Parameter (units)	Oral (n=12)	Intravenous (n=12)
AUC_∞ (mg·h/L)	46.2±1.4	52.3±1.3
$t_{1/2}$ (h)	14.1±1.3	14.1±1.3
C_{max} (mg/L)	3.38±1.41	4.53±1.43
T_{max} (h)	1.75 (0.75–4.00)	1.03 (0.75–2.50)
CL (mL/min)	151±47	132±37

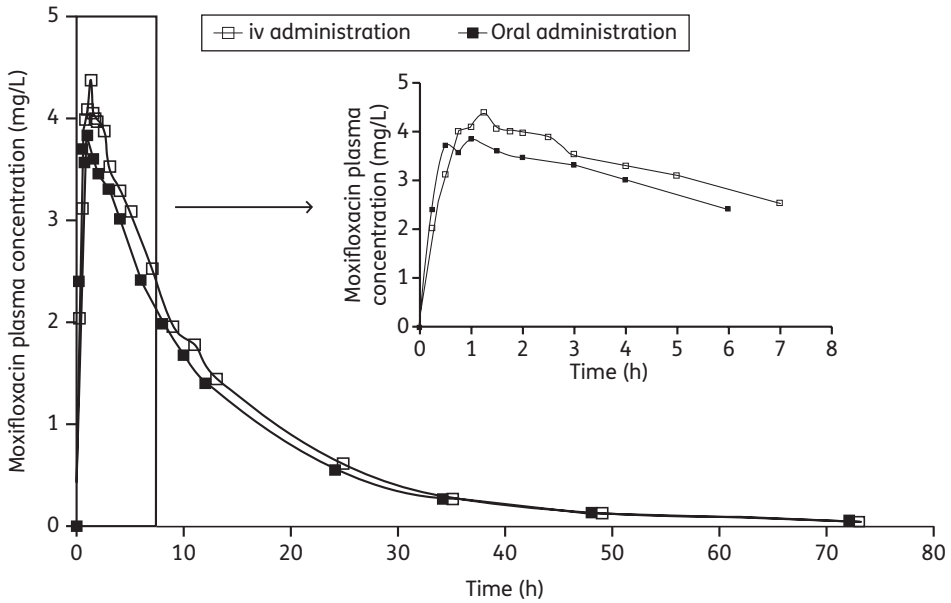

Figure 1. Representative plasma concentration over time profile of moxifloxacin of one patient following a single dose of 400 mg.

for oral and intravenous administration. These observations, as well as the observation that C_{max} values are lower after oral administration compared with intravenous administration, are in accordance with those of other trials investigating the bioavailability of oral moxifloxacin in healthy volunteers without a gastric bypass.[6,7] Therefore, dosage adjustments of moxifloxacin do not seem to be needed in patients with a gastric bypass.

Although a similar bioavailability was described in healthy volunteers without gastric bypass surgery,[6] the absolute values of AUC_{∞} and C_{max} in our study appear to be higher (mean values for AUC_{∞} are approximately 51% and 54% higher for intravenous and oral administration, respectively; for C_{max}, approximately 25% and 35% higher, respectively). The relevance of this observation is not clear. First, no formal statistical comparison could be performed due to the apparent protected nature of the Stass and Kubitza[6] raw data. Second, the study performed by Stass and Kubitza[6] included men only, in contrast to our study population, which consisted of a majority of women. In fact, a population pharmacokinetic study of oral moxifloxacin[8] demonstrated that in the general population, AUC values after oral administration are approximately 18% higher in females compared with the population average. In our study, mean oral AUC was approximately 27% higher in females compared with males.

Another possible explanation for an increased AUC after gastric bypass could be the involvement of enterohepatic recirculation. Moxifloxacin exhibits pronounced enterohepatic recirculation after systemic uptake.[9] Gastric bypass surgery involves anatomical changes of the gastrointestinal tract whereby biliopancreatic secretions are delivered more distally. Patti *et al*.[10] demonstrated that these gastrointestinal alterations affect the enterohepatic recirculation of bile acids, resulting in a 2-fold increase in total serum bile acid concentrations. Also the enterohepatic recirculation of moxifloxacin could be affected, and consequently its hepatic clearance, resulting in an increased AUC after both oral and intravenous administration. Despite the lack of a second peak in the plasma concentration over time profiles, a plateau in the region of C_{max} was observed after intravenous administration (Figure 1). This phenomenon could be explained by enterohepatic recirculation.

The main limitation of this study is the lack of an adequate control group of healthy volunteers. However, this does not alter the conclusion that no dosage adjustments are needed for the potentially lifesaving antibiotic moxifloxacin in patients who underwent gastric bypass surgery. Future studies to investigate the impact of gastric bypass surgery on pharmacokinetics may also need to take into account the role of changed enterohepatic recirculation.

Acknowledgements

These data were presented in part as an oral presentation at the First Benelux Congress on Physiology and Pharmacology, Liège, Belgium, 2011 (Abstract OP03) and at the Tenth Congress of the European Association for Clinical Pharmacology and Therapeutics, Budapest, Hungary, 2011 (Abstract O65).

We thank the Drug Research Unit Ghent of the Ghent University Hospital for clinical study support.

Funding

This study was supported by internal funding.

Transparency declarations

None to declare.

References

1 WHO. *Obesity and Overweight*. Fact Sheet No. 311. http://www.who.int/mediacentre/factsheets/fs311/en/ (2 September 2011, date last accessed).

2 O'Brien PE. Bariatric surgery: mechanisms, indications and outcomes. *J Gastroenterol Hepatol* 2010; **25**: 1358–65.

3 Padwal R, Brocks D, Sharma AM. A systematic review of drug absorption following bariatric surgery and its theoretical implications. *Obes Rev* 2010; **11**: 41–50.

4 De Smet J, Boussery K, Colpaert K *et al*. 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.

5 FDA CDER. *Bioavailability and Bioequivalence Studies for Orally Administered Drug Products—General Considerations*. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070124.pdf (2 September 2011, date last accessed).

6 Stass H, Kubitza D. Pharmacokinetics and elimination of moxifloxacin after oral and intravenous administration in man. *J Antimicrob Chemother* 1999; **43**: 83–90.

7 Ballow C, Lettieri J, Agarwal V *et al*. Absolute bioavailability of moxifloxacin. *Clin Ther* 1999; **21**: 513–22.

8 Stass H, Dalhoff A. The integrated use of pharmacokinetic and pharmacodynamic models for the definition of breakpoints. *Infection* 2005; **33**: 29–35.

9 Stass H, Kubitza D, Moller JG *et al*. Influence of activated charcoal on the pharmacokinetics of moxifloxacin following intravenous and oral administration of a 400 mg single dose to healthy males. *Brit J Clin Pharmacol* 2005; **59**: 536–41.

10 Patti ME, Houten SM, Bianco AC *et al*. Serum bile acids are higher in humans with prior gastric bypass: potential contribution to improved glucose and lipid metabolism. *Obesity* 2009; **17**: 1671–7.