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ORIGINAL CONTRIBUTIONS

Impact of Bariatric Surgery on the Pharmacokinetics Parameters of Amoxicillin

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Abstract

Background Bariatric surgery leads to several anatomo-physiological modifications that may affect pharmacokinetic parameters and consequently alter the therapeutic effect of drugs, such as antibiotics. The pharmacokinetics of oral amoxicillin after Roux-en-Y gastric bypass (RYGB) surgery is unknown.

Objectives The objective of this study was to evaluate the impact of bariatric surgery on the pharmacokinetics of amoxicillin.

Methods This study was performed as a randomized, open-label, single-dose clinical trial, with two periods of treatment, in which obese subjects ($n = 8$) received an amoxicillin 500 mg capsule orally before and 2 months after the RYGB surgery. The amoxicillin plasma concentration was determined by liquid chromatography coupled to mass spectrometry (LC-MS/MS).

Results After the surgery, the mean weight loss was 17.03 ± 5.51 kg, and mean body mass index (BMI) decreased from 46.21 ± 2.82 to 38.82 ± 3.32 kg/m^2. The mean amoxicillin area under the plasma concentration versus time curve from time zero to the time of the last quantifiable concentration ($AUC_{0-tlast}$) increased significantly (3.5-fold); the maximum plasma concentration (C_{max}) increased 2.8-fold after the bariatric surgery. No correlation was found between amoxicillin absorption, BMI, and weight loss percentage.

Conclusion The alterations observed in the amoxicillin pharmacokinetics suggest that obese subjects included in this trial had a substantially increase in amoxicillin systemic exposure after RYGB surgery. However, despite this increase, its exposure was lower than the values reported for non-obese volunteers.

Trial Registration Identifiers: NCT03588273

Keywords Amoxicillin · Bariatric surgery · Pharmacokinetics · Obesity · Gastric bypass

Introduction

The prevalence of obesity is reaching a considered epidemic level [1], and several clinical approaches have been used to combat this disease, including diet, exercise, behavioral, and pharmacological therapy. However, when all these treatments are not able to reach their goal, due to a variety of factors, the morbidly obese may be eligible for bariatric surgery as a last resort [1, 2]. The main representative of the bariatric surgical procedures is the Roux-en-Y gastric bypass (RYGB), considered a gold standard technique due to the reproducibility of results, being the most performed surgical intervention in the world. The combination of a small gastric reservoir and a disabsorbent component caused by the Roux-en-Y reconstruction reduces the intake and absorption capacity of the

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obese individual and consequently increases the weight loss [3, 4].

This type of bariatric surgery leads to anatomical changes that may interfere in the pharmacokinetic processes of several classes of medications. In addition, there are no consensual guidelines for the administration of drugs in obese patients. Therefore, there are some uncertainties about the prediction of how bariatric surgery can influence the pharmacokinetics of specific drugs [4].

Amoxicillin is a semi-synthetic penicillin classified as a β-lactam compound, with a broad bacterial spectrum and good tolerability [5, 6]. It was the most consumed antibacterial agent in primary care in two thirds of the European Union (EU)/European Economic Area (EEA) countries in 2012 [7, 8]. Amoxicillin is used to treat infections caused by bacteria that are normally susceptible and should be administered in adequate amounts to ensure their efficacy [9]. The efficacy of an antimicrobial is dependent on exposure as well as its potency against the microorganism, and this potency is usually expressed as minimum inhibitory concentration (MIC), which, together with the drug pharmacokinetic parameters, is an important factor to be considered to achieve therapeutic success [9, 10].

After oral administration to healthy subjects, the amoxicillin kinetics exhibits dose-dependent absorption [11]. It is almost completely absorbed in the small intestine, mainly in the duodenum and jejunum, and to a lesser extent in the ileum [12]. Its bioavailability is 72% after oral administration of 500 mg amoxicillin. However, the fraction of the dose absorbed is 39% lower after administration of 3 g [11]. Volume of distribution (V_d) of amoxicillin is 0.3 L/kg, and plasma protein binding is around 20% [13, 14]. The elimination of amoxicillin occurs through the kidneys by glomerular filtration and tubular secretion [15]. About 60% of an oral dose of 250 mg is excreted unchanged in the urine within 6 h, producing urinary levels of 0.3 to 1.3 g/L. Hepatic metabolism is a relatively unimportant pathway for the elimination of amoxicillin, as only 10 to 20% of the drug is metabolized by β-lactam hydrolysis to penicillanic acid, which is excreted in the urine. There is a small enterohepatic circulation of the antibiotic [9].

Considering the increase in the number of bariatric surgeries, a small amount of clinical studies to evaluate the effect of this surgical procedure on drug pharmacokinetics, there is an emerging need to perform this kind of study to guide healthcare professionals to prescribe medicines for patients who have undergone this procedure in a safe and effective manner [16]. In addition, there is a need to evaluate the pharmacokinetics of amoxicillin, a drug widely used, in obese patients submitted to bariatric surgery to ensure the therapeutic success. Therefore, the aim of this study was to evaluate the impact of RYGB surgery on the pharmacokinetics of amoxicillin after a single oral dose administration of amoxicillin 500 mg capsule to obese patients before and 2 months after surgery. The amoxicillin plasma concentration was determined by a validated liquid chromatography coupled to mass spectrometry (LC-MS/MS).

Methods

Ethics

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments. The study was approved by the institutional review board (IRB) of the Federal University of Ceará (number 255.607), and the Scientific Committee of the Hospital General Dr. César Cals. Informed consent was obtained from all individual participants included in the study. Trial Registration identifiers: NCT03588273.

Subjects

The obese volunteers ($n = 8$) were selected from the obesity program of Hospital General Dr. César Cals (Fortaleza, Ceará, Brazil). They were of both sexes, aged between 28 and 59 years old, with indication of bariatric surgery based on the criteria established by the Federal Medical Council (2015) and were operated using the RYGB surgery technique.

The subjects with the following conditions were not included in the study: hypersensitivity to amoxicillin or to chemically related compounds, history of serious adverse reactions, hospitalization for any reason during the 8 weeks before the beginning of the study, blood donation or other blood loss of more than 450 mL within 3 months prior to individual enrolment of the subject, surgery of digestive tract prior to bariatric surgery, history or presence of liver, kidney, gastrointestinal or serious heart disease or other conditions that could interfere with the absorption, distribution, excretion or metabolism of the drug, continuous use of the studied medication, and pregnancy and/or breastfeeding in the case of female volunteers.

Study Design and Pharmacokinetic Sampling

This study was performed as a monocentric, open-label, randomized, single-dose study with two treatment periods—before the surgery (Time 0—T0) and 2 months after the bariatric surgery (Time 2—T2). In each period, the obese volunteers received a single oral dose of amoxicillin 500 mg capsule (Amoxil®, GlaxoSmithKline Brazil Ltda.) with 200 mL of water after an overnight fast (approximately 8 h). The subjects remained fasted for 3 h after taking the medication. Standard meals were offered to all subjects. The volunteers who needed

to use any medication (antihypertensive, antidiabetic, and others) were instructed to use it 3 h after the intake of amoxicillin. Blood samples (6 mL) for determination of plasma concentration of amoxicillin were collected via a venous catheter into heparinized tubes at pre-dose (0 h), 0.33, 0.66, 1, 1.5, 2, 2.5, 3, 4, 6, and 8 h post-dose. The plasma samples for chromatographic analysis were obtained by centrifugation (2000×*g* × 12 min at 4 °C) of the blood samples. Plasma samples were stored at − 20 °C until the analysis.

Anthropometric Parameters Before and After Surgery

At each visit (T0 and T2), the weight and height of all volunteers were measured, followed by the calculation of their body mass index (BMI) for anthropometric comparison before and after bariatric surgery.

Bariatric Surgery Procedure

All volunteers included in this trial were operated using the RYGB surgery technique, performed by the same surgical team, following a standardization for the alimentary loop size (1.20 m length) and the biliopancreatic loop (1 m length). The gastrojejunoanastomosis was calibrated by a Fouchet 32F probe, resulting in a diameter of 12 mm.

Analytical Method

Amoxicillin plasma concentration was quantified by liquid chromatography coupled to mass spectrometry (LC-MS/MS) with some modifications of a previously described method [17].

To sample preparation, 100 μL of each plasma sample, 50 μL of the internal standard (IS) cephalexin (2.5 μg/mL), and 500 μL of acetonitrile (100%) were added into a glass tube. The samples were vortexed (30 s) and centrifuged (2000×*g* × 4 min at 4 °C). The organic phase was transferred to another glass tube, which was added of 500 μL of deionized water and vortexed (10 s). The samples were added of 10 mL of dichloromethane (100%), vortexed (10 s), and centrifuged (2000×*g* × 4 min at 4 °C). The organic phase was transferred to the autoinjector PCR plates.

The HPLC system (Agilent, Germany) consisted of a LC-10AD pump, autoinjector model CTC HST PAL/110695, and a G1316A/DE03018295 oven. The extracted solutions (10 μL) were injected into a 150 × 4.6-mm (5 μm particles) Inertsil ODS-C18 column maintained at 65 °C, and the mobile phase was methanol/water (30/70, *v*/*v*) + 0.1% formic acid at a flow rate of 900 μL/min with a split ratio of 1:3. The mass spectrometer used was a Quattro Micro (Micromass, Manchester, UK) with electrospray in positive mode for MRM (multiple reaction monitoring) to monitor the transitions 366.00 > 348.90 and 348.00 > 158.00 for amoxicillin and cephalexin, respectively.

The method validation was performed according to the US Food and Drug Administration (FDA) bioanalytical method validation guidance [18] and the Brazilian National Sanitary Surveillance Agency (ANVISA) [19]. To evaluate the specificity of the method, eight different blank plasma lots (4 normal, 2 hemolysed, and 2 lipemic) were tested for its interferences using the proposed extraction procedure and the chromatographic or spectroscopic conditions and compared with those obtained in the samples processed from the lower limit of quantification (LLOQ). The calibration curves were prepared by assaying standard plasma samples at eight concentrations of amoxicillin (20–5000 ng/mL) in triplicate, and the linearity of each calibration curve was determined by plotting the peak area ratio (*y*) of amoxicillin/IS versus nominal concentration of analyte. The calibration curve was constructed by weighted (1/x) least squares linear regression. The accuracy and precision of assay were evaluated by intra- and inter-assay studies. Seven aliquots of LLOQ and each quality control (QC) plasma samples (60, 850, 2500, 4000, and 12,000 ng/mL) were run in three validation batches on three different days. Inter- and intra-day precisions were determined as coefficient of variation, CV (%) = (SD/M) × 100, and the accuracy as the percentage relative error, RE (%) = [(*E* − *T*)/*T*] × 100, where *M* is the mean, SD is the standard deviation of *M*, *E* is the experimentally determined concentration, and *T* is the theoretical concentration. The matrix effect experiments were performed using the ratio between amoxicillin (60 and 4000 ng/mL) and IS injected directly into the mobile phase and standard solutions added to blank plasma extracts (4 normal, 2 haemolysed, and 2 lipemic). Each sample was obtained by a matrix factor normalized by IS (MFN) according to the following formula: MFN = (response of the analyte in matrix/internal standard response matrix)/(response of the analyte in solution/response of the internal standard solution). Stability QC plasma samples (60 and 4000 ng/mL) were subjected to short-term (6.0 h) room temperature, three freeze–thaw (− 20 to 25 °C) cycles, and 46.5 h autosampler (25 °C) stability tests in triplicate. The stability results were compared with the nominal values.

Pharmacokinetic Analysis

The pharmacokinetic parameters were obtained based on the plasma concentration versus time curves analyzed by a non-compartmental model using the Phoenix WinNonlin® software, version 5.0 (Pharsight Corp, MoutainView, CA, USA). Values for the maximum plasma concentration (C_{max}) and time to C_{max} (t_{max}) were obtained directly from the observed individual plasma concentration versus time curves. The area under the plasma concentration versus time curve from time zero to the time of the last quantifiable concentration ($AUC_{0–tlast}$) was calculated by the linear trapezoidal rule.

Table 1 Summary of obese volunteer characteristics before and after bariatric surgery

Variable	T0—Before surgery ($n = 8$) Mean (SD)	T2—After surgery ($n = 8$) Mean (SD)	Difference (T0 − T2) Mean (SD)	Difference % % (SD)
Age (years)	40.4 (8.9)	40.4 (8.9)	–	–
Body weight (kg)	119.44 (22.40)	102.41 (19.50)	17.03 (5.51)	14.19 (3.64)
Body mass index (kg/m^2)	46.21 (2.82)	39.82 (3.32)	6.38 (1.81)	13.85 (4.07)
Abdominal circumference (cm)	132.44 (12.83)	121.31 (14.48)	11.13 (3.88)	8.52 (3.06)

SD standard deviation

Elimination rate constant (k_e) was obtained by log-linear regression analysis, and the elimination half-life ($t_{1/2}$) was calculated with the equation [$t_{1/2} = \ln(2)/k_e$].

Statistical Analysis

The quantitative variables (continuous and discrete) were initially analyzed by the Kolmogorov–Smirnov test to verify the normality of the distribution. As this requirement was verified in all cases, mean and standard deviation (SD) were calculated for descriptive statistics. Parametric tests were used for analytical statistics.

To compare the pharmacokinetic parameters of the obese volunteers obtained before (T0) and after (T2) bariatric surgery, the *t* test for paired data was used. The mean of differences and their respective 95% confidence interval (95% CI) were also determined. Furthermore, the ratio between the parameter values verified before and after bariatric surgery was calculated, being expressed as geometric mean and its 95% CI. The degree and sign of the linear correlation between two variables were evaluated by the Pearson correlation coefficient, accompanied by its 95% CI.

In all analyses, two-tailed tests were used, establishing the level of significance at 0.05. The GraphPad Prism software, version 5.00 (GraphPad Software, San Diego, CA, USA), was used for both statistical analyses and graphics.

Results

Study Population

Eight obese volunteers were evaluated before (T0) and after (T2) bariatric surgery. Their anthropometric characteristics are

Table 2 Precision and accuracy data from amoxicillin method validation in human plasma

Parameter	Amoxicillin (ng/mL)																	
	LLOQ (20)			QC (60)			QC (800)			QC (2500)			QC (4000)			QC (12000–1:3)		
	Run 1	Run 2	Run 3	Run 1	Run 2	Run 3	Run 1	Run 2	Run 3	Run 1	Run 2	Run 3	Run 1	Run 2	Run 3	Run 1	Run 2	Run 3
Intra-run mean (ng/mL)	18.4	18.6	20.0	59.7	58.5	58.2	894	900	877	2570	2490	2510	4090	3970	3960	4170	4190	4060
Intra-run precision (CV%)	4.8	5.1	4.8	2.0	4.0	3.6	1.8	3.7	2.5	0.8	1.3	2.6	1.7	2.0	1.9	3.6	3.8	2.7
Intra-run accuracy (%)	92.1	93.2	100.1	99.5	97.5	97.0	105.2	105.9	103.1	102.9	99.7	100.3	102.3	99.2	98.9	104.2	104.6	101.4
Inter-run mean (ng/mL)	19.03			58.8			890.4			2524.3			4005.2			4136		
Inter-run precision (CV%)	6.0			3.3			2.9			2.2			2.4			3.6		
Inter-run accuracy (%)	95.1			98.0			104.8			101.0			100.1			103.4		

CV% = [(SD/*M*) × 100]; Accuracy % = [(*E* − *T*)/*T*] × 100

CV coefficient of variation, *M* mean, *SD* standard deviation of *M*, *E* experimentally determined concentration, *T* theoretical concentration, *LLOQ* lower limit of quantification, *QC* quality control

Table 3 Stability of amoxicillin in human plasma

Stability	Mean (ng/mL)	CV (%)	Accuracy (%)
Short term (6.0 h)			
60 ng/mL	57.3	3.0	95.5
4000 ng/mL	4050	3.0	101.3
Freeze/thaw (3 cycles)			
60 ng/mL	58.6	1.4	97.7
4000 ng/mL	4070	2.0	101.8
Post-processing (24 h)			
60 ng/mL	60	5.1	93.2
4000 ng/mL	3990	3.5	99.8

CV % = coefficient of variation [(SD/mean) × 100]; Accuracy % = [(*E* − *T*)/*T*] × 100

E experimentally determined concentration, *T* theoretical concentration

shown in Table 1. In total, four subjects had obesity-related comorbidities such hypertension ($n = 2$), type 2 diabetes ($n = 2$), and some degrees of hepatic steatosis (grade 1 to 3) ($n = 6$).

Analytical Method

The method of amoxicillin analysis presented LLOQ of 20 ng/mL and was linear over the concentration range of 20–5000 ng/mL, and the representative regression equation for the calibration curves was $y = 0.00097x + 0.000264$ ($r = 0.9996$). The within- and between-run precision and accuracy for the LLOQ and QCs are summarized in Table 2. The stability studies did not reveal any significant degradation under the conditions of the experiment in the short-term stability at room temperature (6.0 h), freeze–thaw test (three cycles), and post-processing stability test (46.5 h), as shown by CV and accuracy values (Table 3).

Pharmacokinetics of Amoxicillin Evaluated Before and After RYGB Surgery

The mean plasma concentration versus time curves of amoxicillin obtained before (T0) and after (T2) bariatric surgery for the obese volunteers ($n = 8$) are shown in Fig. 1, and the individual curves are presented in Fig. 2. The individual pharmacokinetic parameters are presented in the Fig. 3, and the statistical comparison of pharmacokinetic parameters is shown in Fig. 4 and Table 4. After bariatric surgery, the obese volunteers presented a significant increase in $AUC_{0-tlast}$ and C_{max}.

Correlation Between BMI and $AUC_{0-tlast}$

To evaluate the correlation between BMI and amoxicillin absorption between groups T0 and T2, a linear correlation was performed by the Pearson correlation coefficient (R) between BMI and $AUC_{0-tlast}$ obtained from participants before and after bariatric surgery. In the T0 group, a moderate negative linear correlation was observed between BMI and $AUC_{0-tlast}$, but without statistical significance (Fig. 5a). For the T2 group,

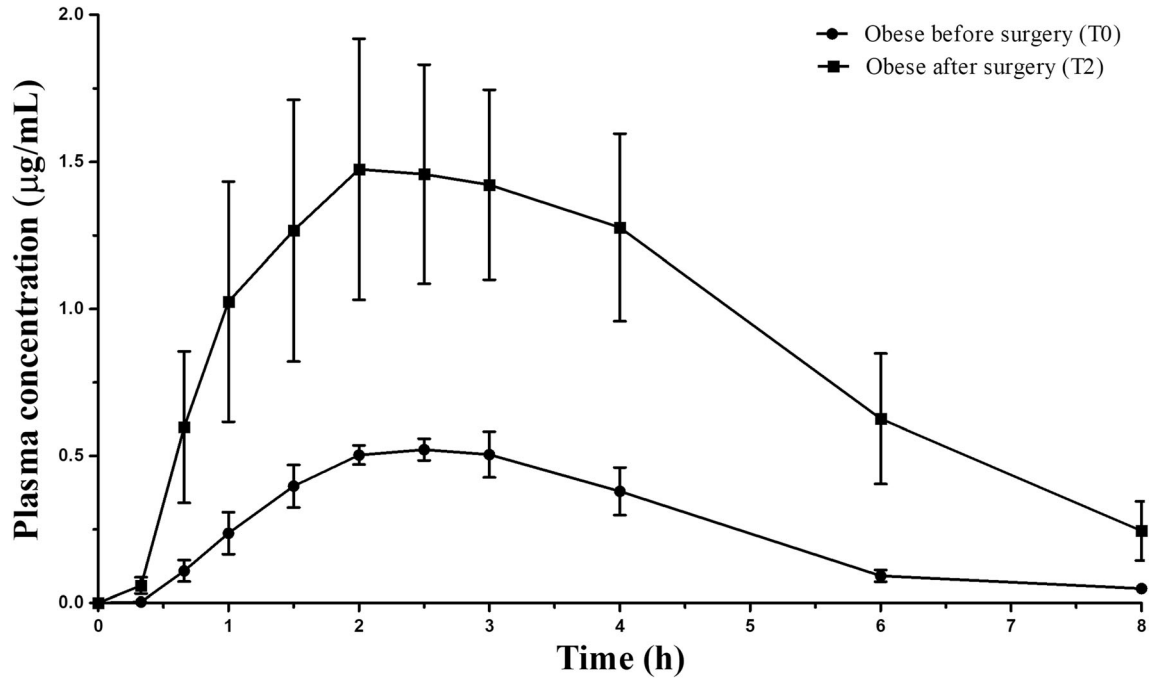

Fig. 1 Plasma concentration versus time of amoxicillin in the obese volunteers obtained before (T0) and after (T2) bariatric surgery. Data expressed as mean and standard deviation

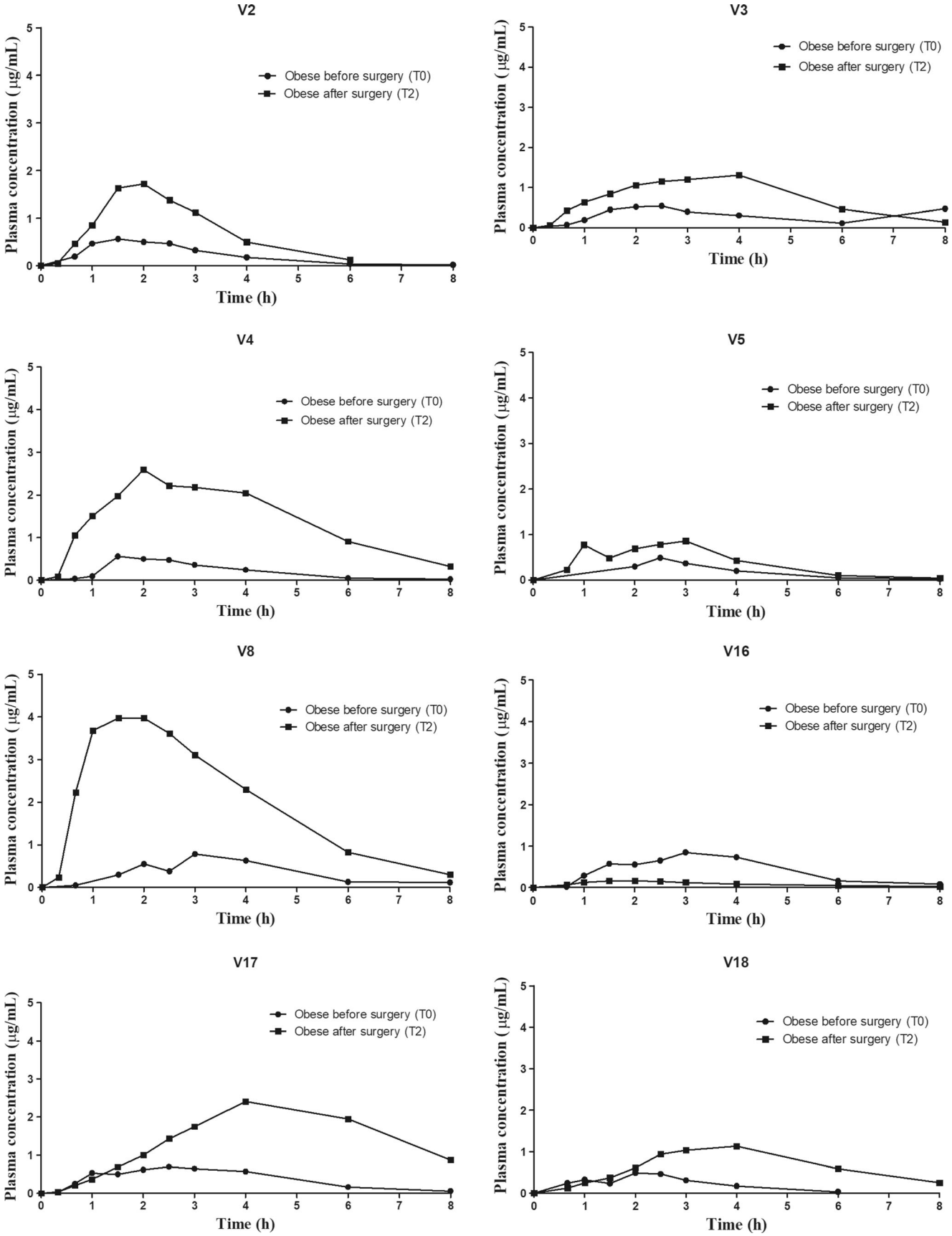

Fig. 2 Individual plasma concentration versus time of amoxicillin in the obese volunteers obtained before (T0) and after (T2) bariatric surgery

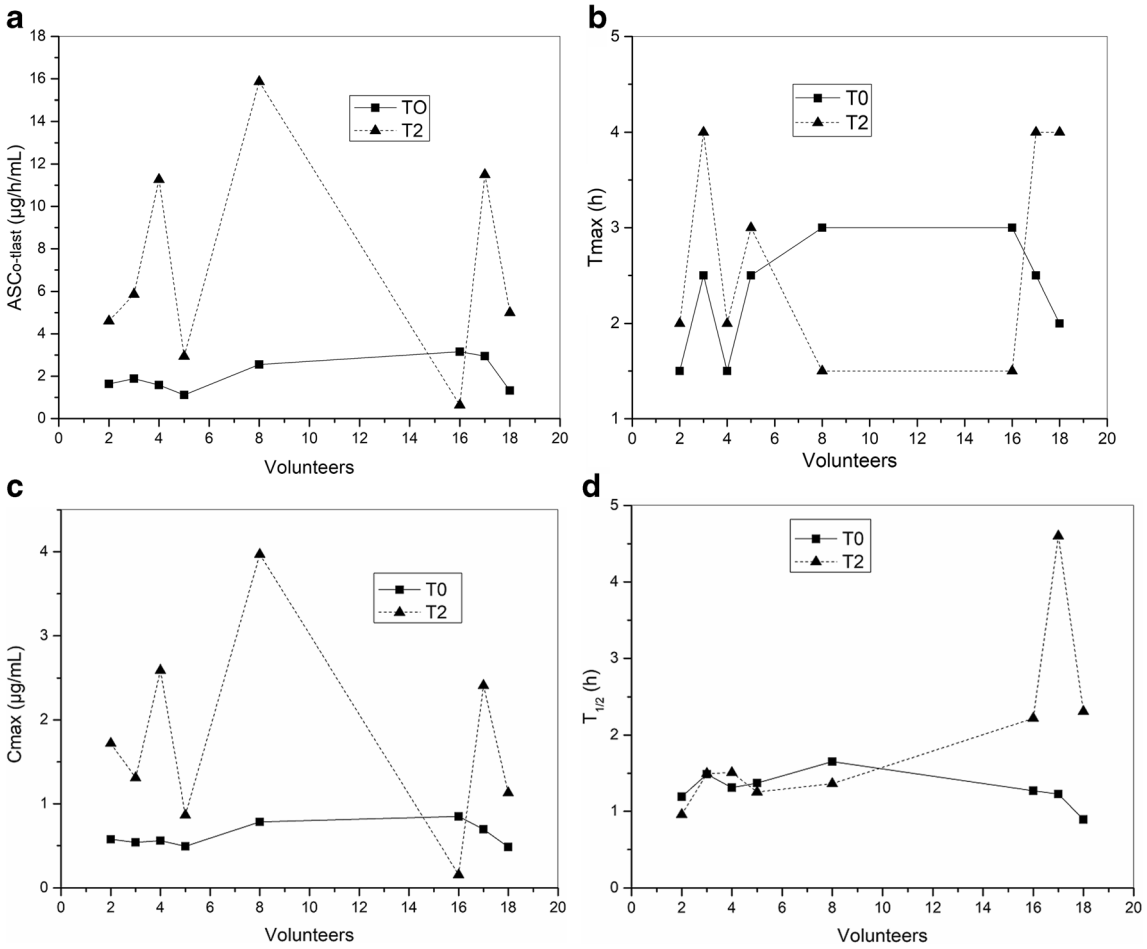

Fig. 3 Individual pharmacokinetic parameters in the obese volunteers analyzed before (T0) and after (T2) bariatric surgery. $AUC_{0–tlast}$ (area under the plasma concentration versus time curve from time zero to the time of the last quantifiable concentration) (**a**), t_{max} (time to reach maximum plasma concentration) (**b**), C_{max} (maximum plasma concentration) (**c**), and $t_{1/2}$ (elimination half-life) (**d**)

a non-statistically significant positive linear correlation between the two parameters was observed (Fig. 5b).

Correlation Between Weight Loss and Pharmacokinetics

In most cases, R values were higher than 0.18 and lower than 0.48, indicating a weak, but non-statistically significant positive linear correlation ($P > 0.05$). An absence of linear correlation was observed in the analysis of age versus t_{max} at T0 ($R = 0.0558$; $P = 0.8956$), while a moderate non-statistically significant positive linear correlation was observed in age versus $t_{1/2}$ in T2 ($R = 0.6307$, $P = 0.0936$) and age versus T2–T0 variation of $t_{1/2}$ ($R = 0.5525$; $P = 0.1555$).

Discussion

The present study reports, for the first time, the impact of bariatric surgery on the pharmacokinetics of amoxicillin after the administration of a single oral dose to obese volunteers. The literature reports a limited number of clinical studies evaluating the effect of bariatric surgery on drug absorption. Moreover, a small proportion of these studies evaluated the same volunteer before and after surgery.

The validation results indicate that the developed LC-MS/MS method is sensitive, precise, and accurate enough for its application in the evaluation of amoxicillin pharmacokinetics after a single oral dose (500 mg) administration to obese volunteers before and after bariatric surgery.

After bariatric surgery, a significant increase in amoxicillin $AUC_{0–tlast}$ (2.03 ± 0.77 µg.h/mL vs. 7.21 ± 5.13 µg.h/mL) and C_{max} (0.62 ± 0.14 µg/mL vs. 1.77 ± 1.19 µg/mL) values was observed (Fig. 1; Table 4). Considering that the procedure leads to several anatomical and physiological alterations, as the exclusion of the duodenum and a portion of the jejunum, which are responsible for amoxicillin absorption [12], a decrease in its systemic exposure was expected. However, despite of the increase in $AUC_{0–tlast}$ and C_{max} of amoxicillin after bariatric surgery, the obese

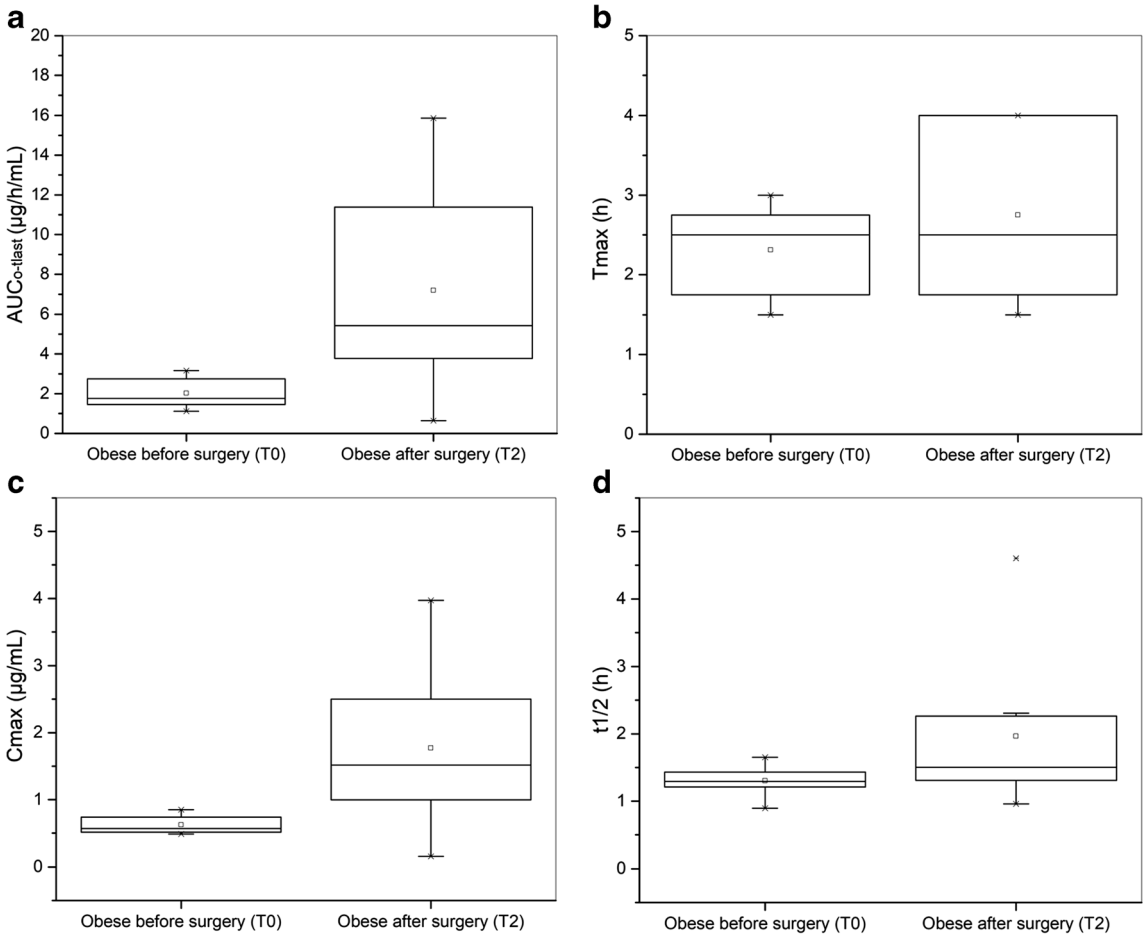

Fig. 4 Statistical comparison of the pharmacokinetic parameters in the obese volunteers analyzed before (T0) and after (T2) bariatric surgery. Statistical comparison of $AUC_{0–tlast}$ (area under the plasma concentration versus time curve from time zero to the time of the last quantifiable concentration) ($n = 8$) (**a**), t_{max} (time to reach maximum plasma concentration) ($n = 8$) (**b**), C_{max} (maximum plasma concentration) ($n = 8$) (**c**), and $t_{1/2}$ (elimination half-life) ($n = 8$) (**d**) between the T0 and T2 groups

subjects still had lower values than non-obese volunteers investigated previously by the same research group, who presented the $AUC_{0–tlast}$ ranging from 12.44 to 12.05 μg h/mL and C_{max} from 4.94 to 5.31 μg/mL after a single oral administration of 500 mg amoxicillin capsule [17]. It is worth mentioning that, even after surgery, these subjects were still obese (mean BMI of 39.82 kg/m_2). These results are in accordance with data reported by Hamilton et al.

Table 4 Statistical comparison of amoxicillin pharmacokinetics in obese volunteers analyzed before (T0) and after (T2) bariatric surgery ($n = 8$)

Parameter	Obese groups—mean (SD)		*P* value	Mean of differences	95% CI
	Before surgery (T0)	After surgery (T2)			
$AUC_{0–tlast}$ (μg h/mL)	2.03 (0.77)	7.21 (5.13)	0.0224	− 5.18	− 9.38 to − 0.98
t_{max} (h)	2. 31 (0. 59)	2. 75 (1 13)	0.3801	− 0.44	− 1.54 to 0.67
C_{max} (μg/mL)	0.62 (0.14)	1.77 (1.19)	0.0279	− 1.15	− 2.13 to − 0.17
$t_{1/2}$ (h)	1.30 (0.22)	1.96 (1.16)	0.1778	− 0.66	− 1.71 to 0.38

SD standard deviation, *95% CI* confidence interval of 95% of the mean difference, $AUC_{0–tlast}$ area under the plasma concentration versus time curve from time zero to the time of the last quantifiable concentration, C_{max} maximum plasma concentration, t_{max} time to reach C_{max}, $t_{1/2}$ elimination half-life

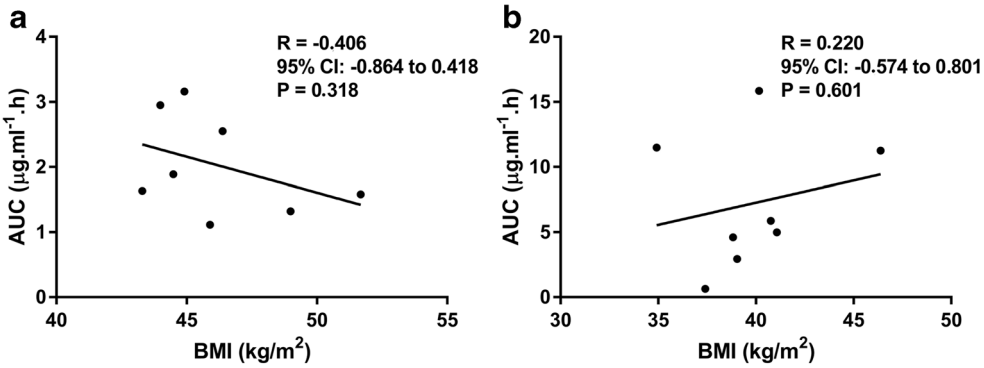

Fig. 5 Correlation between body mass index (BMI) and $AUC_{0-tlast}$ (area under the plasma concentration versus time curve from time zero to the time of the last quantifiable concentration) measured in obese volunteers before (**a**) and after (**b**) bariatric surgery

[20], in which the bioavailability of linezolid in obese patients was more than 50% lower when compared to non-obese individuals, suggesting that higher doses of linezolid are required to reach concentration similar to that of non-obese individuals.

The correlation between overweight and failure in antibiotic treatment, in which the most frequently prescribed antibiotic was amoxicillin, the therapeutic failure occurred in 13.4% of overweight and obese patients in a cohort study performed by Longo et al. [21]. The authors concluded that the obesity is a significant predictor of a risk factor for failure in antibiotic treatment. A possible explanation for these findings is that obese patients have renal hemodynamic alterations, as an increase in the glomerular filtration rate, renal plasma flow and albuminuria. However, after weight loss, these parameters improve (decrease) substantially. The reduction in albuminuria is not only due to a decrease in the glomerular filtration rate but also due to reduction in its CL [22].

In the present study, the effect of RYGB surgery on amoxicillin systemic exposure was varied. An increase in systemic exposure was observed in seven subjects, while one volunteer presented a reduction after the surgical procedure (Fig. 3). Comparable results were reported by Skottheim et al. [23] in a study of the effect of RYGB surgery in the systemic exposure of atorvastatin in morbidly obese patients. While the bioavailability of atorvastatin increased in eight subjects, a reduction in this parameter was observed in three patients 3–6 weeks after surgery. According to them, there is no tendency to increase or decrease the absorption of drugs after surgery, and there is no clear and simple algorithm to predict the kinetic absorption of the drugs. The RYGB surgery also did not alter the bioavailability of linezolid after a single dose of 600 mg linezolid administered orally and intravenously to five obese subjects 3 months before and 3 months after the surgery. A tendency towards greater absorption and a higher C_{max} was observed, but without a significant difference. A clear reduction in CL with weight loss was observed after surgery by a simulation, suggesting a possible correlation between CL of linezolid and body weight [20]. A large variability in t_{max} was observed after surgery (Fig. 4b), but without statistical significance in this parameter. This variability in t_{max} was also observed by Hamilton et al. [20].

An increase in some drugs exposure after RYGB surgery, such as moxifloxacin, can be explained by alteration in the enterohepatic recirculation. The oral bioavailability of moxifloxacin was 88% in subjects ($n = 12$) who received a single 400-mg moxifloxacin orally and intravenously at least 6 months after RYGB surgery and who had reached a stable BMI (23–38 kg/m^2) during the last 3 months, confirming that exposure to moxifloxacin was equivalent for oral and intravenous administration in these volunteers. However, these exposures were more than 50% higher than those described for subjects without bariatric surgery [24]. Considering that there is a small enterohepatic circulation of amoxicillin [9], this phenomenon cannot explain the observed increase in amoxicillin systemic exposure after surgery.

The reduction in the body weight observed in the investigated obese volunteers (mean % total weight loss of 14%; Table 1) after the surgical procedure may have caused (although no correlation was found between BMI and $AUC_{0-tlast}$) the decrease in albuminuria, which increased the binding of amoxicillin to albumin, reducing its distribution and excretion, and leading to an increase in its plasma concentration. Furthermore, as the main route of amoxicillin elimination is through the kidneys by glomerular filtration and tubular secretion [15], an improvement in renal hemodynamic reduced glomerular hyperfiltration and consequently decreased the rate of excretion of amoxicillin, which may also have caused an increase in amoxicillin concentrations (mean and maximum). Data reported by Navarro-Díaz et al. [25] has shown that the renal parameters of patients who presented high morbid obesity (mean BMI = 53.62 kg/m^2) improved after bariatric surgery. Comparing their data with data from healthy volunteers, morbid obese subjects had a higher creatinine clearance, proteinuria, and albuminuria before undergoing surgery. One year after surgery, these obese volunteers had a mean weight loss of 53.3 kg and an improvement in all renal parameters, with a significant decrease in creatinine clearance, proteinuria, and albuminuria.

Correlation of absorption with BMI was not observed in any of the investigated periods (Fig. 5). It was not observed either for absorption with the percentage of weight lost in the operated patients. An important point to be discussed is the time of blood collection for quantification of amoxicillin in the plasma of the investigated participants. As there are no specific guidelines for pharmacokinetic evaluation in the obese population, the number of samples collected was based on the protocol of non-obese volunteers. However, the sample collection should have been prolonged, because it was still possible to detect concentration of amoxicillin in the samples collected in the scheduled last time (8.0 h after drug administration) in most of volunteers (mean of 0.049 μ/mL in T0 and 0.28 μ/mL in T2 period). These data suggest that the volunteers who underwent surgery had an even greater absorption than we could detect and that this same group also excreted amoxicillin more slowly.

This study had some limitations, such as an inappropriate blood collection time schedule and a short postoperative period (2 months) to evaluate the surgery effect in the amoxicillin pharmacokinetics. Although the number of research participants was small, the results were consistent. Further studies to evaluate the effect of surgery as well the weight lost in the amoxicillin pharmacokinetics should be performed after a weight stabilization. Thus, the need for its dose adjustment would be better assessed, and consequently, it would contribute to an effective therapy in obese patients.

Conclusion

The alterations observed in the pharmacokinetic parameters suggest that obese subjects included in this trial had a substantial increase in amoxicillin systemic exposure after RYGB surgery. However, despite this increase, its exposure was lower than the values reported for non-obese volunteers.

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Compliance with Ethical Standards

The study was approved by the institutional review board (IRB) of the Federal University of Ceará (number 255.607) and the Scientific Committee of the Hospital General Dr. César Cals.

Ethical Approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed Consent Informed consent was obtained from all individual participants included in the study.

Conflict of Interest The authors declare that they have no conflict of interest.

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