The Pharmacokinetics of Metronidazole and Gentamicin in a Single Preoperative Dose as Antibiotic Prophylaxis in Colorectal Surgery

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Abstract

Objective: To describe, in patients undergoing colorectal surgery (CRS), the pharmacokinetics of a single, prophylactic preoperative dose of 1500 mg of metronidazole plus 240 mg gentamicin and measure its efficacy in accordance with the accepted pharmacodynamic and microbiological parameters.

Method: Thirty-six patients undergoing CRS agreed to participate in the study. Three blood samples were taken from each. C_{max} 15 minutes after finishing the infusion of the mixture, C_{finIQ} on finishing the surgery, and C_{min} between 12 and 24 hours post-administration. The concentrations of metronidazole and gentamicin in each simple were measured and the pharmacokinetic parameters were estimated (dV-distribution volume, Cl-plasma clearance). For the metronidazole, concentrations in excess of 8 µg/mL were considered effective, and for gentamicin, C_{max} in excess of 9 µg/mL and inhibition quotients above 8.

Results: All the concentrations of metronidazole, both C_{max}^{MTZ} and C_{finIQ}^{MTZ} were above 8 µg/mL and all the C_{max}^{GEN} in excess of 9 µg/mL. The Cl^{GEN} was 13.8 (3.8), with no individual value below 8. For the metronidazole, a dV of 0.68 (0.2) L/kg was estimated and a Cl of 3.15 (1.20) L/h and for the gentamicin, the dV as 0.23 (0.06) L/kg and the Cl was 4.71 (1.95) L/h.

Conclusion: In patients undergoing CRS, surgical intervention did not significantly modify the pharmacokinetics of metronidazole or gentamicin in comparison with other groups of patients. The prophylaxis using a single, pre-surgical dose enables the achievement, for both antimicrobial agents, concentrations of a sufficient size to guarantee clinical efficacy.

Key words: Antibiotic prophylaxis. Colorectal surgery. Pharmacokinetics. Metronidazole. Gentamicins.

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Farmacocinética del metronidazol y la gentamicina en dosis única preoperatoria para profilaxis antibiótica quirúrgica en cirugía colorrectal

Objetivo: Describir, en pacientes sometidos a cirugía colorrectal (CCR), la farmacocinética de una dosis única preoperatoria de metronidazol 1.500 mg más gentamicina 240 mg como pauta profiláctica, y estimar su efectividad de acuerdo con parámetros subrogados farmacodinámicos y microbiológicos.

Método: Treinta y seis pacientes sometidos a CCR aceptaron su participación en el estudio. De cada uno de ellos se tomaron tres muestras de sangre: $C_{máx}$, 15 min tras finalizar la infusión de la mezcla, C_{finIQ} al finalizar la cirugía, y $C_{mín}$ entre las 12 y 24 h posteriores a la administración. Se determinaron las concentraciones de metronidazol y gentamicina en cada muestra y se estimaron los parámetros farmacocinéticos (Vd: volumen de distribución, Cl: aclaramiento plasmático). Para el metronidazol, se consideraron efectivas concentraciones superiores a 8 µg/ml, y para la gentamicina, $C_{máx}$ superiores a 9 µg/ml y cocientes de inhibición superiores a 8.

Resultados: Todas las concentraciones de metronidazol, tanto $C_{máx}^{MTZ}$ como C_{finIQ}^{MTZ} fueron superiores a 8 µg/ml, y todas las $C_{máx}^{GEN}$, superiores a 9 µg/ml. El Cl^{GEN} fue de 13,8 ± 3,8, con ningún valor individual inferior a 8. Para el metronidazol, se estimó un Vd de 0,68 ± 0,2 l/kg y un Cl de 3,15 ± 1,20 l/h, y para la gentamicina, el Vd fue de 0,23 ± 0,06 l/kg, y el Cl, de 4,71 ± 1,95 l/h.

Conclusión: En pacientes sometidos a CCR la intervención quirúrgica no modifica significativamente la farmacocinética del metronidazol y la gentamicina respecto a otros grupos de pacientes. La profilaxis en dosis única prequirúrgica permite alcanzar, para ambos antimicrobianos, concentraciones de magnitud suficiente para garantizar su efectividad clínica.

Palabras clave: Profilaxis antibiótica. Cirugía colorrectal. Farmacocinética. Metronidazol. Gentamicina.

INTRODUCTION

The appearance of antimicrobial agents with a moderately long half-life and a wide antibacterial spectrum has driven the incorporation of single-dose antibiotic surgical prophylaxis in clinical practice. Among the potential advantages of this therapeutic regimen it is important to point out the associated cost savings, reduction in side effects and the reduction to a minimum of the ecological risk of developing bacterial resistance. To ensure sufficient concentrations in plasma and tissues during the entire surgical intervention, the single-dose antibiotic prophylaxis must be administered at high doses within the 2 hours prior to the start of the surgical intervention.[1-4]

Colorectal surgery (CRS) is considered clean-contaminated or contaminated depending on the type of surgery. The rate of post-surgical infection, with antibiotic prophylaxis, is 11.1% when programmed CRS (PCRS) and emergency colorectal surgery are considered together (ECRS). Mortality during the post-surgical stage ranges between 0.9% in patients under the age of 65 and 8.1% in those aged 85 years undergoing PCRS.[3,5-11]

The antimicrobial agents used both single-dose treatments and multiple dose treatments as prophylaxis in CRS, must cover a wide spectrum of potential post-surgical infection-causing bacteria, mainly anaerobic and gram negative enterobacteria. The combination of an antibiotic active against anaerobes (such as metronidazole) and an antibiotic effective against gram negatives (such as gentamicin) is the basis of many healthcare protocols.[2,3,5,12] Metronidazole and gentamicin are bactericide against anaerobic microorganisms and gram-negative sensitive aerobes respectively. Both have a concentration-dependent effect and present a post-antibiotic effect of over 3 hours. These properties mean that they are made more effective when high doses are used with low frequency of administration.[13-14] Unlike other concentration-dependent antibiotics, there is no defined relationship between tissue or serum levels for metronidazole and the Minimum Inhibitory Concentration (MIC) that guarantees, or at least predicts, in vivo efficacy. According to the *summary of antimicrobial susceptibility test results* from Duke University,[15] concentrations in excess of 8 µg/mL are active against 100% of the *Bacteroides* spp strains. Similarly, Credito et al observed that concentrations of metronidazole 4 times higher to the MIC were baceteriacide over 24 hours as against 100% of the strains of anaerobes tested, including *Bacteroids spp,* as against 80% in the 48 hours for MIC between 0.03 and 2 µg/mL.[16] On the other hand, in agreement with the latter consensus proposed by the national committee for laboratory standards in the United States of America[17] (NCCLS 2005) and the *summary of antimicrobial susceptibility test results* at Duke University,[15] the sensitivity threshold of the microorganisms tested (enterobacteria, *Pseudomonas aeruginosa,* and other gram negative non-enterobacteria, *Staphylococcus* spp and *Enterococcus*) for gentamicin is 4 µg/mL. This could be considered a very conservative value in comparison to usual clinical practice, an environment in which the MIC ranges between 0.5 and 1.2 µg/mL for the same microorganisms, except for *Entorococcus faecalis*, whose MIC is found between 4 and 16 µg/mL.[18-21] This value would be key from a pharmacodynamic point of view, as the inhibitory quotient (IQ), predictor of antibacterial activity, is defined as the relationship between the maximum concentration of antibiotic (C_{max}^{GEN}) and the MIC ($CI=C_{max}/MIC$) and is associated with the clinical efficacy of gentamicin. Particularly, to obtain a bactericide response over 90% (CMI_{90}), a $CI^{GEN} \geq 8$-10 is considered necessary, while a ratio of four obtains a bactericide response of 70%. In any case, surpassing these quotients necessarily requires the administration of high doses of gentamicin, which allows a C_{max}^{GEN} in excess of 20 µg/mL[21-23] to be achieved.

This study aims to measure the pharmacokinetic parameters of metronidazole and gentamicin in patients undergoing PCRS, and to try to show that the administration of a single preoperative dose of a mixture of metronidazole 1500 mg and gentamicin 240 mg intravenously, presents a pharmacokinetic profile that guarantees its efficacy in accordance with accepted pharmacodynamic and microbiological parameters.

METHOD

Study Design and Patients

This was a prospective study, approved by the Hospital Clinical Research Ethics Committee, on a group of 36 patients (58% male) undergoing non-laparoscopic PCRS by the same surgical team during 2001, who received prophylactic antibiotic therapy of a single dose of 1500 mg of metronidazole plus 240 mg of gentamicin. For each patient, this mixture was prepared by the centralised unit as an intravenous mixture, and was individually dispensed via the medicine dispensations system in unit doses from the pharmacy department. The administration took place during 15 minutes prior to surgery, during the anaesthetic induction phase before surgery.

The candidates included in the study met the following inclusion criteria: *a)* patients of both sexes aged between 18 and 90 years of age; *b)* patients included in the PCRS protocol from the surgery department of the hospital; *c)* patients without antibiotic treatment during the 48 hours prior to the intervention; and *d)* patients giving informed consent having received sufficient information about the study protocol. No subjects presenting any of the following exclusion criteria were included: *a)* known allergy to aminoglucoside antibiotics and/or nitroimidazoles; *b)* pregnant patients; *c)* creatinine serum clearance (Cl_{crs}) below 20 mL/min; *d)* patients being treated with 5-Fluorouracil; *e)* chronic enolism; and *f)* not meeting the inclusion criteria. The subjects or their legal representative were able to elect not to be included in the study, or the researcher could decide they should not be included when it was considered that continuing in the study would be detrimental to the quality of care provided and/or the patient's quality of life. Based on the above, 1 patient did not consent to

participating in the study and 2 patients were not evaluated because the programmed intervention was cancelled.

Collection of Samples

Using vein puncture, 3 peripheral blood samples were collected from each patient (minimum volume 1 mL) at the following times: 15 minutes after administering the antibiotic mixture (sample 1, equivalent to C_{max}), at the end of the surgical intervention (sample 2), and between 12 and 24 hours after the administration of the antibiotic mixture (sample 3, equivalent to C_{min}). At the beginning of the administration of the antibiotic mixture, this was always done 1 hour immediately prior to the beginning of the surgical intervention, meaning that the C_{max} was collected, either immediately before the surgery began, or during the first few minutes after it had started.

Analytical Techniques

The detection and quantification of metronidazole in serum was carried out using the high resolution liquid chromatography method (HRLC) in inverse phase. A Merck-Hitachi® chromatographic device was used, with an L-6200[a] pump, UV-VIS L-4250 detector and integrator recorder D-2500[a]. All the reagents used were of analytical quality, using for the preparation of the mobile phase specific HPLC grade solvents. The metronidazole used for preparing the standards and the tinidazole used as internal standard were supplied by Sigma Chemical®. As an apolar stationary phase the LichroCART® 125-4 RP-18 column was used 12.5 cm long and with an internal particle diameter of 5 µm, filled with octadecylsilane (C-18) and by a cartridge of purifying precolumn with the same characteristics (LichroCART® 4-4 guard column, RP-18 (5 µm)), supplied by Merck KGaA®. The mobile phase consisted of a solution of acetonitrile: water 15:85 v/v, pH=6.3.

Serum samples were obtained by total blood centrifuge at 5400 rpm for seven minutes. 900 µL of sample were taken, to which were added 100 µL of internal standard solution (tinidazole 100 µg/mL in free serum of metronidazole and tinidazole) and shaken for 1 minute in a "Vortex-Mixter." Eight hundred µL of the above mixture was taken and added to a protein extraction cartridge by ultra-filtration Cetrifree®, by Millipore®. After centrifuging the samples at 3700 rpm for 25 minutes, an ultrafiltration elution was obtained that could be injected directly into the chromatographic system. The volume of the sample injected in the chromatographic system was limited to 20 µL via a loop of this capacity. The elution flow was 1 mL/min and the detection was made at a wavelength of 318 nm. Each sample was processed in duplicate.

Using the free human serum samples of metronidazole and tinidazole, the calibration lines were prepared, at fixed concentrations of tinidazole (10 µg/mL) and metronidazole variables (between 1 and 100 µg/mL). The linearity study of the technique for the relationship between the areas of the peaks of metronidazole and tinidazole and the concentration of metronidazole by simple lineal regression. The recovery of the technique was calculated as a percentage, and the reproducibility, interday and intraday, as variation coefficient (VC) in percentage (100·[standard deviation/mean value]). The detection limit was calculated (DL) for the analytical method, in µg/mL, from the standard error (SE) associated to the slope (m) and the ordinate in the origin (b) and the calibration line in accordance with the 3s criteria ($3 \cdot EE_m/b$).

The determination of the concentration of gentamicin in serum was made using a polarised immunofluorescence technique (AsXYM®, Abbott Diagnostic División). Given that the technique has good sensitivity and specificity and that it is an automated technique, the samples of gentamicin are processed just once.

Pharmacokinetic Analysis

The pharmacokinetic parameters of metronidazole and gentamicin are estimated using their fit to a kinetic monocompartmental model using an iterative method in 2 stages, the first of these via non-lineal regression and the second via a Bayesian model, using the computer application Abbotbase Pharmacokinetic System® version 1.1. The plasmatic clearance (Clp), the elimination half-life ($t_{1/2}$) and the apparent distribution volume (dV) of each drug were calculated for each patient.

Pharmacokinetic-Pharmacodynamic Model (PK-PD). Accepted Parameters for the Efficacy of Antibiotic Treatment

For the metronidazole no usual therapeutic interval has been defined. In this study, the potential efficacy of the antibiotic was evaluated as well as the relationship between the individual concentrations in plasma (C^{MTZ}) and the sensitivity limits for the most common pathogens, established by Credito et al as a MIC below or equal to 2 µg/mL.[16] In accordance with these authors' criteria, C^{MTZ} above 8 µg/mL are considered potentially effective, ie, 4 times higher than the MIC of 2 µg/mL.

For the gentamicin, the inhibition quotient was evaluated (CI^{GEN}) of each patient, calculated as the quotient between the $C_{máx}{}^{GEN}$ and a MIC of 1.2 µg/mL (upper sensitivity in clinical practice). $CI^{GEN} \geq 8$ are considered potentially effective. Furthermore, It was evaluated for gentamicin, as the accepted efficacy criteria, the $C_{max}{}^{GEN}$, meaning that values over 9 µg/mL[24-26] were considered effective.

Statistical Analysis

The comparison of independent quantitative variables complying with the provisions of the normal law and the homogeneity of variances has been achieved using the Student *t* test. If any of these were not complied with, the non-parametric *U* Mann-Whitney test was applied, regardless of the number of cases, as this is a more conservative test than the Student *t* for large samples (>30 cases) that do not comply with the normal rule. The correlations among the clearance values and distribution volume

were estimated via the Pearson (*r*) correlation coefficient. Throughout the test an alpha significance of .05 was considered.

RESULTS

Figure shows the chromatogram of metronidazole in our standard serum sample, obtained after applying the methodology described. The method provides appropriate separation and completes the rest of the substances present in the patients' blood samples. The use in the preparation of the sample of specially designed filters to separate ultrafiltrates free of plasma proteins, has enabled a recovery percentage in no case below 96%. The values of the correlation coefficients obtained in the calibration lines, with and without ordinate in the origin, are in excess of 0.999, confirming an excellent linearity between the areas of the chromatographic peaks and the concentrations of metronidazole. With regard to the precision of the analytical method for metronidazole, it is important to note that the intraday and VC was no greater than 2% for any of the concentrations assayed, while in the interday test it was always below 5%. The sensitivity of the technique is also outstanding, as it enables concentrations of metronidazole of up to 0.41 µg/mL to be quantified, a level well below the serum concentrations that appear between 12 and 24 hours post-administration, whose average value is 8.45 µg/mL.

Table 1 sets out the pre-surgical anthropometric and analytical values of the 36 patients recruited. The average duration of the surgical interventions performed was 83 (52) minutes and the cases intervened most commonly were colonic or rectal resections, carried out in 18 cases.

Table 2 shows average the pharmacokinetic parameters for metronidazole and gentamicin obtained. The elimination half-life was estimated at 11.8 (5.1) h for metronidazole and 2.3 (1.4) h for gentamicin. The correlations between Cl_{Crs} and Cl_{MTZ}, and between Cl_{Crs} and Cl_{GEN} were weak in both cases (r=0.340, r=0.363 respectively). Neither were there any significant correlations between the volumes of distribution (dV_{MTZ}-dV_{GEN}, r=0.207) and the clearance of both drugs (Cl_{MTZ}-Cl_{GEN}, r=0.211). According to the Student *t* test no significant differences in the pharmacokinetic parameters in both drugs according to the sex. In terms of age, taking as the cut-off point the age of 65 years, differences were observed in the Cl_{MTZ}, the dV_{MTZ} and in the Cl_{Crs}, no observations of this behaviour were made with gentamicin. The duration of the surgical intervention does not change significantly for the pharmacokinetic parameters of both drugs, although a significantly lower Cl_{Crs} was seen in patients undergoing interventions with a duration of over 1 hour.

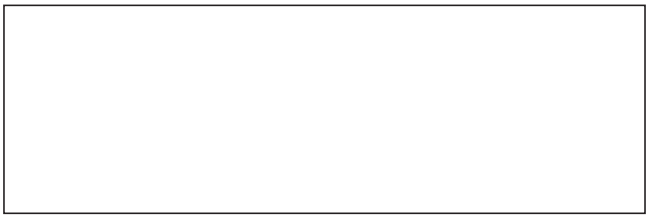

Figure 1. *Chromatogram of metronidazole in a sample of serum containing 50 µg/mL of metronidazole and 10 µg/mL of tinidazole (internal standard). Metronidazole, retention time 2.65 minutes. Tinidazole, retention time 5.13 minutes.*

Table 1. Anthropometric, Biochemical, and Haematological Values Prior to Surgery[a]

Parameter	Average Value (SD)
Age, y	59 (19)
Weight, kg	73 (13)
Height, cm	163 (7)
Creatinine in serum (Crs), mg/dL	0.99 (0.29)
Serum creatinine clearance (ClCrs),[b] mL/min	78 (29)
Urea in serum (Us), mg/dL	37 (15)
Albumin in serum, g/dL	3.76 (0.45)
GPT (alanine aminotransferases), IU/L	21 (15)
Haemoglobin in serum, g/dL	12.5 (2.4)
Hematocrit, %	37.3 (5.6)
Glycaemia, g/dL	116 (44)
Total bilirubin in serum, mg/dL	0.79 (0.40)

[a]SD indicates standard deviation.
[b]Clearance of creatinine in serum (Cl_{Crs} in mL/min) measured using the Cockroft-Gault method.

Table 3 shows the average metronidazole and gentamicin concentrations in serum. In all the cases, the $C_{máx}^{GEN}$ were higher than 9 µg/mL, and in 18 of the patients, these concentrations were higher than 15 µg/mL. With regard to the C_{min}^{GEN}, in 1 patient a value higher than 1 µg/mL was observed and in no patients was the concentration higher than 2 µg/mL. All the concentrations of metronidazole, whether after finishing the perfusion (C_{max}^{MTZ}), and after finishing the surgical intervention (C_{finIQ}^{MTZ}), were higher than 8 µg/mL, a value four times higher than the permitted MIC limit allowed (CMI=2 µg/mL). The average value of CI^{GEN} was 13.8 (3.8), with no values lower than 8.

DISCUSSION

Different combinations of antibiotics have been shown to be effective in the prevention of post-surgical infection in CRS and, among these, the combination of metronidazole and gentimicin. The prophylactic administration of a single dose leads to unarguable logistical advantages, particularly facilitating its centralised preparation and guaranteeing the complete administration at the correct moment of the antibiotic mixture. Furthermore, this regime has been shown to be similarly effective to multiple doses, and is accompanied by a reduction in costs.[27]

It is to be expected, in accordance with the biological changes caused by surgery, that the pharmacokinetic parameters of both drugs will be modified with regard to the standard in comparison to the standard values for other populations. However, in this

Table 2. Average Pharmacological Parameters of Metronidazole and Gentamicin Stratified by Age, Sex, and Duration of the Surgical Intervention[a]

Grup	No.	Metronidazole		Gentamicin		Cl_{Crs}
		dV, L/kg	Cl, L/h	dV, L/kg	Cl, L/h	mL/min
Total	33	0.68 (0.20)	3.15 (1.20)	0.23 (0.06)	4.71 (1.95)	78 (29)
Gender						
Male	19	0.66 (0.16)	3.40 (0.94)	0.22 (0.05)	5.08 (1.94)	82 (31)
Female	14	0.69 (0.25)	2.80 (1.45)	0.23 (0.07)	4.20 (1.92)	73 (26)
Age						
<65 y	16	0.77 (0.21)[b]	3.57 (1.26)[b]	0.23 (0.04)	5.04 (1.98)	98 (26)[b]
>65 y	17	0.59 (0.13)[b]	2.75 (1.03)[b]	0.22 (0.07)	4.39 (1.93)	60 (15)[b]
SI duration						
<60 min	13	0.67 (0.17)	3.57 (1.01)	0.23 (0.04)	4.79 (2.05)	93 (27)[b]
>60 min	20	0.68 (0.22)	2.87 (1.26)	0.23 (0.07)	4.66 (1.94)	69 (26)[b]

[a]Cl indicates total clearance; dV, apparent distribution volume.
[b]Significant differences (*P*<.05 Student *t*).

Table 3. Average Serum Concentrations of Metronidazole (C_{MTZ}) and Gentamicin (C_{GEN})

Sample	t ext[a]	C_{MTZ}, µg/mL	C_{GEN}, µg/mL
C_{max}	39 (9) min	34.74 (11.10)	16.54 (4.59)
End SI	119 (47) min	25.60 (8.38)	9.46 (4.24)
C_{min}	1374 (108) min	8.45 (4.10)	0.44 (0.24)

[a]Time at which the sample was drawn in minutes from the time the infusion of the mixture of antibiotics was started.

work, the values recorded for the pharmacokinetic parameters of metronidazole and gentamicin do not differ in magnitude from the standard values in adult patients, undergoing CRS or not.[21,24,28] No differences were observed in the kinetic behaviour of gentamicin regarding sex or age, although creatinine clearance is significantly reduced in patients aged over 65. This finding is in agreement with the weak correlation found between the Cl_{Crs} and the Cl_{GEN}, confirming the fact that the Cl_{Crs} is not necessarily a good predictor of the clearance of gentamicin.[29] In contrast to gentamicin, for metronidazole, patients aged below 65 years present distribution and clearance volumes significantly higher than those obtained in patients aged over 65 years. This apparent greater distribution volume is most likely due to the confluence of a greater percentage of body fat and a greater percentage of lean mass in young patients, circumstances that lead to a higher diffusion through the tissues and an equally faster return to plasma. The fastest elimination of metronidazole in patients under the age of 65 can be attributed to greater metabolic function, given that clearance, like that of gentamicin, does not correlate with creatinine clearance.

The duration of the surgical intervention in colorectal surgery is very variable, because of the different procedures and diagnoses included. Interventions taking less than 60 minutes are mainly minor surgical procedures (anal or haemorrhoids), in patients with acute and less complicated pathology from the point of view of hepatic or renal functioning. It is usually the youngest patients who undergo this type of simple surgery. The major colorectal surgery profile is an elderly patient, generally diagnosed with intestinal neoplasia. It is therefore logical that creatinine clearance in patients undergoing shorter operations should be greater. This finding has not conditioned the fact that the dV and the Cl, both of metronidazole and gentamicin are significantly modified by the duration of the surgical intervention.

Among the factors involved in post surgical infection in CRS are the concentration in serum of antibiotics at the end of the intervention, the presence of diabetes mellitus, stomas, and the advanced age of the patient.[24] Given that both antibiotics follow a pharmacokinetic-pharmacodynamic dependent concentration, the efficacy of both depends mainly on the maximum concentrations (C_{max}) which, in turn, determine the concentrations at the end of the surgical intervention. The fact that no threshold limit for the CI of metronidazole is known means, in most cases, an estimation of its potential efficacy comparing the magnitude of its concentrations with the MIC. In this work, the facts guarantee the antibiotic cover against the most common anaerobic bacilli. On the one hand, all the concentrations of metronidazole on finishing the intervention were greater than 8 µg/mL and, on the other, estimates that 47 hours is the time necessary for the concentration of metronidazole to fall below 2 µg/mL (standard value as MIC).[16]

In all the patients, the C_{max}^{GEN} was greater than 9 µg/mL, surpassing the target concentration that is currently recommended in treatment protocols and prophylaxis with a single dose of gentamicin.[24-26] Likewise, in all the cases, the C_{max}^{GEN} measured in this study enable us to estimate, taking into account the usual MIC of the majority of sensitive microorganisms, CI higher than 8, with the exception of microorganisms presenting a MIC ≥4 µg/mL, in which case the gentamicin example would be questioned. These values guarantee, indirectly, an appropriate bactericide activity and post antibiotic effect.[22,30]

In conclusion, an heterogeneous sample of subjects undergoing PCRS has been studied, but which is representative of the real situation. In patients, surgical intervention did not significantly modify the pharmacokinetics of metronidazole or gentamicin in comparison with other groups of adult patients.

The prophylactic regime of single doses of 1500 mg of metronidazole plus 240 mg of gentamicin enables concentrations of both antimicrobial agents to be reached which are sufficient in magnitude to guarantee the clinical efficacy in pharmacodynamic and microbiological terms.

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