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Population pharmacokinetic models for cefuroxime and metronidazole used in combination as prophylactic agents in colorectal surgery: Model-based evaluation of standard dosing regimens

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ABSTRACT

The antibiotics used for prophylaxis in colorectal surgery must maintain appropriate plasma concentrations during the entire surgery to avoid surgical site infections caused by aerobes and anaerobes; cefuroxime plus metronidazole is one of the combinations used. The aim of this study was to evaluate the adequacy of cefuroxime plus metronidazole administration as prophylaxis in colorectal surgery. In total, 63 patients electively undergoing rectal or colon surgery were administered 1500 mg of cefuroxime and 1500 mg of metronidazole in 15-min and 1-h infusions, respectively, prior to surgery. Blood samples were withdrawn during and after surgery for determination of plasma concentrations by high-performance liquid chromatography. Population pharmacokinetic models were developed using NONMEM 7.2.0. Pharmacokinetic/pharmacodynamic (PK/PD) simulations were performed to explore the ability of different dosage regimens to achieve the pharmacodynamic targets. Pharmacokinetics for both antibiotics were best described by a two-compartment model. Elimination of cefuroxime was conditioned by creatinine clearance (CL_{Cr}). The half-life of cefuroxime was 1.5 h for patients with normal renal function and 4.9 h in patients with renal impairment. Elimination and distribution of metronidazole were affected by patient body weight (BW). PK/PD analysis revealed that a single-dose protocol of 1500 mg of cefuroxime and metronidazole is adequate in short surgeries ($\leq$2 h). However, for longer surgeries, recommendations are suggested depending on the patient's CL_{Cr} and BW. Additional doses of cefuroxime are needed for patients with moderate renal impairment or those presenting normal renal function. For metronidazole, an additional dose is needed for patients with a BW of 90 kg.

1. Introduction

Following elective colorectal surgery, a high incidence of surgical site infections (SSIs) has been reported during recent years [1]. Incisional SSI complicates 20–30% of elective colorectal surgery cases [2]. Nevertheless, there are few data regarding appropriate management and prevention strategies. Although attitudes vary with regard to the significance or impact of their development, yearly costs associated with SSIs have been estimated to be US$1–1.8 billion in the USA [3].

There is strong evidence that treatment with antibiotics significantly lowers post-operative septic complications. To maximise the benefits of antimicrobial prophylaxis, a safe and inexpensive bactericidal agent with an in vitro spectrum against the most probable intra-operative micro-organisms should be selected. Therapeutic concentrations of the antimicrobial agent should also be maintained both in plasma and tissues throughout the operation and

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until a few hours after the incision is closed [4]. Concurrently, the choice of prophylactic agent must be based on the micro-organisms usually found in the surgical site, the drug's plasma pharmacokinetics and its distribution to tissues. The latest published Cochrane review regarding antimicrobial prophylaxis reports that antibiotics covering aerobic and anaerobic bacteria should be delivered prior to colorectal surgery. However, the best antibiotic choice as well as the timing and route of administration remain undetermined [5].

Although different options have been studied in an attempt to reduce SSIs, the cephalosporin family is considered as the preferred group of drugs [6]. Cefuroxime possesses in vitro activity that justifies its use as a prophylactic agent in colorectal surgery, although combination with metronidazole is necessary to cover anaerobic bacteria. The pharmacokinetics of both antibacterial drugs have been widely investigated [7–12]. However, their use as prophylactic agents has not been evaluated by coupling population pharmacokinetic modelling and Monte Carlo simulation to determine the probability of target attainment (PTA) against bacteria frequently isolated in surgical sites.

The aim of this study was to evaluate the adequacy of cefuroxime and metronidazole as prophylactic agents in colorectal surgery. Population pharmacokinetic models were developed for each antimicrobial agent with the objective of identifying the physiological and pathological factors that change dose–concentration relationships and of quantifying the interindividual variability (IIV). Moreover, the study also estimated whether the used prophylactic protocol was able to maximise the probability of maintaining free drug concentrations above the minimum inhibitory concentrations (MICs) of the micro-organisms involved in SSIs during the entire surgical procedure.

2. Methods

2.1. Study design and settings

A prospective, open-label study was conducted in patients electively undergoing rectal or colon surgery at University Hospital of Alava (Vitoria-Gasteiz, Spain). All study procedures were approved by the Ethics Committee of the hospital and were conducted in accordance with Good Clinical Practice. Written informed consent was required from all patients. Patients aged ≥18 years scheduled to undergo elective colon or rectal surgery were included in the study. Clinical and demographic characteristics of the patients are listed in Table 1. Creatinine clearance (CL_{Cr}) was estimated for each patient using the Cockcroft–Gault equation and with the Modification of Diet in Renal Disease (MDRD) reduced equation [13]. Patients were excluded if they were allergic to β-lactam antibiotics, were diagnosed with a previous systemic infection or were given antibiotic therapy in the last 72 h before the surgery.

Table 1
Summary of patient characteristics.

Characteristic	Mean (S.D.)	Range
Continuous covariates		
Age (years)	69.1 (12.3)	33–91
Weight (kg)	68.6 (10.4)	43–88
Haemoglobin (g/dL)	12.96 (2.23)	7.6–17.4
Leucocytes (cells/mm^3)	6977 (1960)	2700–14300
Serum creatinine (mg/dL)	0.90 (0.30)	0.52–1.85
Glucose (mg/dL)	110.5 (25.8)	55–194
Albumin (g/dL)	4.12 (0.89)	1.5–8
Total proteins (g/dL)	6.73 (0.93)	3.3–8.2
CL_{Cr} (C-G) (mL/min)[a]	76.5 (27.2)	23.5–138.2
CL_{Cr} (MDRD) (mL/min)[b]	86.8 (25.1)	35.1–141.2
Categorical covariates	No. of patients	
Sex	37 M/26 F	–
Perioperative blood transfusion (yes/no)	8/55	–
ASA index (1/2/3/4)[c]	16/27/17/3	–
McCabe index (NF/UF/RF)[d]	50/12/1	–
Diabetes mellitus (yes/no)	14/49	–

S.D., standard deviation; CL_{Cr}, creatinine clearance.
[a] CL_{Cr} estimated by the Cockcroft–Gault formula.
[b] CL_{Cr} estimated with the Modification of Diet in Renal Disease (MDRD) reduced equation.
[c] Health score set by the American Society of Anesthesiologists (ASA): 1, normal healthy patient; 2, patient with mild systemic disease; 3, patient with severe systemic disease; 4, patient with severe systemic disease that is a constant threat to life; 5, moribund patient who is not expected to survive without the operation; and 6, a declared brain-dead patient whose organs are being removed for donor purposes.
[d] McCabe index: NF, non-fatal disease; UF, ultimately fatal disease (in 6 years); and RF, rapidly fatal disease (in 6 months).

2.2. Drug administration, sampling procedure and analytical method

According to the surgical protocol of the hospital, patients received 1500 mg of cefuroxime and 1500 mg of metronidazole administered as an intravenous infusion (ca. 15 min and 1 h duration, respectively) prior to surgery (within 1 h). One pre-dose blood sample (to be used as a blank during drug quantification) and two to four samples were collected from each patient during the next 24 h.

Determination of cefuroxime and metronidazole concentrations in plasma was performed by a validated high-performance liquid chromatography (HPLC) method with a Waters apparatus (Waters Corp., Milford, MA) coupled to a spectrophotometric detector [14,15]. For cefuroxime quantification, following protein precipitation in plasma samples with acetonitrile containing cefoxitin as internal standard, the supernatant was diluted with mobile phase consisting of acetate buffer/acetonitrile (95:5, v/v). Separation was performed on a μBondapak C18 (30 cm × 3.9 mm × 10 μm) with ultraviolet (UV) detection (296 nm). The assay was linear over the concentration range of 0.5–200 μg/mL. The intraday and interday coefficients of variation (CV) ranged from 0.94% to 5.13% and bias ranged from 0.21% to 12.33%.

The method for quantification of metronidazole consisted of protein precipitation with a zinc sulphate solution in methanol and direct injection of the obtained supernatant. Ornidazole was used as an internal standard. Separation was carried out with a Nucleosil® 120 C18 (25 cm × 0.4 mm × 10 μm) with UV detection (312 nm). The mobile phase contained methanol:water (28:72, v:v). The assay was linear over the concentration range of 0.5–100 μg/mL. The intraday and interday CV ranged from 0.03% to 6.22% and bias ranged from 0.56% to 9.45%.

Stock solution stability, long-term storage stability, short-term temperature stability, freeze–thaw stability of the analyte in the matrix from freezer storage conditions to room temperature, and auto-sampler rack stability were confirmed for both analytes.

2.3. Population pharmacokinetic model estimation and pharmacokinetic/pharmacodynamic (PK/PD) analysis

2.3.1. Base population model

Population pharmacokinetic models for cefuroxime and metronidazole were developed separately using NONMEM® 7.2.0 (ICON Development Solutions, Ellicott City, MD) and the first-order conditional estimation (FOCE) method with interaction. Compartmental models were used to fit the disposition of the total drug plasma concentrations. Based on the distribution of the residuals, cefuroxime data were logarithmically transformed. Selection between models was based on: (a) the decrease of the minimum of the objective function value (OFV), which is approximately equal to – two times Log(Likelihood); (b) the precision of the parameter estimation expressed as the relative standard error [RSE (%)] and calculated as the ratio between the standard error and final