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Pharmacodynamic modelling of intravenous antibiotic prophylaxis in elective colorectal surgery

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ABSTRACT

Surgical-site infections are the leading cause of post-operative morbidity and mortality as well as increased costs following colorectal surgery. The purpose of this study was to evaluate different β-lactam antimicrobial dosing regimens currently used for prophylaxis in elective colorectal procedures with the aim of identifying optimal antibiotics and dosing regimens. Serum pharmacokinetic (PK) parameters specific to each drug for use in pharmacodynamic (PD) modelling were obtained from the published literature. Susceptibility data for *Escherichia coli*, *Bacteroides fragilis* and *Staphylococcus aureus* for use in modelling simulations were obtained from the European Committee on Antimicrobial Susceptibility Testing (EUCAST). Monte Carlo simulation was used to evaluate the influence of dose and dosing frequency of tested antibiotics to achieve a prophylaxis target *fT* > MIC (time during which the free drug concentration exceeds the pathogen minimum inhibitory concentration) of 100% for up to 4 h. Ertapenem 1 g, cefuroxime 1.5 g and cefazolin 2 g were the only antibiotic regimens that consistently yielded target *fT* > MIC of 100% for the entire 4-h post-dose interval and against all targeted organisms more than 90% of the time. In contrast, cefoxitin, cefotetan and ampicillin/sulbactam yielded very poor predicted PK/PD performances. In conclusion, this study demonstrates the value of, and need for, applied PD research in the area of surgical prophylaxis. Whether cefoxitin, cefotetan or ampicillin/sulbactam should continue to be advocated as first-line agents for prophylaxis during elective colorectal surgery, particularly at the standard doses currently being used, is debatable.

1. Introduction

Surgical-site infections (SSIs) are the leading cause of post-operative morbidity and mortality following colorectal surgery and add significantly to the cost of care [1]. Prophylactic antibiotics for patients undergoing colorectal surgery are therefore considered imperative [1–6]. Recommendations regarding the use of specific antibiotics for prophylaxis during colorectal procedures have been published since the early 1990s and have frequently been revisited since that time [1–6]. More recently, specific recommendations provided by the national Surgical Infection Prevention (SIP) Project have focused on appropriate timing of administration of prophylactic antibiotics, appropriate drug selection, and discontinuation of prophylactic antibiotics within 24 h after surgery [2,5]. However, the actual recommended drugs and dosing regimens for colorectal prophylaxis have been relatively unchanged over the past 20 years.

Limited published data exist regarding appropriate antimicrobial dosing for prophylaxis. It is generally stated that drugs should be given in adequate doses based on patient weight [2,5]. Furthermore, antibiotic administration should be repeated intra-operatively if the procedure continues beyond one to two pharmacokinetic half-lives after the dose to ensure adequate antibiotic concentrations until surgical closure [2,5]. β-Lactam antibiotics such as cefoxitin and cefotetan, which are among the established gold-standard parenteral antibiotics recommended for colorectal prophylaxis, exhibit time-dependent bactericidal action, with efficacy being maximised when their concentrations continuously exceed a threshold value best approximated by the in vitro minimum inhibitory concentration (MIC) for target pathogens [7]. Thus, the time during which free (unbound) drug concentrations exceed pathogen MICs (*fT* > MIC) is the pharmacokinetic/pharmacodynamic (PK/PD) parameter best correlated with bacterial killing and clinical efficacy of β-lactam antibiotics [7]. Specific values for *fT* > MIC, expressed as a percentage of the dosing interval, that have been correlated with maximal bactericidal activity of β-lactam antibiotics are *T* > MIC of 50–70% for penicillins and cephalosporins and 40–50% for carbapenems [7]. However, because intra-operative contamination may potentially occur at any time during the procedure, the goal of antimicrobial prophylaxis should be to achieve serum and tissue drug concentrations that exceed

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pathogen MICs for the entire duration of the operation and, at most, a few hours beyond closure of the incision [2,5]. The importance of adequate antibiotic concentrations at closure on wound infection following colorectal surgery has been clearly shown [8]. Therefore, for effective prophylaxis with β-lactam antibiotics, an *fT* > MIC of 100% should be targeted over the expected duration of the surgical procedure.

To compound the problem, the antibiotic susceptibilities of clinically isolated anaerobes and enteric Gram-negative aerobes have substantially changed over the past two decades, whilst recommended drug doses have not. For example, *Escherichia coli* generally remains susceptible to many older β-lactams and cephalosporins; however, the MIC at which 90% of tested strains were inhibited (MIC_{90}) of cefoxitin for *E. coli* was reported to be 16 μg/mL (range 2 μg/mL to >32 μg/mL) in 1998 compared with 8 μg/mL (range 2 to 16 μg/mL) in the 1980s [9,10]. Whilst antibiotic susceptibilities have decreased and the concentrations required for activity against common surgical pathogens have approximately doubled, recommended doses of prophylactic agents have remained unchanged. Thus, it is questionable whether appropriate dosing regimens of prophylactic antibiotics are currently being used.

The aim of the present study was to perform PK/PD analyses using Monte Carlo simulation in order to evaluate the influence of dose and dosing frequency of cefoxitin and cefotetan on achievement of a prophylaxis target of *fT* > MIC of 100% for at least 4 h. Furthermore, these drugs were compared with other β-lactam antibiotics that are potentially useful for this indication.

2. Methods

2.1. Antimicrobials

Seven β-lactam antimicrobials were evaluated based on their inclusion in current surgical prophylaxis guidelines, routine or potential use in elective colorectal prophylaxis, and availability of comparative MIC data for use in PD modelling simulations. The following intravenous (i.v.) antibiotics and doses were evaluated: cefoxitin 1 g and 2 g; cefotetan 1 g and 2 g; ceftriaxone 1 g and 2 g; cefazolin 1 g and 2 g; ampicillin/sulbactam (SAM) 1.5 g and 3 g; cefuroxime 1.5 g; and ertapenem 1 g.

2.2. Pharmacokinetic data

Serum PK parameters specific to each drug were obtained from studies of surgical prophylaxis in adult patients (preferably for intra-abdominal procedures) whenever such studies were available, or from PK studies in non-critically ill adult populations or healthy volunteers if data from surgical populations were not available (Table 1) [11–19]. Studies were included if they evaluated clinically relevant dosing regimens and provided appropriate descriptive data (e.g. statistical mean and standard deviation) for pertinent parameters. Characteristics of patients in whom the individual PK studies were conducted are given in Table 1.

2.3. Microbiological data

Escherichia coli and *Bacteroides fragilis* are the chief aerobic and anaerobic bacteria, respectively, found in the lower gastrointestinal tract and are representative of organisms against which prophylactic antibiotics used for colorectal procedures are directed. *Staphylococcus aureus* is also a common cause of SSI and is an important target for prophylactic antibiotics. Since *E. coli*, *B. fragilis* and *S. aureus* are most representative of potential pathogens of interest in this setting, these organisms were thus targeted for PK/PD modelling in this analysis. Susceptibility data for wild-type organisms of these species were obtained from the European Committee on Antimicrobial Susceptibility Testing (EUCAST) website (http://www.eucast.org/organization).

The EUCAST database was chosen for this analysis because it provided the most current and comprehensive collection of MIC data for the specific antibiotics and organisms evaluated in this study. Both meticillin-susceptible *S. aureus* (MSSA) and meticillin-resistant *S. aureus* (MRSA) are included in the EUCAST database; however, for the purposes of this study, Monte Carlo simulations were performed using susceptibility data only for MSSA. The purpose of this study was not to determine whether the antibiotics evaluated in this study are still appropriate for routine prophylaxis in institutions with high rates of MRSA or in patients at high risk for MRSA infection. Since none of the agents evaluated in this study are active against MRSA, and since the purpose of the study was to evaluate PK/PD performance against organisms that are otherwise considered to be susceptible to these drugs, only MSSA was included in the analysis.

The EUCAST database does not report cefotetan susceptibilities, and recent cefotetan data could not be located from published or Internet-based sources. *Escherichia coli* susceptibility data for cefotetan were thus obtained from the clinical microbiology laboratory at the authors' institution and were based on a limited number of tested isolates ($n = 370$). *Staphylococcus aureus* susceptibility data were not available for cefotetan or SAM and these analyses were not conducted. For *B. fragilis*, MIC data for SAM were also not available and data for ceftriaxone, cefuroxime and cefazolin were not collected because these drugs have little useful activity against abdominal anaerobes and would typically be administered in combination with a more active anti-anaerobic agent (e.g. metronidazole) for colorectal prophylaxis.

Susceptibility breakpoints used in this study are those currently recommended by the Clinical and Laboratory Standards Institute (CLSI) in the USA [20].

2.4. Monte Carlo simulation

A 5000-patient Monte Carlo simulation (Oracle Crystal Ball, Fusion Edition Release 11; Oracle Corp., Redwood Shores, CA) was conducted for each antibiotic regimen, and the overall probability of achieving the PD target, referred to as the probability of target attainment (PTA), was calculated over a range of doubling MICs between 0.004 mg/L and 256 mg/L. The methods used to determine PD exposures have been well described elsewhere [21]. Briefly, descriptive statistics (mean, standard deviations, range of minimum and maximum values) of the steady-state volume of distribution, total body clearance, terminal half-life and unbound protein fraction were used as input variables in a simple one-compartment PK model for determination of *fT* > MIC. A one-compartment model was used for all analyses because population-based PK studies, or other sources of PK data needed for two-compartment analyses, are currently unavailable for most of the drugs evaluated in this study. Antibiotic doses were assumed to have been administered over 15 min, with the end of the infusion occurring just prior to incision. PK parameters, including percent protein binding, were assumed to occur in a normally distributed fashion. Previous guidelines for surgical prophylaxis state that antibiotics with short PK half-lives (e.g. cefoxitin) should be re-dosed every 3 h during longer procedures [3], whilst an advisory statement from the SIP Project further stated that antimicrobials should be re-administered at intervals of 1–2 times the half-life of the drug [2]. Recommended re-dosing intervals for cefoxitin, cefotetan, cefazolin and cefuroxime are therefore 2–3 h, 3–6 h, 2–5 h and 3–4 h, respectively [2]. Since the goal of perioperative antimicrobial prophylaxis is to achieve free (unbound) serum and tissue drug levels that exceed the MICs for likely pathogens across