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PHARMACOLOGY

Oral Tobramycin Prophylaxis Prior to Colorectal Surgery Is Not Associated with Systemic Uptake

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ABSTRACT Preoperative oral prophylaxis with nonabsorbable antibiotics has been reported to reduce the risk of surgical site infections after colorectal surgery. This prospective study was conducted to evaluate the risk of toxic side effects by measuring postoperative serum tobramycin levels in patients who received a 3-day prophylaxis with tobramycin and colistin prior to colorectal surgery. In all patients, serum tobramycin concentrations were below the detection limit (0.3 mg/liter), implying a low risk of toxicity.

KEYWORDS antibiotic prophylaxis, surgery, tobramycin

Surgical site infections (SSIs) are common complications after colorectal surgery, affecting approximately 15% of all patients (1). SSIs are associated with substantial morbidity and often require extensive therapeutic interventions. To reduce the risk of SSIs, international infection control guidelines recommend administration of a perioperative systemic antibiotic prophylaxis (2, 3). Preoperative oral antibiotic prophylaxis (OAP) with nonabsorbable antibiotics can be administered additionally to further reduce infection rates (4–6). The nonabsorbable nature of the antibiotics suggests absence of enteral absorption after oral administration. Therefore, the risk of toxic systemic side effects following OAP is presumed to be low. Findings of previous studies in critically ill patients questioned the low risk of systemic side effects. Although it was believed that nonabsorbable antibiotics remain restricted to the gastrointestinal tract, increased serum concentrations of these antibiotics were found after oral administration. Antibiotic leakage from the gut (7, 8) and acute renal insufficiency (9) were proposed as conditions that could lead to increased serum concentrations. It is unknown whether increased serum concentrations of nonabsorbable antibiotics are also present during treatment with OAP prior to colorectal surgery. It can be hypothesized that underlying colorectal diseases or iatrogenic manipulation during surgery facilitate antibiotic leakage from the gut to the systemic circulation. Also, postoperative renal insufficiency might lead to increased serum levels of antibiotics. Therefore, the aim of this study was to investigate whether 1-day postoperative tobramycin concentrations reach clinically relevant trough levels in patients who receive 3-day OAP prior to colorectal surgery.

We conducted a prospective exploratory study from October 2016 through January 2017. The study was performed in a Dutch hospital where preoperative OAP is a standard of care prior to elective colorectal surgery. OAP is a solution containing tobramycin (16 mg/ml) and colistin (20 mg/ml) that is administered orally in doses of

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TABLE 1 Patient preoperative and surgical characteristics[a]

Variable[b]	*n* (%) or median (IQR)
Preoperative characteristics	
Male	33 (51.6)
Age (yrs)	67.0 (58.3–75.0)
BMI (kg/m^2)	24.9 (22.3–27.5)
ASA classification, ≥3	21 (32.8)
History of chronic renal insufficiency	7 (10.9)
Chronic renal replacement therapy	0 (0.0)
Glomerular filtration rate of <90 ml/min 1 day after surgery	35 (54.7)
Serum creatinine 1 day after surgery (μmol/liter)	71.5 (64–96.8)
Antibiotic use	
Systemic use of tobramycin prior to or during surgery	0 (0.0)
Adequate perioperative intravenous prophylaxis[c]	61 (95.3)
Additional preoperative enema with OAP	21 (32.8)
Surgery characteristics	
Indication for surgery	
Colorectal malignancy	49 (76.6)
Inflammatory bowel disease	5 (7.8)
Benign polyps	3 (4.7)
Other	7 (10.9)
Type of procedure	
Colon resection	33 (51.6)
Rectum or sigmoid resection	24 (37.5)
Creation or removal of stoma	7 (10.9)
Surgical technique	
Open procedure	14 (21.9)
Laparoscopic procedure	27 (42.1)
Robot-assisted laparoscopic procedure	23 (35.9)
Blood loss during procedure (ml)	50.0 (0.0–137.5)

[a]Total number of subjects is 64.
[b]ASA, American Society of Anesthesiologists; BMI, body mass index; IQR, interquartile range; OAP, oral antibiotic prophylaxis.
[c]Adequate perioperative intravenous prophylaxis entails the choice of appropriate antimicrobial agents, as well as the appropriate timing of the prophylaxis according to the Dutch infection control guideline (3).

5 ml. Patients are instructed to take the OAP 4 times daily during the 3 days prior to surgery. Patients who undergo a rectal resection receive 1 additional enema with the antibiotic solution when it is possible to admit the patient 1 day before surgery. Perioperative intravenous antibiotic prophylaxis is routinely administered according to the national infection control guideline for colorectal surgery (3). Mechanical bowel preparation was not administered, as it is not part of routine clinical care in this hospital. All consecutive patients who underwent elective colorectal surgery during the study period and who received OAP were included. Serum tobramycin was measured in blood samples that were routinely drawn on the day after surgery. Quantification of tobramycin was performed with a homogeneous enzyme immunoassay (Roche, Almere, The Netherlands) (10). The lower limit of detection was 0.3 mg/liter. Serum tobramycin levels of 1 mg/liter or higher were considered clinically relevant. The Medical Ethics Committee of the UMC Utrecht (Utrecht, The Netherlands) reviewed the study (METC number 16/490) and judged the study to be beyond the scope of the Medical Research Involving Human Subjects Act (WMO). A waiver of informed consent was granted.

In total, 64 patients were included in the study. Baseline patient characteristics are shown in Table 1. The median age was 67 years. Half of the patients had a normal renal function 1 day after surgery and the majority had no history of renal insufficiency. An additional enema with the antibiotic prophylaxis was administered to 32.8% of the patients. None of the patients received systemic tobramycin prior to or during surgery. Postoperative serum tobramycin levels were below 0.3 mg/liter for all patients.

In this study, the administration of OAP prior to colorectal surgery was not associated with increased serum tobramycin concentrations. These findings are in contrast to previous studies that investigated tobramycin absorption during selective decontam-

ination of the digestive tract (SDD). Comparably to OAP, SDD is applied orally for several days. Besides tobramycin and colistin, an antifungal agent is a common component of SDD. Serum analysis demonstrated leakage of tobramycin from the gut to the serum in the majority of intensive care unit (ICU) patients treated with SDD. Leakage resulted in concentrations that were clinically relevant and in potentially toxic trough levels (>1.0 mg/liter) in a few cases (7). Tobramycin-related toxic side effects, however, were not reported. A disrupted gut barrier, which is a potential consequence of critical illness, and acute renal failure were identified as risk factors for increased systemic tobramycin levels (9, 11). The absence of detectable serum tobramycin levels in our less severely ill patient population indicates that a 3-day course of preoperative OAP is not associated with clinically relevant enteral absorption of tobramycin in patients undergoing colorectal surgery, even when patients have impaired renal function. Although we were unable to perform subgroup analyses because of a limited sample size, our findings did not provide evidence for an altered risk of tobramycin leakage due to underlying colorectal disease. Serum levels of colistin, the other component of OAP, were not measured in this study. As tobramycin has a higher potential to cross the gut barrier because of its lower molecular mass (1,425 Da) compared to colistin (1,748 Da), tobramycin levels are considered to be a more sensitive indicator for antibiotic leakage than colistin (12). Besides pharmacological side effects, the risk of antimicrobial resistance needs to be considered as a possible complication of prophylactic antibiotics. Previous studies on ICU patients did not report a significant increase in antimicrobial resistance during SDD administration (13–15). Because of the short treatment duration, we hypothesize that the risk of development of antibiotic resistance is negligible after OAP use as well. However, further investigation is required to monitor this.

To the best of our knowledge, this is the first study to investigate postoperative serum tobramycin concentrations in patients who receive OAP prior to colorectal surgery. Based on our findings, we consider OAP not to be associated with an increased risk of toxic side effects. Because of the short treatment duration, we expect that the risk of other complications is low as well. We therefore consider OAP to be a safe infection prevention strategy for patients undergoing elective colorectal surgery.

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