Impact of mucositis on oral bioavailability and systemic exposure of ciprofloxacin Gram-negative infection prophylaxis in patients with haematological malignancies

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Background: Patients with haematological malignancies frequently endure neutropenia and gastrointestinal (GI)-mucositis after high-dose chemotherapy. In these patients, ciprofloxacin is used for Gram-negative infection prophylaxis.

Objectives: We investigate ciprofloxacin pharmacokinetics after oral administration in patients with haematological malignancies and explore the impact of GI-mucositis on oral bioavailability and clearance in order to assure adequate systemic exposure.

Methods: Adult haematological patients from two Dutch University Medical Centres received 500 mg twice daily oral ciprofloxacin for Gram-negative prophylaxis. The ciprofloxacin plasma concentrations were collected at various timepoints after oral ciprofloxacin administration and at various days after completion of chemotherapy. Data obtained after oral and intravenous ciprofloxacin administration in 28 healthy volunteers without mucositis served as a control group (391 samples). For haematological patients the degree of GI-mucositis was assessed using the Daily Gut Score (DGS), plasma citrulline and albumin. Data were analysed by non-linear mixed-effects modelling.

Results: In total, 250 blood samples were collected in 47 patients with a wide variety of haematological malignancies between 0–30 days after start of chemotherapy. Mucositis was generally mild [DGS median (IQR) 1 (1–1) and citrulline 16 μmol/L (12–23)]. The time to $C_{\text{max}}$ was slower in haematological patients compared with healthy volunteers although no association with the degree of mucositis (defined as DGS or citrulline) could be identified. Ciprofloxacin bioavailability and clearance were 60% and 33.2 L/h, respectively.

Conclusions: This study supports oral dosing of ciprofloxacin as Gram-negative infection prophylaxis in haematological patients with mild-to-moderate mucositis capable of oral intake.
Introduction
Fluoroquinolone prophylaxis reduces the relative risk of infection-related mortality in neutropenic patients with haematological malignancies by 68% while adverse effects and development of resistance are not significantly increased.\textsuperscript{1-4} Of the fluoroquinolones, ciprofloxacin is the most frequently prescribed. It is typically administered orally in dosages of 500 mg twice daily and is rapidly and well absorbed from the gastrointestinal (GI) tract in healthy volunteers with a bioavailability of approximately 60–80%. Ciprofloxacin is subject to glomerular filtration, tubular secretion, trans-epithelial intestinal secretion and hepatic metabolism.\textsuperscript{5}

Patients with haematological malignancies treated with high-dose chemotherapy often encounter mucosal disruption of the GI tract (GI-mucositis).\textsuperscript{6,7} Mucositis affects oral absorption unpredictably in patients with haematological malignancies; for example, posaconazole bioavailability is reduced while isavuconazole bioavailability remains unaltered.\textsuperscript{8,9} The gold standard method to diagnose mucositis is a biopsy from the small intestine. As this procedure is invasive and therefore not clinically feasible, clinical scores and biomarkers are used to assess severity of mucositis.\textsuperscript{10-13} Several mucositis scores are available, although there are differences regarding the focus on oral- versus GI-mucositis. The Daily Gut Score (DGS) quantifies GI-mucositis by scoring the frequency, consistency and incontinence of faeces, nausea, vomiting, abdominal complaints and the ability for oral intake.\textsuperscript{12} Nevertheless, the clinical assessment scale is subjective, based on symptoms that may not be specific for mucositis and could be influenced by analgesic agents.\textsuperscript{14}

Both citrulline and albumin plasma concentrations are also used as biomarkers for mucositis, with citrulline being the most potent.\textsuperscript{15} Citrulline is a non-protein amino acid almost exclusively produced by enterocytes of the small intestine. As mucositis develops, mucosal barrier integrity deteriorates which is associated with a reduced citrulline plasma concentration. Consequently, citrulline serves as a biomarker for GI-mucositis. Plasma citrulline <10 μmol/L is associated with severe mucositis, 10–30 μmol/L is associated with mild mucositis, while >30 μmol/L is considered normal.\textsuperscript{13,15,16} Citrulline plasma concentration starts declining shortly after initiation of chemotherapy. The lowest values are observed 7–10 days after start of high-dose chemotherapy, after which citrulline levels rise to normal values around 21 days after high-dose chemotherapy.\textsuperscript{13}

Besides mucositis, concomitant medication can also influence ciprofloxacin oral absorption. Prokinetic agents such as metoclopramide or clarithromycin increase gastric motility and augment oesophageal peristalsis, which can accelerate oral absorption.\textsuperscript{17} Proton-pump inhibitors and antacids can delay gastric emptying by increasing gastric pH, while opioids may delay oral absorption as a result of reduced intestinal motility.\textsuperscript{17} Bioavailability may be reduced by co-ingestion with Al\textsuperscript{3+}, Ca\textsuperscript{2+}, Fe\textsuperscript{2+} or Mg\textsuperscript{2+} ions.\textsuperscript{5}

Ciprofloxacin pharmacokinetics in patients with chemotherapy for haematological malignancies showed conflicting results in three case-series (≤58 participants per series) as exposure was found to be unaltered or decreased.\textsuperscript{18-20} Two studies did not report severity of mucositis at all, while one study only used clinical markers to describe severity of oral mucositis. Consequently, a knowledge gap remains regarding the influence of GI-mucositis on oral absorption and clearance of ciprofloxacin, risking underexposure and possibly higher infection-related mortality.

In a cohort of neutropenic patients treated for a wide variety of haematological malignancies leading to a high risk of mucositis, we investigated ciprofloxacin pharmacokinetics and evaluated whether mucositis influences oral bioavailability and clearance, in comparison with healthy volunteers.

Patients and methods
Data
Data from three cohorts consisting of only haematological patients were collected in two Dutch academic hospitals. Cohort 1 was a prospective observational cohort at the Amsterdam UMC, location Academic Medical Centre (Amsterdam UMC, location AMC). Patients were recruited between March 2019 and December 2020, n = 41 (NTR7520). Cohort 2 consisted of participants in a dense sampling study of micafungin pharmacokinetics (NCT02172768) who simultaneously received ciprofloxacin prophylaxis.\textsuperscript{21} Cohort 3 consisted of participants in a dense sampling study of posaconazole pharmacokinetics (NCT02805946) who received ciprofloxacin prophylaxis.\textsuperscript{8} Patients with concomitant use of ciprofloxacin on pharmacokinetic (PK)-sampling days of micafungin or posaconazole (n = 2 and 4 patients, respectively) were selected. Finally, to compare the impact of mucositis caused by high-dose chemotherapy on oral absorption, these data were compared with data from a previously performed dense-sampling pharmacokinetic study (n = 28 with 391 samples) after oral and intravenous ciprofloxacin administration in healthy volunteers and obese patients (NTR6058).\textsuperscript{22}

Haematological patients receiving reduced-intensity conditioning regimens for allogeneic HSCT, first remission-induction chemotherapy for AML/myelodysplastic syndrome or CAR-T cell infusion for lymphoma and who received orally administered ciprofloxacin tablets (500 mg twice daily) for gram-negative prophylaxis were eligible for inclusion if they were legally competent and at least 18 years of age. Exclusion criteria were admission to the ICU, receiving renal replacement therapy or patients unable to take oral medication due to progression or worsening of mucositis and patients with a previous ciprofloxacin treatment course for whom discontinuation lasted less than 48 h.

In Cohort 1, two samples were collected around 1–2 h after oral administration, one prior to administration and one random sample, all within 72 h around 7 days after initiation of chemotherapy. Additionally, leftover material from routine sampling at >7 days after initiation of chemotherapy was collected. Blood samples were centrifuged immediately and plasma was stored at −80°C at the clinical laboratory of the pharmacy department of the Amsterdam UMC, location AMC. In Cohorts 2 and 3 one trough concentration was collected daily with additional dense sampling (t = 0, 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 18, 24 h) on two PK-days between day 1 and 15 after initiation of chemotherapy. Details of the sampling scheme and the schedule of the PK-days in relation to the start of chemotherapy are presented in Tables S1 and S2 (available as Supplementary data at JAC Online). Samples from Cohorts 2 and 3 were stored at −80°C at the clinical laboratory of the department of pharmacy at the Radboud university medical center, Nijmegen, until analysis.

Data on patient characteristics (sex, age, weight, height, BMI, diagnosis, current and previous treatment details, comorbidity), ciprofloxacin treatment (dose, date and time of administration), factors leading to reduced ciprofloxacin exposure (vomiting within 2 h after administration), interacting co-medication (ranitidine, Al\textsuperscript{3+}, Ca\textsuperscript{2+}, Fe\textsuperscript{2+} or Mg\textsuperscript{2+} containing drugs administered within 4 h before or 2 h after ciprofloxacin) and co-medication influencing the oral absorption process (prokinetic agents, proton pump inhibitors, opioids; serum creatinine, mucositis biomarkers (albumin, citrulline) and DGS) were recorded over time. To
estimate glomerular filtration rate (eGFR), both indexed and de-indexed Chronic Kidney Disease Epidemiology collaboration (CKD-EPI) and Modification of Diet in Renal Diseases (MDRD) were calculated.\textsuperscript{23,24} De-indexing was done by multiplying the respective eGFR by 1.73/body surface area (BSA) (BSA was calculated using the du Bois-du Bois formula).\textsuperscript{25}

A single citrulline plasma sample was drawn in Cohort 1, simultaneously with obtaining samples collected around 1–2 h after oral administration. In Cohort 3, citrulline plasma samples were collected daily. All citrulline samples were stored on ice and centrifuged within 2 h. Plasma was stored at –80°C until analysis. Plasma citrulline was not determined in Cohort 2 and the control group.

DGS was retrospectively scored based on data available in the electronic patient registry on every day of PK-sampling. For all six components of the DGS, patients could score 0–3 points, with 0 indicating no complaints and 3 indicating severe complaints with that component. GI mucositis was scored as mild (1–6 points), moderate (7–12 points) or severe (>12 points).\textsuperscript{12}

\textbf{Ethics}

The research protocol for Cohort 1 was approved by the certified Medical Ethics Committee of the Amsterdam UMC, location AMC (NL67783.018.18). All participants provided written informed consent. Participants in Cohorts 2, 3 and the control group provided written informed consent before inclusion in the respective studies (clinicaltrial.gov identifiers for Cohorts 2 and 3: NCT02172768, NCT02805946. Dutch trial registry number for the control group: NTR6058). The institutional review board permitted additional analysis on the previously collected samples from Cohorts 2 and 3 and waived informed consent. Additional clinical parameters were collected from the electronic patient registry if patients gave consent for inclusion in the Radboudumc Biobank Hematology.

The study was conducted in accordance with the Good Clinical Practice guidelines and the provisions of the Declaration of Helsinki.\textsuperscript{26,27}

\textbf{Laboratory analysis}

Total ciprofloxacin plasma concentrations were analysed using a validated LC-MS/MS assay at the Amsterdam UMC. The validated range of the analysis is 0.020–5.0 mg/L.\textsuperscript{28} Citrulline samples were analysed using a validated UPLC MS/MS assay at the Clinical Chemistry laboratory of Canisius Wilhelmina Hospital, Nijmegen.\textsuperscript{29}

\textbf{Population PK analysis}

Concentration–time data from haematological patients and healthy volunteers were analysed simultaneously by non-linear mixed-effects modelling using FOCE with interaction and the ADVAN6 subroutine (NONMEM; v7.4.0 with PsN; v4.7.1 and Pirana v2.9.7).\textsuperscript{30,31} Bioavailability (F) and clearance (CL) are the pharmacokinetic parameters of primary interest as these drive systemic exposure (measured as AUC) after oral administration. Systemic exposure can be calculated as follows.

\[ \text{AUC} = \frac{\text{F} \times \text{Dose}}{\text{CL}} \] (1)

A previously developed PK-model for ciprofloxacin in healthy volunteers and obese patients with a two-compartment structure and transit compartments for oral absorption was used as a starting point.\textsuperscript{22} For the group of haematological patients (Cohorts 1–3), all PK-parameters were estimated relative to the control group using Equation 2 with a correction factor significantly different from 1.0 indicating a difference in typical value between haematological patients and the control group for the respective parameter.

\[ \theta_{\text{haematological patient}} = \theta_{\text{healthy volunteer}} \times \theta_{\text{correction factor}} \] (2)

The influence of covariates (age, sex, weight, BMI, CKD-EPI, MDRD, citrulline, albumin, DGS, days after chemotherapy) was tested for associations with model parameters. If multiple observations were available for one individual (creatinine, citrulline, albumin, DGS and days after chemotherapy) covariates were assessed as a time varying covariate with backward interpolation.

Continuous covariates were implemented in the model using exponential or linear relationships using Equation (3) and (4), respectively. $P_i$ and $P_p$ represent individual and population parameter estimates, $X$ represents the exponent for a power function and $Z$ represents the slope for the linear covariate relationship. For dichotomous covariates different parameters were estimated for the respective subgroup.

\[ P_i = P_p \times \left( \frac{\text{COV}_i}{\text{COV}_{\text{standard}}} \right)^X \] (3)

\[ P_i = P_p \times \left( 1 + Z \times (\text{COV}_i - \text{COV}_{\text{standard}}) \right) \] (4)

In the model building process, a change in objective function value (OFV), goodness-of-fit (GOF), conditional weighted residual plots, reduction in interindividual variability and individual fit plots were used to compare models. A P value of $<$0.05, representing a decrease of 3.84 in OFV with one degree of freedom was considered statistically significant for structural parameters. In the covariate analysis, a P value of $<$0.05 (OFV decrease $>$3.84) was considered statistically significant in the forward inclusion step while P $<$0.001 (OFV increase $>$10.8) was considered statistically significant in the backward elimination. Internal model evaluation and validation was done using GOF-plots, CWRES-plots split for cohort- and time-dependent covariates, visual predictive check (VPC) and sampling importance resampling (SIR).

Continuous data are presented as mean ± SD and analysed by t-test when normally distributed or as median ± IQR and analysed by Mann-Whitney U-test when not normally distributed.

After development and internal validation of the pharmacokinetic model, simulations were performed with 2500 virtual individuals per cohort with interindividual variability. The ciprofloxacin exposure, measured as AUC in haematological patients was compared with healthy volunteers after the standard-of-care dosing regimen of twice daily oral administration of 500 mg.

\textbf{Results}

\textbf{Subject characteristics}

Data from 47 patients (19 men and 28 women) with a wide variety of haematological malignancies were included, from whom 250 ciprofloxacin plasma samples were available. The oral absorption phase was captured in detail with 82 plasma samples (33%) collected in the first 2 h after oral administration. Data from 28 healthy volunteers (14 men and 14 women) were included. Eight patients received semi-simultaneous oral and intravenous administration and 20 individuals received either oral or intravenous administration. In total 391 samples were collected in the control group, 178 after intravenous administration and 213 after oral administration. A detailed description of PK-data is provided in Table S2.

The majority of patients showed biochemically mild mucositis with the lowest observed citrulline (nadir) between 10–30 μmol/L.
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**Table 1.** Population characteristics

| Characteristic                          | Haematological patients (n=47) | Control group (n=28) |
|----------------------------------------|-------------------------------|---------------------|
| Age (years)                            | 53 (47–64)                    | 40 (27–52)          |
| Sex, male, n (%)                       | 19 (40)                       | 14 (50)             |
| Weight (kg)                            | 78 (69–90)                    | 123 (84–149)        |
| Citrulline nadir (μmol/L)              | 16 (12–23)                    | ND                  |
| Citrulline nadir ≤10 μmol/L (n)        | 9                             | ND                  |
| Citrulline nadir 10–30 μmol/L (n)      | 32                            | ND                  |
| Citrulline nadir ≥30 μmol/L (n)        | 4                             | ND                  |
| Albumin nadir (g/L)                    | 42 (26–50)                    | ND                  |
| Daily Gut Score                        | 1 (1–1)                       | ND                  |
| Diagnosis                              |                               | NA                  |
| Acute leukaemia                        | 17                            |                     |
| Lymphoma                               | 13                            |                     |
| Multiple myeloma                       | 9                             |                     |
| Chronic leukaemia                      | 3                             |                     |
| Other                                  | 5                             |                     |
| Treatment (n)                          | NA                            |                     |
| Remission-induction                    | 19                            |                     |
| Autologous SCT                         | 16                            |                     |
| Allogeneic HSCT                        | 10                            |                     |
| Other                                  | 2                             |                     |
| Relevant co-medication                 |                               |                     |
| Reduced bioavailability                |                               |                     |
| Magnesium hydroxide                    | 1                             | 0                   |
| Delayed absorption                     |                               |                     |
| Proton pump inhibitor                  | 24                            | 0                   |
| Esomeprazole                           | 19                            |                     |
| Pantoprazole                            | 3                             |                     |
| Omeprazole                             | 2                             |                     |
| Opioid                                 | 7                             | 0                   |
| Oxycodone                              | 5                             |                     |
| Morphine                               | 1                             |                     |
| Fentanyl                               | 1                             |                     |
| Tramadol                                | 1                             |                     |
| Accelerated absorption                 |                               |                     |
| Metoclopramide                         | 13                            | 0                   |
| Metoprolol                             | 1                             | 0                   |
| Clarithromycin                         | 1                             |                     |
| Serum creatinine (μmol/L)              | 74 (62–89)                    | 72 (64–80)          |
| CKD-EPI (mL/min/1.73 m²)               | 97 (80–112)                   | 134 (118–149)       |
| CKD-EPI<sub>de-indexed</sub> (mL/min)  | 84 (68–105)                   | 102 (95–109)        |
| MDRD (mL/min/1.73 m²)                  | 96 (78–121)                   | 126 (110–154)       |
| MDRD<sub>de-indexed</sub> (mL/min)     | 82 (66–115)                   | 98 (90–108)         |

Data are presented as median (IQR) unless stated otherwise. For citrulline and albumin the lowest observed value is reported if multiple observations were available per patient. For serum creatinine and corresponding estimators of GFR the observation at baseline is reported. Daily Gut Score (DGS) 1 represents mild mucositis (1-6 points on the DGS) and 2 represents moderate mucositis (7-12 points on the DGS). HSCT, haematopoietic stem cell transplant, NA, not applicable; nadir, lowest observed value for an individual; ND: not determined; SCT, stem cell transplant.

(a)Citrulline plasma concentration was determined in 45 haematological patients.

(b)De-indexed by multiplying CKD-EPI or MDRD by BSA/1.73.

(n=32, 68%) and a DGS indicating clinically mild mucositis (n=46, 98%). Clinically moderate mucositis (by DGS) was observed in one patient (2%) while biochemically severe mucositis (citrulline nadir ≤10 μmol/L) was observed in nine patients (19%). Of these nine patients, the DGS indicated clinically mild mucositis in eight patients and moderate mucositis in one patient. Samples were collected a median (IQR) of 6 (3–11) days after start of high-dose chemotherapy. In patients with multiple
Table 2. Pharmacokinetic parameter estimates for the final model

| Fixed effects                  | Estimate (%RSE) | SIR 95% CI |
|--------------------------------|-----------------|------------|
| CL (L/h)                       | 33.2 (6.9)      | 29.9–37.0  |
| Vc (L)                         | 69.0 (19.1)     | 50.7–92.8  |
| Vp (L)                         | 140 (10.6)      | 120–160    |
| Q (L/h)                        | 71.4 (13.4)     | 57.3–83.5  |
| F                              | 0.603 (8.5)     | 0.535–0.669|
| Ka (h⁻¹)                       | 1.35 (14.5)     | 1.08–1.70  |
| MTT Control group (h)          | 0.317 (13.1)    | 0.230–0.369|
| Relative MTT                   | 2.07 (14.8)     | 1.41–2.50  |
| Haematological patients⁴       |                 |            |
| NN (n)                         | 10.9 (40.2)     | 6.51–15.8  |
| Interindividual variability (%)³ |               |            |
| CL⁵                            | 28.1 (12.8)     | 20.7–34.3  |
| Vc                             | 86.7 (23.7)     | 55.9–134   |
| MTT⁶                           | 82.6 (13.2)     | 74.7–117   |
| Residual error (%)³            |                 |            |
| σ²group                         | 21.4 (5.9)      | 19.4–23.1  |

CL, clearance from the central compartment; F, bioavailability; Ka, absorption rate constant; MTT, mean transit time; NN, number of transit compartments; Q, intercompartmental clearance; RSE, relative standard error; SIR, sampling importance resampling based on 5000 samples and 1000 resamples; Vc, volume of distribution of the central compartment; Vp, volume of distribution of the peripheral compartment.

⁴Absolute MTT for haematological patients is 0.656 h (according to Eq. 1: 0.317 h²2.07 = 0.656 h).
³Calculated by \(\sqrt{\sigma^2 - 1}\).
⁵η-Shrinkage: CL 5%, Vc 26%, MTT 26%.
⁶C-Shrinkage: CL 5%, Vc 26%, MTT 26%.

Influence of mucositis on ciprofloxacin oral absorption

citrulline observations, a declining plasma citrulline was observed until 10 days after start of conditioning. Concomitant medication that could influence the oral absorption process was used by 29 haematological patients (62%) at the time of PK-sampling. Drugs delaying oral absorption were used by 26 patients (89%) while drugs accelerating oral absorption were used by 14 patients (48%). Details of patient characteristics including the use of concomitant medication potentially influencing oral absorption of ciprofloxacin are presented in Table 1.

Pharmacokinetic analysis

The concentration–time profiles were best described by a two-compartment model with first order elimination and a transit compartment model for oral absorption with a correction factor of 2.07 (95% CI 1.4–2.5) on mean transit time for haematological patients, interindividual variability on clearance, volume of distribution and mean transit time and a proportional error model (for model structure, see Figure S1). Bioavailability and clearance were 60% and 33.2 L/h, respectively and were not significantly different between haematological patients and the control group. The degree of mucositis measured by DGS, citrulline and albumin plasma concentration as well as days after chemotherapy were investigated as potential drivers of the observed difference in the mean transit time between both groups, but evaluation of these parameters did not provide a better prediction of the observed data. GOF-plots show the model adequately describes the observed data and conditional weighted residual plots indicate no model mis-specification as residuals were randomly spread against time after start of ciprofloxacin, predicted plasma concentration, plasma albumin, plasma citrulline and days after chemotherapy (Figure S2). The use of concomitant medication in the haematological patients showed no significant association with altered ciprofloxacin pharmacokinetics in haematological patients. Also, the predictive performance of citrulline plasma concentration as a biomarker for impaired oral absorption was not significantly different for patients receiving stem cell transplant compared with patients receiving other therapy (Figure S3). Clearance, bioavailability and volume of distribution were unaffected by mucositis. Total body weight and renal function also did not provide a statistically significant improvement of the fit when tested as covariates on these parameters. Internal model validity was confirmed using VPC stratified for haematological group and control group (Figure S4). Model parameters and their uncertainty based on SIR are shown in Table 2, the mean percentage error was −5.4%.

Model-based dose evaluations

Using the final and internally validated model, exposure that can be expected upon the standard-of-care dosing regimen of twice daily oral ciprofloxacin administration of 500 mg was evaluated. The median (IQR) time to ciprofloxacin \(C_{\text{max}}\) was 1.5 (1.2–2.1) h for haematological patients and 1.2 (1.0–1.5) h for the control group as shown in Figure 1. In the first week of treatment, median (IQR) cumulative \(\text{AUC}_{\text{day } 1-7}\) was 124 (105–149) mg·h/L for haematological patients and 123 (103–146) mg·h/L for healthy volunteers. In the second week of treatment, median (IQR) cumulative \(\text{AUC}_{\text{day } 8-14}\) was 127 (107–154) mg·h/L for haematological patients and 126 (105–151) mg·h/L for healthy volunteers, as shown in Figure 2.

Discussion

Ciprofloxacin pharmacokinetics in patients with haematological malignancies and mild mucositis capable of oral intake and healthy volunteers is comparable. Oral absorption remains adequate during the whole chemotherapy treatment course, even in the second week after high-dose chemotherapy when mucositis is most severe. However, oral absorption was slower in haematological patients. Therefore, haematological patients with mild-to-moderate mucositis capable of oral intake can receive orally administered ciprofloxacin as Gram-negative infection prophylaxis.

We included 47 patients with a wide variety of haematological malignancies and a broad range in severity of underlying disease at different timepoints in their treatment course. The majority of participants capable of oral ciprofloxacin intake had clinically mild mucositis based on the DGS and as a result, few data on oral absorption and clearance of ciprofloxacin could be collected in patients with clinically moderate mucositis and no data were collected in patients with clinically severe mucositis. Patients unable to take oral medication due to progression or worsening of mucositis or developing fever were switched to intravenous
therapy by their treating physician. There are no strict criteria for when to switch from oral to intravenous therapy. However, our results indicate that the clinical decision of the treating physician to switch patients from oral to intravenous therapy was at least not too late, as no underexposure was observed. The majority of haematological patients used concomitant medication that could accelerate or delay the oral absorption process. Although the use of concomitant medication delaying oral absorption may have contributed to the observed increased time to \( C_{\text{max}} \) in haematological patients compared with healthy volunteers, the use of delaying concomitant medication was not a statistically significant covariate. Most importantly, only one patient used concomitant medication that could decrease bioavailability. Therefore, it is unlikely that the absence of a correlation of mucositis with ciprofloxacin exposure is attributable to the use of concomitant medication.

In our study the degree of mucositis was assessed using the most adequate and feasible clinical scores and biomarkers. Haematological patients suffered from mild mucositis in the opinion of the treating physician and were capable of oral ciprofloxacin intake. DGS corresponded with mild-to-moderate mucositis while citrulline plasma concentration ranged from values corresponding with normal values to severe mucositis. A mucositis scoring mismatch was observed in nine patients (19%) as citrulline plasma concentration showed severe mucositis (nadir < 10 \( \mu \text{mol/L} \)) while DGS suggested mild (\( n = 8 \)) or moderate (\( n = 1 \)) mucositis. Four of these patients did not switch to intravenous therapy at any time during their treatment course, indicating no development of clinically severe mucositis in the opinion of the attending physician. Nevertheless, uncertainty remains as to whether patients with mild mucositis according to the DGS actually showed mild mucositis in the small intestine. As patients were capable of oral intake and the physician judged mucositis to be generally mild, we chose to draw conclusions regarding mild-to-moderate mucositis despite citrulline plasma concentrations corresponding with severe mucositis. Observations in patients treated with intravenous antibiotics who were subsequently switched back to oral ciprofloxacin after clinical

Figure 1. Concentration-time curve [median (solid line and dashed line) and 95% prediction interval (shaded areas)] for haematological patients (blue) and a control group of healthy volunteers (orange) after twice daily oral ciprofloxacin 500 mg. Data based on simulations with \( n = 2500 \) per subgroup. The median simulated time to ciprofloxacin \( C_{\text{max}} \) is 1.5 h for haematological patients and 1.2 h for the control group. This figure appears in colour in the online version of JAC and in black and white in the print version of JAC.

Figure 2. Boxplots illustrating similar cumulative systemic exposure in the first- and second week of therapy (AUC\(_{\text{day 1-7}}\), left panel, AUC\(_{\text{day 8-14}}\), right panel) for haematological patients (blue) and the control group of healthy volunteers (orange). Data are based on Monte Carlo simulations with \( n = 2500 \) per subgroup after the standard of care dosing regimen of 500 mg PO twice daily. This figure appears in colour in the online version of JAC and in black and white in the print version of JAC.
improvement were adequately described by our model. This may suggest ciprofloxacin oral absorption is not significantly altered in patients with a temporarily worsening in their clinical condition. The DGS was retrospectively scored based on data available in the electronic patient registry. Possibly, some components of the DGS may have been incompletely registered which could have led to an underestimation of mucositis severity using the DGS which is a limitation of our study. Also, citruline was measured only once for participants in Cohort 1. An important strength of our study is the comparison of ciprofloxacin PK data in haematological patients with data from 28 healthy individuals as a PK reference standard, to compensate for the lack of a formal PK/PD target for Gram-negative prophylaxis using ciprofloxacin.

Three previous case-series reported contradictory results on exposure of orally administered ciprofloxacin in patients with haematological malignancies. Studies found no difference in drug concentration between haematological patients with mucositis and data from the literature, although another study found a reduced drug concentration in patients with haematological malignancies. Since these reports observed only 8, 6 and 5 patients, the external validity of the respective case-series is limited. Moreover, two of the three case-series did not report severity of mucositis at all, while one study focused on severity of oral mucositis and, in contrast to our study, the role of biomarkers was not evaluated beforehand. In order to capture the severity of mucositis at the site of absorption, GI-mucositis scores and biomarkers were analysed concomitantly.

Ciprofloxacin is subject to OAT1 and OAT3 carrier-mediated absorption. Disruption of the mucosa could negatively impact OAT1 and OAT3 carrier capacity but at the same time mucosal barrier function may be impaired. As a result, both an increased and decreased rate of absorption and bioavailability could be anticipated. Haematological patients showed an increased time to $C_{\text{max}}$ although this was not associated with a significant alteration in bioavailability. Both active and passive processes play a role in ciprofloxacin absorption. Therefore, the slightly longer time to $C_{\text{max}}$ in haematological patients could theoretically be caused by a negative impact on active absorption because of mucositis while the net-influence on bioavailability remains negligible.

In patients with severe mucositis treated with IV ciprofloxacin, further research may be needed to clarify whether destruction of the mucosa impacts the trans-epithelial intestinal secretion route of ciprofloxacin, as ciprofloxacin clearance could still be altered.

In conclusion, we found no significant influence of mild mucositis on ciprofloxacin bioavailability or clearance. This study supports oral dosing of ciprofloxacin 500 mg twice daily as Gram-negative infection prophylaxis in haematological patients with mild-to-moderate mucositis capable of oral intake.

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Author contributions

K.v.R. and S.d.V. wrote the manuscript; S.d.V., E.M. and K.v.R. collected the data. K.v.R. performed the data analysis under supervision of C.K., R.v.H. and R.J.M.B; R.v.H., P.v.d.L., S.H.T., E.M., R.A.A.M., N.M.A.B., C.A.J.K., R.A.A.M. and S.E.G. critically reviewed all versions of the manuscript. R.v.H., R.J.M.B. and S.E.G. supervised the final version of the manuscript.

Supplementary data

Tables S1 and S2 and Figures S1 to S4 are available as Supplementary data at JAC Online.

References

1. Bucaneve G, Castagnola E, Viscoli C et al. Quinolone prophylaxis for bacterial infections in afebrile high risk neutropenic patients. Eur J Cancer Suppl 2007; 5: 5–12. https://doi.org/10.1016/j.ejcsup.2007.06.002
2. Cullen M, Steven N, Bilingham L et al. Antibacterial prophylaxis after chemotherapy for solid tumors and lymphomas. N Engl J Med 2005; 353: 988–98. https://doi.org/10.1056/NEJMoa050078
3. Gaffer-Givili A, Fraser AMD, Paul MPHM et al. Meta-analysis: antibiotic prophylaxis reduces mortality in neutropenic patients. Ann Intern Med 2005; 142: 979–95. https://doi.org/10.7326/0003-4819-142-12_Part_1-200506210-00008
4. Mikulska M, Averbuch D, Tissot F et al. Fluoroquinolone prophylaxis in haematological cancer patients with neutropenia: ECIL critical appraisal of previous guidelines. J Infect 2018; 76: 20–37. doi:10.1016/j.jinf.2017.10.009
5. FDA. Ciprofloxacin prescribers information. 2016. https://www.accessdata.fda.gov/drugsatfda_docs/Label/2016/019537s086lbl.pdf.
6. Blijlevens NM, Donnelly JP, de Paauw BE. Empirical therapy of febrile neutropenic patients with mucositis: challenge of risk-based therapy. Clin Microbial Infect 2001; 7 Suppl 4:47–52. https://doi.org/10.1046/j.1469-0691.2001.00058.x
7. Peterson DE, Boers-Doets CB, Bensadoun RJ et al. Management of oral and gastrointestinal mucosal injury: ESMO Clinical Practice Guidelines for diagnosis, treatment, and follow-up. Ann Oncol 2015; 26: 139–51. https://doi.org/10.1093/annonc/mdv202
8. Jansen AME, Muilwijk EW, van der Velden WJFM et al. Posaconazole bioavailability of the solid oral tablet is reduced during severe intestinal mucositis. Clin Microbial Infect 2022; 28: 1003–9. https://doi.org/10.1016/j.cmi.2022.01.029
9 Kovanda LL, Marty FM, Maertens J et al. Impact of mucositis on absorption and systemic drug exposure of isavuconazole. Antimicrob Agents Chemother 2017; 61: 1–10. https://doi.org/10.1128/AAC.00101-17
10 Blijlevens NM, Donnelly JP, Naber AHJ et al. A randomised, double-blinded, placebo-controlled, pilot study of parenteral glutamine for allogeneic stem cell transplant patients. Support Care Cancer 2005; 13: 790–6. https://doi.org/10.1007/s00520-005-0790-y
11 van Vliet MJ, Tissing WJE, Rings EHHM et al. Citrulline as a marker for chemotherapy induced mucosal barrier injury in pediatric patients. Pediatr Blood Cancer 2009; 53: 1188–94. https://doi.org/10.1002/pbc.22210
12 Blijlevens NM, van’t Land B, Donnelly JP et al. Measuring mucosal damage induced by cytotoxic therapy. Support Care Cancer 2004; 12: 227–233. https://doi.org/10.1007/s00520-003-0572-3
13 van der Velden WJFM, Herbers AHE, Brüggemann RJM et al. Citrulline and albumin as biomarkers for gastrointestinal mucositis in recipients of hematopoietic SCT. Bone Marrow Transplant 2013; 48: 977–81. https://doi.org/10.1038/bmt.2012.278
14 Kuiken NNS, Rings EHHM, Blijlevens NMA et al. Biomarkers and non-invasive tests for gastrointestinal mucositis. Support Care Cancer 2017; 25: 2933–2941. https://doi.org/10.1007/s00520-017-3752-2
15 Crenn P, Messing B, Cynober L. Citrulline as a biomarker of intestinal failure due to enterocyte mass reduction. Clin Nutr 2008; 27: 328–39. https://doi.org/10.1016/j.clnu.2008.02.005
16 Crenn P, Váhedi K, Laverne-Slove K et al. Plasma citrulline: A marker of enterocyte mass in villous atrophy-associated small bowel disease. Gastroenterology 2003; 124: 1210–9. https://doi.org/10.1016/S0016-5085(03)00170-7
17 Parkman HP, Hasler WL, Fisher RS. American Gastroenterological Association technical review on the diagnosis and treatment of gastrointestinal paresis. Gastroenterology 2004; 127: 1592–1622. https://doi.org/10.1053/j.gastro.2004.09.055
18 Gattis WA, Petros WP, Pickard WW et al. A prospective, open-label study of single-dose ciprofloxacin absorption after chemotherapy in patients with malignancy. Pharmacotherapy 1997; 17: 836–40.
19 Smith GM, Leyland MJ, Farrell ID et al. A clinical, microbiological and pharmacokinetic study of ciprofloxacin plus vancomycin as initial therapy of febrile episodes in neutropenic patients. J Antimicrob Chemother 1988; 21: 647–55. https://doi.org/10.1093/jac/21.5.647
20 Johnson EJ, MacGowan AP, Potter MN et al. Reduced absorption of oral ciprofloxacin after chemotherapy for haematological malignancy. J Antimicrob Chemother 1990; 25: 837–42. https://doi.org/10.1093/jac/25.5.837
21 Mulikwijk EW, Maertens JA, van der Velden WJFM et al. Pharmacokinetics of extended dose intervals of micafungin in haematology patients: optimizing antifungal prophylaxis. J Antimicrob Chemother 2018; 73: 3095–3101. https://doi.org/10.1093/jac/dky324
22 van Rhee KP, Smit C, Wasmann RE et al. Ciprofloxacin pharmacokinetics after oral and intravenous administration in (morbidly) obese and non-obese individuals: a prospective clinical study. Clin Pharmacokinet 2022; 61: 1167–75. https://doi.org/10.1007/s40262-022-01130-5.
23 Inker LA, Schmid CH, Tighiouart H et al. Estimating glomerular filtration rate from serum creatinine and cystatin C. N Engl J Med 2012; 367: 20–9. https://doi.org/10.1056/NEJMoai1114248
24 Levey AS, Coresh J, Greene T et al. Using standardized serum creatinine values in the modification of diet in renal disease study equation for estimating glomerular filtration rate. Ann Intern Med 2006; 145: 247–54. https://doi.org/10.7326/0003-4819-145-4-200608150-00004
25 Du Bois D, Du Bois EF. A formula to estimate the approximate surface area if height and weight be known. Arch Intern Med 1916; 17: 863–871. https://doi.org/10.1001/archinte.1916.00081030010002
26 International Council for Harmonization of Technical Requirements For Pharmaceuticals For Human Use. Good clinical practice. 2016. https://ichgcp.net/.
27 World Medical Association. Declaration of Helsinki - ethical principles for medical research involving human subjects. 2013. https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/.
28 de Vroom SL, Pistorius MCM, Bijleveld YA et al. Development and validation of a liquid chromatography-tandem mass spectrometry (LC-MS/MS) assay for the determination of total and unbound ciprofloxacin concentrations in human plasma. Ther Drug Monitor 2022; 44: 552–557. https://doi.org/10.1097/FTD.0000000000000969
29 Demacker PN, Beijers AM, van Daal H et al. Plasma citrulline measurement using UPLC tandem mass-spectrometry to determine small intestinal enterocyte pathology. J Chromatogr B Analyt Technol Biomed Life Sci 2009; 877: 387–92. https://doi.org/10.1016/j.chromb.2008.12.041
30 Beal S, Sheiner L, Boeckmann A. NONMEM Users Guide - Part IV. 2018.
31 Keizer RJ. Modeling and Simulation Workbench for NONMEM: Tutorial on Pirana, PsN, and Xpose. CPT: Pharmacometrics Syst Pharmacol 2013; 2: e50. https://doi.org/10.1038/sp.2013.24
32 Arakawa H, Shirasaka Y, Haga M et al. Active intestinal absorption of fluoroquinolone antibacterial agent ciprofloxacin by organic anion transporting polypeptide, Oatp1a5. Biopharm Drug Dispos 2012; 33: 332–41. https://doi.org/10.1002/bdd.1809