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GUIDE TO AUTHORS

Effect of selected meals and dosing conditions on the absorption and bioavailability of ciprofloxacin

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ABSTRACT

This study evaluated the effects of different dietary patterns and feeding schedules on the pharmacokinetics and tolerability of an orally administered drug. Five dosing conditions were compared: fasted state, high-fat diet, ketogenic diet, carbohydrate-rich diet, and 6 PM time-restricted feeding. The fasted condition produced the highest Cmax ($p < 0.001$) and the fastest Tmax ($p < 0.001$), but was associated with a significantly higher incidence of gastrointestinal (GI) side effects ($p = 0.002$) compared to fed states. High-fat feeding significantly delayed Tmax ($p = 0.004$) and reduced Cmax ($p = 0.006$), while markedly decreasing GI side effects ($p = 0.01$). The ketogenic diet demonstrated slightly improved bioavailability ($p = 0.03$) relative to other diets but was linked to mild tolerability issues such as dry mouth and dizziness ($p = 0.02$). In contrast, the carbohydrate-rich diet exhibited intermediate Cmax and Tmax values, with a more favorable tolerability profile ($p > 0.05$ vs. high-fat and ketogenic groups). The 6 PM time-restricted feeding pattern mirrored the fasted group in terms of adverse events ($p = 0.07$) but displayed moderate pharmacokinetic outcomes between fasted and fed conditions. These results emphasize the substantial influence of dietary and feeding conditions on drug absorption and tolerability, suggesting the need for tailored dosing recommendations. Future research should explore individualized nutrition-drug strategies to optimize therapeutic outcomes.

Keywords: Pharmacokinetics, Dietary fats, Fasting, Ketogenic diet, Gastrointestinal diseases, Time-restricted feeding

Introduction

Ciprofloxacin, a second-generation fluoroquinolone, remains a cornerstone in the management of various bacterial infections, including respiratory, urinary tract, gastrointestinal, and skin infections. Its widespread clinical use is largely attributed to its broad-spectrum bactericidal activity, favorable pharmacokinetic profile, and oral bioavailability [1]. However, like many orally administered drugs, the absorption and bioavailability of ciprofloxacin can be significantly influenced by extrinsic factors, particularly the presence and composition of food, as well as other dosing conditions. Understanding these influences is critical for optimizing therapeutic outcomes and minimizing the risk of therapeutic failure or antibiotic resistance.

The absorption of ciprofloxacin occurs predominantly in the upper gastrointestinal tract, specifically in the duodenum and jejunum, regions where the drug demonstrates moderate permeability characteristics. Its oral bioavailability ranges from 60% to 80% in fasting individuals. Nevertheless, concurrent intake of meals, especially those high in minerals like calcium, magnesium, and iron, has been shown to interfere with the drug's absorption through chelation and formation of insoluble complexes [2]. This interaction can lead to clinically significant reductions in systemic drug concentrations, thereby potentially compromising efficacy.

The influence of meal composition on ciprofloxacin pharmacokinetics has been an area of active research, with studies suggesting that high-fat and high-protein meals may delay the time to peak concentration (Tmax) without markedly affecting the area under the plasma concentration-time curve (AUC) or maximum concentration (Cmax) [3]. Conversely, meals rich in divalent or trivalent cations can significantly lower both AUC and Cmax, indicating a substantial reduction in bioavailability [4]. Consequently, understanding the impact of different types of meals is essential for developing optimized dosing guidelines, particularly in populations where dietary habits vary widely.

Recent research has also examined the effects of dosing conditions such as timing of administration relative to meals, co-administration with other medications or supplements, and the physicochemical characteristics of ciprofloxacin formulations. These factors collectively contribute to the complexity of ciprofloxacin's pharmacokinetic profile. For instance, delayed gastric emptying caused by fatty meals or gastrointestinal disorders can prolong drug absorption time, while acidic beverages may alter drug solubility and thus affect absorption kinetics [5].

One emerging concern in the context of ciprofloxacin therapy is the global rise in antibiotic resistance. Sub-bioavailability not only diminish clinical efficacy but also promote the selection of resistant bacterial strains [6]. Therefore, ensuring optimal absorption through appropriate meal and dosing recommendations is not merely a pharmacokinetic consideration but also a crucial antimicrobial stewardship measure.

Mechanistically, ciprofloxacin belongs to the Biopharmaceutics Classification System (BCS) Class III category, characterized by high solubility but low permeability [7]. Drugs in this class are typically more sensitive to changes in gastrointestinal transit time and membrane transport mechanisms. This further underscores the importance of controlling external variables such as meal composition and dosing schedules to maintain consistent drug exposure [7].

Contemporary studies have employed advanced pharmacokinetic modeling and simulation techniques to predict and quantify the impact of various meals on ciprofloxacin bioavailability [8]. These approaches, along with clinical bioequivalence studies, have provided valuable insights that can inform labeling instructions and patient counseling strategies. However, variability remains a significant challenge, influenced by factors such as inter-individual differences in gastric pH, motility, and the presence of gastrointestinal diseases like inflammatory bowel disease (IBD) [9].

Additionally, the development of novel ciprofloxacin formulations, including gastro-retentive and controlled-release delivery systems, aims to mitigate food-drug interactions and provide more stable pharmacokinetic profiles regardless of meal conditions [10]. These innovations may eventually alter current recommendations regarding meal timing and ciprofloxacin administration.

In clinical practice, it is often recommended that ciprofloxacin be taken either two hours before or six hours after meals or dairy products to minimize chelation and maximize absorption [11]. However, adherence to these guidelines is suboptimal, especially in outpatient settings where patients may not fully appreciate the pharmacokinetic rationale behind such instructions. Education on the importance of dosing conditions and their impact on treatment success is therefore an essential component of antibiotic therapy.

Several recent randomized controlled trials and observational studies have further elucidated the extent of meal effects on ciprofloxacin pharmacokinetics. For example, a study by Kumar et al. (2022) demonstrated a significant reduction in ciprofloxacin Cmax by 30% when administered with a high-calcium meal compared to fasting conditions [12]. Another investigation by Zhang et al. (2021) found that high-fat meals delayed Tmax by up to 1.5 hours but did not significantly alter AUC, suggesting that delayed absorption does not necessarily equate to

Furthermore, patient-specific factors such as age, gender, co-morbidities, and concomitant medication use can modulate the extent of meal effects on ciprofloxacin absorption [14]. Elderly patients, for instance, may exhibit slower gastric emptying and altered gastrointestinal physiology, potentially exacerbating the impact of food on drug bioavailability. Personalized dosing strategies considering these variables could improve therapeutic outcomes.

Importantly, regulatory agencies such as the United States Food and Drug Administration (FDA) and the European Medicines Agency (EMA) require food-effect studies as part of the drug development process for orally administered drugs [15]. These studies not only assess the impact of meals on pharmacokinetics but also inform labeling requirements that guide clinicians and patients in proper drug use.

Given the critical role of ciprofloxacin in clinical practice and the potential consequences of reduced bioavailability, there is a pressing need for a comprehensive evaluation of how different meals and dosing conditions affect its absorption. This study aims to systematically investigate the effect of various meal types and dietary lifestyle on the pharmacokinetics of ciprofloxacin. Furthermore, it seeks to evaluate the influence of dosing schedules relative to meal timing and to identify practical recommendations for clinical use.

Method

Study design

This study followed a non-randomized design, where each participant receives ciprofloxacin under different dosing conditions at different time points.

Study Design and Analysis Plan

This was a non-randomized, parallel-group study. Participants were assigned to one of five feeding conditions: fasted state, high-fat diet, ketogenic diet, carbohydrate-rich diet, or time-restricted feeding at 6pm. Each participant received a single oral dose of the study drug under their assigned conditions.

Participants

Healthy adult volunteers aged 18–45 years with a body mass index (BMI) between 18.5 and 25 kg/m² were recruited. Participants were screened to exclude any significant medical conditions, medication use, or dietary restrictions.

Participant recruitment

Inclusion criteria

Healthy adult volunteers (18-50 years old) and with no history of gastrointestinal or hepatic diseases, or other conditions affecting drug absorption were allowed to participate in the study. Participants with no ongoing use of drugs that can interfere with ciprofloxacin metabolism (e.g., antacids, anti-ulcer medications) were admissible to the recruitment.

Exclusion criteria

Pregnant or breastfeeding women are excluded from the study.Individuals with known allergies to fluoroquinolones are also excluded.Individuals with renal or hepatic dysfunction were excluded from the study.

Feeding conditions

The five dietary conditions included had 10 members randomly assigned to each group

Fasted State: Participants fasted overnight for at least 10 hours prior to dosing.

High-fat meal: Participants consumed standardized high-fat meals (approximately 900 kcal; 60% fat, 25% carbohydrates, 15% protein) for 7 daysand 30 minutes before dosing.

Ketogenic Diet: Participants followed ketogenic diet (≥75% fat, ≤5% carbohydrates) for three days before dosing, for 7 days, and 30 minutes before dosing.

Carbohydrate-rich meal: Participants consumed mealsrich in carbohydrates (approximately 800 kcal; 65% carbohydrates, 20% fat, 15% protein) for 7 days and 30 minutes before dosing.

Time-Restricted Feeding: Participants ate a standardized meal at 6 pm only once daily and at the evening prior, as an overnight fasting until dosing the next morning.

Drug dosing

Ciprofloxacin in the form of oral tablets (standard dose, e.g., 500 mg) was employed for the research. The study assessed different dosing conditions that could influence systemic availability, including (a) fasted state (administering ciprofloxacin after at least 8 hours of fasting), and fed state conditions involving administered ciprofloxacin (b) 30 minutes after a high-fat meal and high-fat meal for one week (c) 30 minutes after a ketogenic diet and ketogenic diet in the previous one week, (d) 30 minutes after a carbohydrate-rich diet and carbohydrate-rich diet in the prior 1 week, and (e) on an empty stomach with (fasting and eating at 6pm in the previous 1 week).Each participant was assigned to a dosing condition and received ciprofloxacin under a specified condition in a random order.

Blood sampling and analysis

Blood samples were collected at multiple time points after drug administration to measure plasma concentrations of ciprofloxacin. These time points included pre-dose (baseline), 0.5, 1, 2, 4, 6, and 8 hours post-dose.Plasma concentrations of ciprofloxacin were measured using high-performance liquid chromatography (HPLC) according to the method of Elgendy et al, 2023 [16]. The key pharmacokinetic parameters to be determined from the plasma concentration-time profiles include:Cmax (maximum plasma concentration), Tmax (time to

reach Cmax), AUC (area under the plasma concentration-time curve), $t_{1/2}$ (half-life), bioavailability (F), which can be calculated by comparing AUC under different dosing conditions.

Safety and tolerability assessment

Adverse events were monitored throughout the study using standardized questionnaires and clinical assessments. Particular attention was given to gastrointestinal symptoms, dry mouth, and dizziness.

Adverse event monitoring

Participants were monitored for any adverse events or side effects during the study. These may include gastrointestinal disturbances, dizziness, or other typical ciprofloxacin-related side effects.

Blood tests were conducted to monitor renal function (e.g., creatinine) and liver function (e.g., AST, ALT) to ensure the drug is not causing any harm to vital organs.

Pharmacokinetic analysis

Pharmacokinetic parameters (Cmax, Tmax, $AUC_{0-\infty}$, and t½) were calculated for each participant using non-compartmental analysis. Group mean values and standard deviations (SD) were computed.

Comparative statistics

Between-group comparisons were performed using one-way analysis of variance (ANOVA) for continuous variables (e.g., Cmax, Tmax, AUC).Where ANOVA showed significant differences ($p < 0.05$), Tukey's post-hoc test was used for pairwise comparisons between groups for continuous variables (like Cmax, Tmax, AUC) and Chi-square test for categorical data (like GI side effects rates). All tests were two-sided, and ap-value < 0.05 was considered statistically significant. Analyses were performed using SPSS version 26.0.

Ethical considerations

All participants provided informed consent, acknowledging their understanding of the study's objectives, potential risks, and procedures. The study protocol was reviewed and approved by University of UyoInstitutional Review Board (IRB) to ensure compliance with ethical standards and participant safety.

Result

A total of 50 healthy volunteers completed the study, with 10 participants assigned to each feeding condition. Baseline demographic characteristics (age, sex, BMI) were comparable across all groups ($p > 0.05$). Table 1 presents the demographics and statistics of some measured parameters of participants.

Table 1: Demographics of participants and the respective dosing conditions

DOSING CONDITION	AGE	GENDER (M/F)	BMI (KG/M²)	ETHNICITY	WEIGHT (KG)
Fasted	27.2±3.4	4/6	56.5±9.7	African	23.4±0.4
High Fat	31.4±4.2	5/5	58.3±8.5	African	21.9±1.2
Ketogenic	25.8±6.3	3/7	65.4±4.8	African	22.8±1.5
Carbohydrate-rich	31.9±4.4	4/6	64.9±6.9	African	23.4±0.6
Time-restricted feeding	28.5±3.7	5/5	64.9±5.9	African	24.3±1.1

Table 2: Pharmacokinetic parameters of ciprofloxacin under different dosing conditions

Dosing condition	Cmax (µg/ml)	Tmax (h)	AUC_{0-8} (µg.h.ml)	Significant difference relative to the fasted state
Fasted	118±11	1.3±0.1	Reference	Reference
High-fat	94±8	3.2±0.7	Decreased, P=0.01	Decreases Cmax (p=0.003); increased Tmax (p=0.007)
Ketogenic	104±12	2.4±0.4	Increased, P=0.03	Increased AUC; P=0.01
Carbohydrate-rich	113±13	1.8±0.2	NSD, P=0.09	NSD; P=0.09
Time-restricted feeding	105±14	1.5±0.3	NSD, P=0.08	NSD; P=0.07

**NSD=No significant difference; AUC=area under the curve plasma concentration versus time)*

The time-restricted feeding group produced pharmacokinetic parameters lying between those of the fasted and high-fat meal groups, with a Cmax of 105 ± 14 ng/mL and a Tmax of 1.5 ± 0.3 hours ($p = 0.07$ vs. fasted). Table 2 presents the abdominal discomfort. The high-fat group had the comparison of the different dosing conditions with the fasted group.

Tolerability and adverse events

Adverse events varied significantly by feeding conditions. The fasted group reported the highest incidence of gastrointestinal (GI) side effects (70%, $p = 0.002$ vs. fed groups), including nausea and lowest GI side effect rate (20%, $p = 0.01$ compared to fasted). The ketogenic group showed mild tolerability issues, including dry mouth (30%) and dizziness (20%) ($p = 0.02$ vs. other diets). The carbohydrate-rich and 6 pm feeding groups exhibited moderate rates of adverse events (30–40%), with no significant differences between them ($p > 0.05$). Table 3 presents the tolerability and adverse event profile of the participants in this study.

Table 3: **Tolerability and adverse effects of ciprofloxacin under different dosing conditions**

DOSING CONDITIONS	PERCENTAGE OCCURRENCE		COMPARISON WITH FASTED GROUP
	Gastrointestinal side effect	Other side effect Nausea, dizziness	
Fasted	67		High GI side effect Increased GI side effects vs. all fed groups (p = 0.002)
High Fat	28	None	Low GI side effect Decreased GI side effects vs. fasted (p = 0.01)
Ketogenic	36	Dry mouth (17), dizziness (23)	Mild tolerability Mild tolerability issues (p = 0.02 vs. other diets)
High Carbohydrate	34	Moderate nausea	NS vs. 6 PM feeding (p > 0.05)
Time-restricted feeding	43	Moderate nausea	NS vs. carbohydrate-rich group (p > 0.05)

Discussion

This study investigated the influence of various feeding conditions—fasted state, high-fat diet, ketogenic diet, carbohydrate-rich diet, and time-restricted feeding patterns on the tolerability of the studied drug. The findings underscore the significant role that dietary patterns and meal timing play in modulating drug absorption, bioavailability, and side effect profiles [17].

Participants in the fasted state exhibited the highest peak plasma concentration (Cmax) and the shortest time to reach this peak (Tmax), indicating rapid and extensive drug absorption. However, this condition was also associated with a higher incidence of gastrointestinal (GI) side effects. These results align with previous studies demonstrating that fasting can enhance drug absorption due to the absence of food-induced delays in gastric emptying and alterations in gastrointestinal pH, which can affect drug solubility and stability [18]. Nevertheless, the increased GI side effects observed suggest that while fasting may improve pharmacokinetic parameters, it may also compromise tolerability [19].

The high-fat diet group showed a significant delay in Tmax and a reduction in Cmax compared to the fasted group. High-fat meals are known to slow gastric emptying and alter bile secretion, which can impact drug dissolution and absorption rates [20]. Interestingly, participants on the high-fat diet reported fewer GI side effects, suggesting improved tolerability. This trade-off between delayed absorption and enhanced tolerability highlights the need to consider meal composition when optimizing drug administration schedules.

Participants following a ketogenic diet demonstrated slightly improved bioavailability, as evidenced by a modest increase in the area under the concentration-time curve (AUC). However, this group also reported mild tolerability issues, including dry mouth and dizziness. The ketogenic diet's high-fat, low-carbohydrate nature can induce metabolic changes that affect drug metabolism and transport [21]. These findings suggest that while the ketogenic diet may enhance drug exposure, it may also introduce new tolerability challenges that need to be managed.

The carbohydrate-rich diet group exhibited intermediate pharmacokinetic parameters, with Cmax fasted and high-fat groups. This diet provided a relatively stable absorption profile and a favorable tolerability profile, with fewer reported side effects. Carbohydrate-rich meals can influence insulin secretion and gastrointestinal motility, which may contribute to these observations. This feeding condition may offer a balanced approach for drugs requiring consistent absorption and minimal side effects.

The 6 PM time-restricted feeding pattern resulted in pharmacokinetic outcomes similar to the fasted group, with moderate absorption rates and side effect profiles. Time-restricted feeding aligns food intake with circadian rhythms, which can influence drug metabolism and efficacy[22]. While this feeding pattern may mimic fasting in terms of drug absorption, it may offer improved tolerability and adherence, making it a viable alternative for certain patient population.

These findings have important clinical implications for optimizing drug administration. Understanding the impact of feeding conditions on drug pharmacokinetics and tolerability can inform personalized dosing strategies. For drugs with narrow therapeutic windows or significant side effect profiles, tailoring administration schedules to align with specific dietary patterns may enhance efficacy and minimize adverse effect [23].

This study's non-randomized design and limited sample size may affect the generalizability of the findings. Future randomized controlled trials with larger, more diverse populations are needed to confirm these results. Additionally, exploring the underlying mechanisms by which different diets influence drug metabolism and transport could provide further insights into optimizing pharmacotherapy.

Conclusion

Dietary patterns and meal timing significantly influence the pharmacokinetics and tolerability of orally administered drugs. The fasted state enhances absorption but may increase GI side effects, while high-fat and ketogenic diets alter absorption rates and introduce new tolerability considerations. Carbohydrate-rich diets offer stable absorption with favorable tolerability, and time-restricted feeding presents a promising approach that balances absorption and side effect profiles. These insights

clinical pharmacology to optimize therapeutic outcomes.

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